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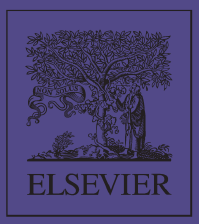

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The International Federation of Gynecology and Obstetrics (FIGO) Initiative on Gestational Diabetes Mellitus: A Pragmatic Guide for Diagnosis, Management, and Care

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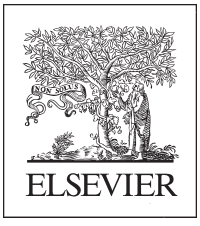

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Editorial Office: FIGO Secretariat, FIGO House
Suite 3 - Waterloo Court, 10 Theed Street,
London, SE1 8ST, UK
Tel: +44 20 7928 1166
Fax: +44 20 7928 7099
E-mail: ijgo@figo.org

The International Federation of Gynecology and Obstetrics (FIGO) Initiative on Gestational Diabetes Mellitus: A Pragmatic Guide for Diagnosis, Management, and Care

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Moshe Hod [a], Anil Kapur [b], David A. Sacks [c], Eran Hadar [d,e], Mukesh Agarwal [f], Gian Carlo Di Renzo [g], Luis Cabero Roura [h], Harold David McIntyre [i], Jessica L. Morris [j,*], Hema Divakar [k]

[a] Division of Maternal Fetal Medicine, Rabin Medical Center, Tel Aviv University, Petah Tikva, Israel
[b] World Diabetes Foundation, Gentofte, Denmark
[c] Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA, USA
[d] Helen Schneider Hospital for Women, Rabin Medical Center, Petah Tikva, Israel
[e] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[f] Department of Pathology, UAE University, Al Ain, United Arab Emirates
[g] Centre of Perinatal and Reproductive Medicine, Department of Obstetrics and Gynecology, University of Perugia, Perugia, Italy
[h] Maternal Fetal Medicine Unit, Vall d'Hebron University Hospital, Barcelona, Spain
[i] University of Queensland Mater Clinical School, Brisbane, Australia
[j] International Federation of Gynecology and Obstetrics, London, UK
[k] Divakars Specialty Hospital, Bangalore, India

Contributors

In addition to the authors, the following people provided important contributions during the creation of the document. Thanks go to international experts: Tao Duan, Huixia Yang, Andre Van Assche, Umberto Simeoni, Tahir Mahmood, Biodun Olagbuji, Eugene Sobngwi, Maicon Falavigna, Rodolfo Martinez, Carlos Ortega, Susana Salzberg, Jorge Alvariñas, Gloria Lopez Steward, Silvia Lapertosa, Roberto Estrade, Cristina Faingold, Silvia García, Argyro Syngelaki, Stephen Colagiuri, Yoel Toledano, Mark Hanson, and Blami Dao. Special thanks, for FIGO guidance and coordination, go to President Sabaratnam Arulkumaran, President Elect CN Purandare, Chief Executive Hamid Rushwan, and Chair of the SMNH Committee, William Stones.

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Conflict of interest

The authors have no conflicts of interest to declare.

Women queue for gestational diabetes services in Barranquilla, Colombia. Photograph by Jesper Westley for the World Diabetes Foundation.

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* Corresponding author at FIGO House, Suite 3, Waterloo Court, 10 Theed Street, London, SE1 8ST. Tel.: +44 207 928 1166
E-mail address: Jessica@figo.org (J.L. Morris).

List of abbreviations/acronyms

ACOG	American College of Obstetrics and Gynecology
ADA	American Diabetes Association
BMI	Body mass index
CGM	Continuous glucose monitoring
DIP	Diabetes mellitus in pregnancy
FPG	Fasting plasma glucose
GCT	Glucose challenge test
GDM	Gestational diabetes mellitus
GI	Glycemic index
HbA1c	Glycosylated hemoglobin (hemoglobin A1c)
IADPSG	International Association of Diabetes in Pregnancy Study Groups
IDF	International Diabetes Federation
IGT	Impaired glucose tolerance
IOM	Institute of Medicine
LGA	Large for gestational age
NICE	National Institute for Health and Care Excellence
NPH	Neutral protamine Hagedorn insulin
OAD	Oral antidiabetic agents
OGTT	Oral glucose tolerance test
PCOS	Polycystic ovarian syndrome
POC	Point of care
SGA	Small for gestational age
SMBG	Self-monitoring of blood glucose
T2DM	Type 2 diabetes mellitus

1. Executive summary

Hyperglycemia is one of the most common medical conditions women encounter during pregnancy. The International Diabetes Federation (IDF) estimates that one in six live births (16.8%) are to women with some form of hyperglycemia in pregnancy. While 16% of these cases may be due to diabetes in pregnancy (either pre-existing diabetes—type 1 or type 2—which antedates pregnancy or is first identified during testing in the index pregnancy), the majority (84%) is due to gestational diabetes mellitus (GDM).

The occurrence of GDM parallels the prevalence of impaired glucose tolerance (IGT), obesity, and type 2 diabetes mellitus (T2DM) in a given population. These conditions are on the rise globally. Moreover, the age of onset of diabetes and pre-diabetes is declining while the age of childbearing is increasing. There is also an increase in the rate of overweight and obese women of reproductive age; thus, more women entering pregnancy have risk factors that make them vulnerable to hyperglycemia during pregnancy.

GDM is associated with a higher incidence of maternal morbidity including cesarean deliveries, shoulder dystocia, birth trauma, hypertensive disorders of pregnancy (including pre-eclampsia), and subsequent development of T2DM. Perinatal and neonatal morbidities also increase; the latter include macrosomia, birth injury, hypoglycemia, polycythemia, and hyperbilirubinemia. Long-term sequelae in offspring with in utero exposure to maternal hyperglycemia may include higher risks for obesity and diabetes later in life.

In most parts of low-, lower middle-, and upper middle-income countries (which contribute to over 85% of the annual global deliveries), the majority of women are either not screened or improperly screened for diabetes during pregnancy—even though these countries account for 80% of the global diabetes burden as well as 90% of all cases of maternal and perinatal deaths and poor pregnancy outcomes.

Given the interaction between hyperglycemia and poor pregnancy outcomes, the role of in utero imprinting in increasing the risk of diabetes and cardiometabolic disorders in the offspring of mothers with hyperglycemia in pregnancy, as well as increasing maternal vulnerability to future diabetes and cardiovascular disorders, there needs to be a greater global focus on preventing, screening, diagnosing, and managing hyperglycemia in pregnancy. The relevance of GDM as a priority for maternal health and its impact on the future burden of noncommunicable diseases is no longer in doubt, but how best to deal with the issue remains contentious as there are many gaps in knowledge on how to prevent, diagnose, and manage GDM to optimize care and outcomes. These must be addressed through future research.

The International Federation of Gynecology and Obstetrics (FIGO) brought together international experts to develop a document to frame the issues and suggest key actions to address the health burden posed by GDM. FIGO's objective, as outlined in this document, is: (1) to raise awareness of the links between hyperglycemia and poor maternal and fetal outcomes as well as to the future health risks to mother and offspring, and demand a clearly defined global health agenda to tackle this issue; and (2) to create a consensus document that provides guidance for testing, management, and care of women with GDM regardless of resource setting and to disseminate and encourage its use.

Despite the challenge of limited high-quality evidence, the document outlines current global standards for the testing, management, and care of women with GDM and provides pragmatic recommendations, which because of their level of acceptability, feasibility, and ease of implementation, have the potential to produce significant impact. Suggestions are provided for a variety of different regional and resource settings based on their financial, human, and infrastructure resources, as well as for research priorities to bridge the current knowledge and evidence gap.

To address the issue of GDM, FIGO recommends the following:

Public health focus: There should be greater international attention paid to GDM and to the links between maternal health and noncommunicable diseases on the sustainable developmental goals agenda. Public health measures to increase awareness, access, affordability, and acceptance of preconception counselling, and prenatal and postnatal services for women of reproductive age must be prioritized.

Universal testing: All pregnant women should be tested for hyperglycemia during pregnancy using a one-step procedure and FIGO encourages all countries and its member associations to adapt and promote strategies to ensure this.

Criteria for diagnosis: The WHO criteria for diagnosis of diabetes mellitus in pregnancy [1] and the WHO and the International Association of Diabetes in Pregnancy Study Groups (IADPSG) criteria for diagnosis of GDM [1,2] should be used when possible. Keeping in mind the resource constraints in many low-resource countries, alternate strategies described in the document should also be considered equally acceptable.

Diagnosis of GDM: Diagnosis should ideally be based on laboratory results of venous serum or plasma samples that are properly collected, transported, and tested. Though plasma-calibrated handheld glucometers offer results that are less accurate and precise than those from quality-controlled laboratories, it is acceptable to use such devices for the diagnosis of glucose intolerance in pregnancy in locations where laboratory support is either unavailable or at a site remote to the point of care.

Management of GDM: Management should be in accordance with available national resources and infrastructure even if the specific diagnostic and treatment protocols are not supported by high-quality evidence, as this is preferable to no care at all.

Lifestyle management: Nutrition counselling and physical activity should be the primary tools in the management of GDM. Women with GDM must receive practical nutritional education and counselling that will empower them to choose the right quantity and quality of food and level of physical activity. They should be advised repeatedly during pregnancy to continue the same healthy lifestyle after delivery to reduce the risk of future obesity, T2DM, and cardiovascular diseases.

Pharmacological management: If lifestyle modification alone fails to achieve glucose control, metformin, glyburide, or insulin should be considered as safe and effective treatment options for GDM.

Postpartum follow-up and linkage to care: Following a pregnancy complicated by GDM, the postpartum period provides an important platform to initiate beneficial health practices for both mother and child to reduce the future burden of several noncommunicable diseases. Obstetricians should establish links with family physicians, internists, pediatricians, and other healthcare providers to support postpartum follow-up of GDM mothers and their children. A follow-up program linked to the child's vaccination and regular health check-up visits provides an opportunity for continued engagement with the high risk mother–child pair.

Future research: There should be greater international research collaboration to address the knowledge gaps to better understand the links between maternal health and noncommunicable diseases. Evidence-based findings are urgently needed to provide best practice standards for testing,

management, and care of women with GDM. Cost-effectiveness models must be used for countries to make the best choices for testing and management of GDM given their specific burden of disease and resources.

References

[1] World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. WHO/NMH/MND/13.2. Geneva: WHO; 2013. http://apps.who.int/iris/bitstream/10665/85975/1/WHO_NMH_MND_13.2_eng.pdf

[2] International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33(3):676–82.

2. The target audience of the FIGO Initiative on gestational diabetes mellitus

This document is directed at multiple stakeholders with the intention of bringing attention to hyperglycemia in pregnancy, with particular focus on gestational diabetes. GDM is a hitherto less-prioritized but common medical condition associated with pregnancy that has serious consequences. This document proposes to create a global framework for action to improve the diagnosis and care of women with GDM.

The intended target audience includes:

Healthcare providers: All those who are qualified to care for women with GDM and their offspring (obstetricians, diabetologists, endocrinologists, internists, pediatricians, neonatologists and general practitioners, midwives, nurses, advance practice clinicians, nutritionists, pharmacists, community health workers, laboratory technicians, etc.)

Healthcare delivery organizations and providers: governments, federal and state legislators, healthcare management organizations, health insurance organizations, international development agencies, and nongovernmental organizations.

Professional organizations: international, regional, and national professional organizations of obstetricians and gynecologists, endocrinologists, diabetologists, internists, family practitioners, pediatricians, neonatologists, and worldwide national organizations dedicated to the care of pregnant women with diabetes.

3. Quality assessment of evidence and grading of strength of recommendations

In assessing the quality of evidence and grading of strength of recommendations, the document follows the terminology proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group (http://www.gradeworkinggroup.org/index.htm). This system uses consistent language and graphical descriptions for the strength and quality of the recommendations and the evidence on which they are based. Strong recommendations are numbered as 1 and conditional (weak) recommendations are numbered 2. For the quality of evidence, cross-filled circles are used: ⊕◯◯◯ denotes very low-quality evidence; ⊕⊕◯◯ low quality; ⊕⊕⊕◯ moderate quality; and ⊕⊕⊕⊕ high quality of evidence (Tables 1 and 2).

The overall quality of evidence was assessed for each of the recommendations and expressed using four levels of quality: very low, low, moderate, and high (Table 2). Considerations for quality of evidence include primarily the study design and methodology. As such, evidence based on randomized controlled trials is considered high-quality evidence, observational studies provide moderate or low quality of evidence, and all others are very low. However, other parameters must be considered while assessing the level of evidence: risk of bias, study limitations, directness, consistency of results, precision, publication bias, indirectness of evidence, and scarcity of evidence. Therefore, a limited randomized trial is downgraded and level of evidence is considered moderate or low. These limitations include loss to follow-up, inadequacy of allocation concealment, or an unblinded study with subjective outcomes susceptible to bias. Similarly, an observational study may be upgraded if it supplies large and consistent estimates of the magnitude of a treatment effect.

Additionally, each recommendation is denoted with its strength (strong or weak) while considering the balance of desirable and undesirable consequences, quality of evidence, values and preferences, and resource use (Table 2). Therefore, the quality of evidence is only one possible consideration for the strength of evidence. The decision to apply a possible examination or intervention is also based on potential risk–benefit, cost, and resource allocation. Some recommendations may be based on low-quality evidence but still represent a benefit that outweighs the risks and burdens, and therefore may be strongly recommended.

A pregnant woman waits for her gestational diabetes screening in Tamil Nadu, India. Photograph by Jesper Westley for the World Diabetes Foundation.

Table 1
Interpretation of strong and conditional (weak) recommendations according to GRADE.[a]

	1 = Strong recommendation phrased as "we recommend"	2 = Conditional (weak) recommendation phrased as "we suggest"
For patients	Nearly all patients in this situation would accept the recommended course of action. Formal decision aids are not needed to help patients make decisions consistent with their values and preferences.	Most patients in this situation would accept the suggested course of action.
For clinicians	According to the guidelines, performance of the recommended action could be used as a quality criterion or performance indicator, unless the patent refuses.	Decision aids may help patients make a management decision consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations.	Stakeholders need to discuss the suggestion.

[a]Adapted with permission from Swiglo et al. A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. J Clin Endocrinol Metab. 2008;93(3):666-73. Copyright Endocrine Society (2008).
Note: Both caregivers and care recipients need to be involved in the decision-making process before adopting recommendations.

Table 2
Interpretation of quality of evidence levels according to GRADE. [a]

Level of evidence	Definition
High ⊕⊕⊕⊕	We are very confident that the true effect corresponds to that of the estimated effect.
Moderate ⊕⊕⊕◯	We are moderately confident in the estimated effect. The true effect is generally close to the estimated effect, but it may be slightly different.
Low ⊕⊕◯◯	Our confidence in the estimated effect is limited. The true effect could be substantially different from the estimated effect.
Very low ⊕◯◯◯	We have very little confidence in the estimated effect. The true effect is likely to be substantially different from the estimated effect.

[a]Adapted with permission from Balshem et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6. Copyright Elsevier (2011).

4. Gestational diabetes mellitus: Background, definition, epidemiology, pathophysiology

4.1. Introduction

Despite decades of research, multiple studies, and numerous global consensus conferences, aspects of hyperglycemia in pregnancy—particularly those related to classification and diagnosis of GDM—remain controversial [1]. GDM diagnosis was originally linked to an increased risk of maternal diabetes in later life. Due to remarkable advances in recent years, the metabolic processes that occur during pregnancy and their effect on intrauterine fetal development have been clarified. Consequently, clinicians are more aware of the need to precisely identify and manage metabolic dysfunction in pregnancy manifested especially by aberrant glucose metabolism. This has led to an increased focus on the ability to predict and prevent many potential fetal and maternal complications in the index pregnancy [1].

4.2. Classification of hyperglycemia in pregnancy and definition of GDM

The definition of GDM is evolving. Until recently, the accepted definition was "any degree of glucose intolerance with onset or first recognition during pregnancy" [2]. Because this definition includes women with pre-existing diabetes who were not identified prior to pregnancy and because this definition blurs the line between morbidities associated with diabetes in pregnancy and gestational diabetes, renewed efforts are being made to improve the definition and classification of hyperglycemia during pregnancy. These efforts are also spurred by the increasing prevalence of diabetes and GDM [3] and of greater prevalence of maternal and fetal complications resulting from diabetes mellitus antedating pregnancy. Therefore, hyperglycemia first detected at any time during pregnancy should be classified either as diabetes mellitus in pregnancy (DIP) or GDM [4].

4.3. Diabetes in pregnancy

DIP may either have been pre-existing diabetes (type 1 or type 2) antedating pregnancy, or diabetes first diagnosed during pregnancy (Figure 1).

Notwithstanding its severity, hyperglycemia that is already present at conception and embryogenesis increases the women's vulnerability and risk of complications. A woman with undiagnosed diabetes antedating pregnancy may also have undiagnosed diabetic complications including retinopathy and nephropathy, which markedly increase pregnancy risks [5]. Furthermore, hyperglycemia during the critical period of organogenesis may lead to a high risk of spontaneous abortions and congenital anomalies. Diabetes in pregnancy, because of the attendant greater risk of hyperglycemia, may also result in aberrations in fetal growth and macrosomia. This can lead to additional short-term complications, for example, obstructed labor, shoulder dystocia, neonatal hypoglycemia, or risk of neurological damage. Moreover, there is a risk of onset or exacerbation of microvascular complications, such as retinopathy or nephropathy during pregnancy. For these reasons, ensuring meticulous glucose control before conception and throughout pregnancy is recommended.

The age at onset of T2DM is decreasing globally and many women with previously unknown T2DM may become pregnant, with their diabetes first detected during routine testing in pregnancy. Alternatively, women at high risk of diabetes may be unable to withstand the metabolic stress of pregnancy and develop diabetes for the first time during pregnancy (Figure 2).

When the level of hyperglycemia first detected by testing at any time during the course of pregnancy meets the criteria for diagnosis of diabetes in the nonpregnant state, the condition is called DIP. Those criteria are: fasting plasma glucose (FPG) ≥7.0 mmol/L or 126 mg/dL, and/or 2-hour 75-g oral glucose tolerance test (OGTT) value ≥11.1 mmol/L or 200 mg/dL, or random plasma glucose (RPG) ≥11.1 mmol/L or 200 mg/dL associated with signs and symptoms of diabetes. In DIP the vulnerability to complications is high because of the degree of hyperglycemia and the uncertainty as to whether the onset of hyperglycemia was prior to pregnancy or developed during early pregnancy. While diabetes diagnosed for the first time in pregnancy might be type1 or type 2, a diagnosis of type 2 is more likely. Compared with gestational diabetes, DIP is more likely to be detected as early as the first trimester provided appropriate testing is undertaken.

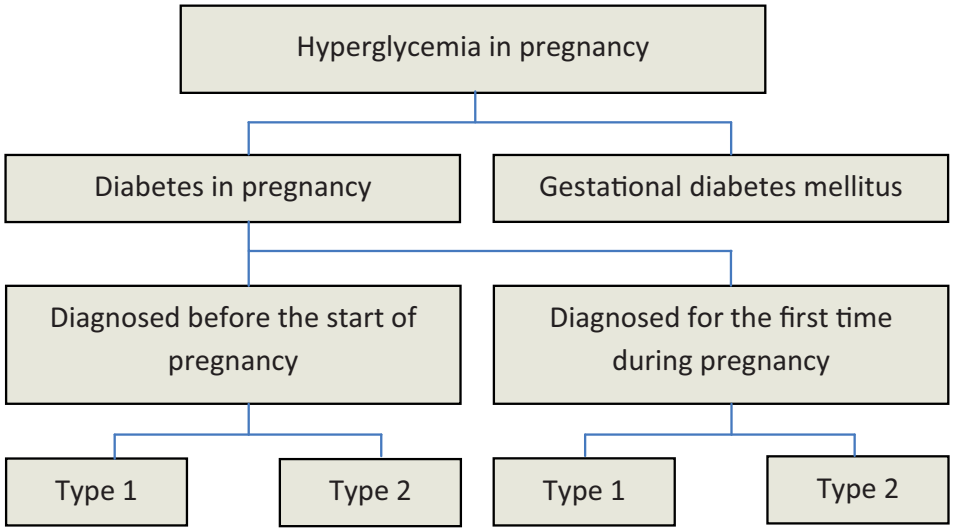

Figure 1 Types of hyperglycemia in pregnancy.

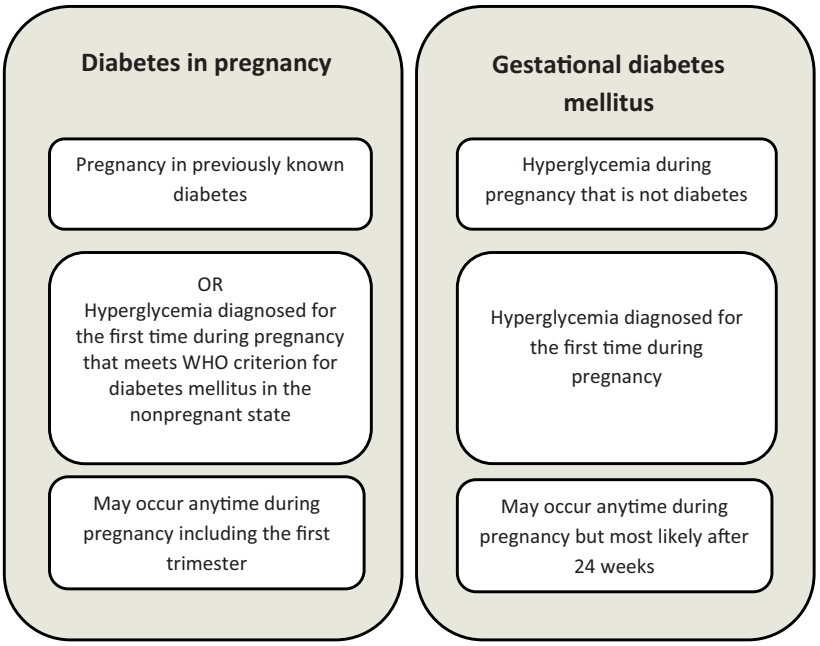

Figure 2 The difference between diabetes in pregnancy and gestational diabetes mellitus.

4.4. Gestational diabetes mellitus

When hyperglycemia detected during routine testing in pregnancy (generally between 24 and 28 weeks) does not meet the criteria of DIP it is called GDM. Diagnostic criteria and glucose cut-off values of GDM have been proposed by a number of organizations and professional groups and are described later in this document.

Due to its usual diagnosis and appearance later in pregnancy and less severe hyperglycemia, GDM implies a relatively milder form of hyperglycemia compared with that of DIP, but is nonetheless associated with a heightened risk of poor pregnancy outcome and future risk of diabetes and cardiovascular disease, and must be managed appropriately.

4.5. Epidemiology of GDM

Hyperglycemia is one of the most common medical conditions associated with pregnancy. The occurrence of GDM parallels the prevalence of impaired glucose tolerance (IGT), obesity, and T2DM in a given population, conditions that have risen globally during recent years [6–8]. Moreover, the age of onset of diabetes and pre-diabetes is declining, while the age of childbearing is rising in some countries. An increasing number of women of reproductive age are overweight and obese, thus more women entering pregnancy are vulnerable to hyperglycemia during pregnancy [9,10]. Global GDM prevalence rates show wide variations due to ethnicity and ethnic heterogeneity among different populations tested, which are further exacerbated by the different screening and diagnostic criteria used. GDM prevalence has been reported to vary between 1%–28% [11], while the International Diabetes Federation (IDF) estimates that one in six live births (16.8%) are to women with some form of hyperglycemia in pregnancy; 16% of these may be due to DIP, while the majority (84%) is related to GDM [8].

4.6. Risk factors

Publications show that risk factors for GDM include ethnicity and maternal factors such as older age, high parity, overweight and obesity, excessive weight gain in the index pregnancy, short stature, polycystic ovarian syndrome (PCOS), history of diabetes mellitus in first degree relatives, a past history of poor pregnancy outcome (abortion, fetal loss), macrosomia in previous and/or index pregnancy, GDM in a previous pregnancy, pre-eclampsia, and multifetal pregnancy [12]. In practice, slightly over half of the women with GDM have one or more of these risk factors, supporting the contention that identification of women who have GDM requires testing of all pregnant women [13–16].

4.7. Fetal and maternal morbidity associated with GDM

GDM is associated with a higher incidence of maternal morbidity, including cesarean deliveries, birth trauma, hypertensive disorders of pregnancy (including pre-eclampsia), and subsequent development of T2DM. Perinatal and neonatal morbidities are also increased; the latter include macrosomia, shoulder dystocia and other birth injuries, respiratory distress, hypoglycemia, polycythemia, and hyperbilirubinemia. Long-term sequelae in offspring with in utero exposure to maternal hyperglycemia include higher risks of obesity, impaired glucose metabolism, and diabetes later in life. Table 3 summarizes the implications of GDM for both the mother and her offspring from fetal through adult life [17–25] and Figure 3 shows the short-term fetal and neonatal complications from intrauterine exposure to maternal hyperglycemia.

4.8. Pathophysiology

Pregnancy induces changes in maternal metabolism to accommodate and nurture the growth of the fetus in the womb from conception until full term birth. Even though the mother eats intermittently, the fetus must be nourished continuously. This is achieved by complex interactions of the feto-placental-maternal unit, through secretion of hormones and metabolic mediators that create insulin resistance and modify maternal carbohydrate, lipid, and amino acid metabolism to ensure adequate nutrient supply to the fetus. These interactions are geared to create a harmonious balance between the needs of the mother, those of the fetus, and the mother's ability to provide for

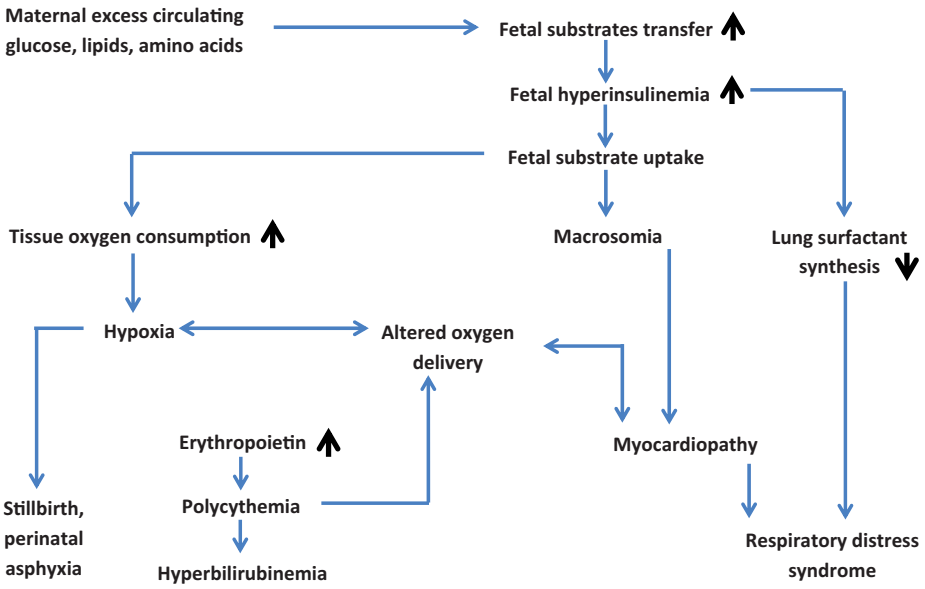

Figure 3 Intrauterine exposure to maternal hyperglycemia: Fetal and neonatal complications in the short term. Adapted and republished with permission from Elsevier, from: Mitanchez D, Yzydorczyk C, Siddeek B, Boubred F, Benahmed M, Simeoni U. The offspring of the diabetic mother--short- and long-term implications. Best Pract Res Clin Obstet Gynaecol 2015;29(2):256–69.

Table 3
Maternal and fetal morbidity associated with gestational diabetes mellitus.

Maternal morbidity	Fetal/neonatal/child morbidity
Early pregnancy	Stillbirth
Spontaneous abortions	Neonatal death
Pregnancy	Nonchromosomal congenital malformations
Pre-eclampsia	Shoulder dystocia
Gestational hypertension	Respiratory distress syndrome
Excessive fetal growth (macrosomia, large for gestational age)	Cardiomyopathy
Hydramnios	Neonatal hypoglycemia
Urinary tract infections	Neonatal polycythemia
Delivery	Neonatal hyperbilirubinemia
Preterm labor	Neonatal hypocalcemia
Traumatic labor	Erb's palsy (as consequence of birth injury)
Instrumental delivery	Programming and imprinting; fetal origins of disease: diabetes, obesity, hypertension, metabolic syndrome
Cesarean delivery	
Postoperative/postpartum infection	
Postoperative/postpartum hemorrhage	
Thromboembolism	
Maternal morbidity and mortality	
Hemorrhage	
Puerperium	
Failure to initiate and/or maintain breastfeeding	
Infection	
Long-term postpartum	
Weight retention	
GDM in subsequent pregnancy	
Future overt diabetes	
Future cardiovascular disease	

these needs. In response to increasing insulin resistance, maternal insulin secretion increases and euglycemia is maintained. This is achieved at the cost of higher maternal insulin level and lower than normal nonpregnant fasting glucose levels.

Insulin resistance continues to increase as pregnancy advances and is well established by the 24th week. As long as the maternal pancreas continues to increase insulin production and secretion, hyperglycemia is prevented. When this capacity is overwhelmed by rising insulin resistance, maternal hyperglycemia ensues. Maternal insulin production capacity is thus put under immense stress during pregnancy. This explains why women with pre-existing insulin resistance (e.g. overweight, obese, or excessive weight gain during pregnancy, PCOS, IGT, or metabolic syndrome) or those with lower ability to produce insulin (e.g. short stature, stunted) are more prone to GDM.

4.9. Fetal implications

Growth and development of the human conceptus occurs within the metabolic milieu provided by the mother, and the fetus

is totally dependent on transfer of nutrients from the maternal circulation via the placenta. As early as 1954, Pedersen et al. [26] demonstrated that newborns of diabetic mothers suffered from hypoglycemia and hypothesized that this was due to fetal hyperinsulinism as a result of increased transplacental transfer of sugar. Van Assche and Gepts [27] later confirmed the presence of hyperplasia of the insulin-producing beta cells in infants of diabetic mothers and postulated that the hyperplasia was related to beta-cell hyperactivity and could have consequences in later life.

In animal experiments, Aerts and Van Assche [28] showed that modifications in the endocrine pancreas during intrauterine life caused persistent changes that manifest in later adult life (in the second generation). Though not perceptible under basal conditions, these changes become apparent in situations stressing the beta cell activity, such as pregnancy. Pregnancy in second generation rats showed increased nonfasting blood glucose, with no apparent adaptation of the beta cells. This inadequate adaptation to pregnancy caused changes in the fetal endocrine pancreas in fetuses of the third generation, thereby suggesting a transgenerational transmission of risk.

It is now evident that an abnormal intrauterine environment has consequences in later life mediated through epigenetic changes. This phenomenon is known as developmental programming. An increasing body of evidence supports the hypothesis that the abnormal metabolic environment of the mother with diabetes mellitus may affect certain developing fetal tissues, organs, and control systems, eventually leading to permanent long-term functional implications in adult life. The fetal tissues most likely to be affected are neural cells, adipocytes, muscle cells, and pancreatic beta cells. Freinkel [29] introduced the concept of pregnancy as a "tissue culture experiment," in which the placenta and the fetus develop in an "incubating medium" totally derived from maternal fuels. All these fuels traverse the placenta from the maternal compartment either with (e.g. glucose, lipids) or against (e.g. amino acids) concentration gradients and contribute to the fetal milieu. Since these constituents are regulated, in part, by maternal insulin, disturbances in its supply or action influence the nutritional environment to which the fetus is exposed; maternal hyperglycemia leads to fetal hyperglycemia and eventually to fetal hyperinsulinemia.

According to Freinkel's hypothesis, the abnormal mixture of metabolites from the mother gains access to the developing fetus in utero, modifying the phenotypic expression in newly formed cells, which in turn determine permanent, short- and long-term effects in the offspring. Depending upon the timing of (embryonic–fetal) exposure to the aberrant fuel mixture, different events may develop. Early in the first trimester, intrauterine growth restriction and organ malformation, described by Freinkel as "fuel-mediated teratogenesis" may occur. During the second trimester, at the time of brain development and differentiation, behavioral, intellectual, or psychological damage may occur. During the third trimester, abnormal proliferation of fetal adipocytes and muscle cells, together with hyperplasia of pancreatic beta cells and neuroendocrine cells may be responsible for the development of obesity, hypertension, and T2DM mellitus later in life.

4.10. Maternal implications

Until the discovery of insulin by Banting and Best in 1921, very few women with diabetes based on severe insulin deficiency became pregnant spontaneously, and even fewer achieved a successful pregnancy outcome. At that time, about 50% of such women died during pregnancy from diabetes-related complications (mainly ketoacidosis) and about 50% of the fetuses failed to develop in utero. Women with diabetes mellitus had a markedly higher risk of poor pregnancy outcome, as described earlier. These complications, together with the increased rate of vascular dysfunction (retinopathy and nephropathy), contributed to higher maternal morbidity and mortality among patients with diabetes mellitus. Moreover, hyperglycemia first appearing during pregnancy was associated with a high risk of developing diabetes and cardiovascular diseases in later life [30–34].

Currently, pregnant women with diabetes mellitus enjoy the benefits of extraordinary progress made in all areas of medicine and in obstetrics in particular. State-of-the-art tools have been developed for diagnosis, treatment, and follow-up of both mother and fetus, such as fetal heart rate monitors, ultrasonography, glucose self-monitors, and insulin pumps. As a result, leading medical centers worldwide report a major reduction in maternal and fetal complications of diabetic pregnancies reaching levels similar to those in normal pregnancy. Clinicians working in these centers recognize unequivocally that early diagnosis, adequate treatment, and close follow-up are essential to decrease the incidence of most complications of diabetes in pregnancy and to achieve a successful outcome.

Despite these developments, the majority of women in low-, lower middle-, and upper middle-resource countries (contributing to over 85% of global deliveries annually), are not properly screened for diabetes during pregnancy. These countries also account for 80% of the global burden of diabetes as well as 90% of the global burden of maternal and perinatal deaths and poor pregnancy outcomes.

Maternal vulnerability to future diabetes and cardiovascular disorders is rising. Given the interaction between hyperglycemia and poor pregnancy outcomes and the role of the in utero environment in increasing risk of diabetes and cardiometabolic disorders in offspring of mothers with hyperglycemia in pregnancy, there needs to be a greater focus on preventing, screening, diagnosing, and managing hyperglycemia in pregnancy, globally, but particularly in low-resource countries.

- FIGO recommends and supports the call for greater attention and focus on the links between maternal health and noncommunicable diseases in the sustainable developmental agenda.

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5. Diagnosing gestational diabetes mellitus

5.1. Problems of multiple criteria

Global healthcare organizations and professional bodies have advocated a plethora of diverse algorithms for screening and diagnosis of GDM. Unfortunately, even the endocrine, diabetes, and obstetric associations within particular countries often used markedly dissimilar protocols and cut-off values for screening and diagnosis of GDM. These recommendations for GDM were criticized for lacking validation, as they were developed based on tenuous data, the result of expert opinions, were biased owing to economic considerations, or convenience-oriented [1], thereby creating confusion and uncertainty among care providers. One underlying yet fundamental problem, as shown consistently by several studies including the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, is that the risk of poor pregnancy outcomes associated with hyperglycemia is continuous with no clear inflection points [2–6].

It is therefore clear that any set of criteria for the diagnosis of GDM proposed will need to evolve from a consensus approach, balancing risks and benefits in particular social, economic, and clinical contexts [7]. In 2010, International Association of Diabetes in Pregnancy Study Groups (IADPSG) proposed consensus derived cut-off values for fasting, 1-hour, and 2-hour 75-g OGTT threshold values, defining GDM based on odds ratio thresholds of 1.75 in comparison with the mean, for markers of diabetic fetopathy (LGA, excess fetal adiposity, and fetal hyperinsulinemia) in the multinational observational HAPO study [8]. These criteria have been widely accepted and recently adopted by the WHO and the American Diabetes Association (ADA) [9,10]. However, LGA and fetal adiposity are also dependent on factors other than maternal glucose alone. For example, using the 2-hour glucose cut-off value of 8.5 mmol/L (153 mg/dL) selected by the IADPSG may not be as efficient in identifying women at-risk for fetal overgrowth as those identified by a 2-hour glucose value corresponding to that at a slightly lower odds ratio of 1.5 compared with the mean. The latter corresponds to the older, WHO criteria 2-hour value of 7.8 mmol/L (140 mg/dL).

Apart from the different cut-off values, the lack of consensus among the different professional bodies for an algorithm for screening and diagnosis of GDM is perhaps an even larger problem. Despite repeated pleas for a single process and criteria [11], the ideal protocol for the diagnosis of GDM continues to be debated.

5.2. Universal versus selective testing

Selective testing based on clinical risk factors for GDM evolved from the view that in populations with a low risk of GDM, subjecting all pregnant women to a laboratory test was not considered cost-effective. Traditionally, the risk factor-based approach was popular in Europe. Some of the aforementioned risk factors used were: age and BMI (at varying thresholds); ethnicity; polyhydramnios; macrosomia (current or past pregnancy); GDM in the past; unexplained stillbirth; T2DM in a first-degree relative; and PCOS. The Toronto Tri-hospital Gestational Diabetes Project [12] developed a scoring system based on maternal age, BMI, and race. However, variations in risk factors have resulted in different approaches, generally with poor sensitivity and specificity. The major problem of risk factor-based screening is its high demand on the healthcare providers with more complex protocols for testing, which result in lower compliance by both patients and healthcare providers.

Given the high rates of hyperglycemia in pregnancy in most populations and that selective testing based on known risk factors has poor sensitivity for detection of GDM, it seems appropriate to recommend universal rather than risk factor-based testing. This approach is strongly recommended by FIGO and is particularly relevant to low-, low–middle, and middle-resource countries, where 90% of all cases of GDM are found and ascertainment of risk factors is poor owing to low levels of education and awareness, and poor record keeping. In many of these countries there is little justification for selective testing, as they also have ethnic populations considered to be at high risk [13].

In 2010 the IADPSG proposed screening of all pregnant women with a single step 75-g OGTT [8]. This position has since been supported by the ADA and the IDF (2014) [14]. However, there continues to be a lack of uniformity of testing protocols within and between hospitals in the same city, county, and country [15], let alone internationally.

The case for universal testing (i.e. testing all pregnant women) with some biochemical test has its supporters [16,17]. However, even among advocates of universal testing there is a lack of uniformity in approach to testing methodology.

(1) The 50-g glucose challenge test (GCT) has been the most popular test for this purpose. This is part of the two-step algorithm (50-g GCT followed by the 100-g OGTT) still advocated by ACOG and offered as an alternative diagnostic strategy in the latest ADA guideline.
(2) The 1-step 75-g OGTT in all women is endorsed by the WHO, IDF, and many other organizations that agree with the recommendations of the IADPSG.

In the overall cost of providing care to women with GDM the cost of administering a glucose tolerance test (GTT) to all pregnant women is likely to be minimal if the initial fasting GTT level result can be used to decide if the full GTT is needed [18,19]. In situations where women may not be able to come for testing in a fasting state, a single step 75-g 2-hour nonfasting test, as used in India, may be applied [20,21].

The FIGO initiative for GDM is meant to provide a practical guide for national associations to adopt and promote a uniform approach to testing, diagnosis, and management of GDM for all countries and regions based on their financial, human, and infrastructure resources.

- FIGO adopts and supports the IADPSG/WHO/IDF position that all pregnant women should be tested for hyperglycemia during pregnancy using a one-step procedure.
- FIGO encourages all countries and its member associations to adapt and promote strategies to ensure universal testing of all pregnant women for hyperglycemia during pregnancy.

5.3. Diagnostic criteria

5.3.1. Diabetes in pregnancy

The diagnosis of diabetes in pregnancy as defined by the WHO criteria [9] should be based on one or more of the following results recorded by routine testing at any time during the course of pregnancy:

(1) Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL); and/or
(2) 2-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) following a 75-g oral glucose load; or
(3) Random plasma glucose ≥11.1 mmol/L (200 mg/dL) in the presence of diabetes symptoms.

Additionally, the ADA also recommends HbA1c (≥6.5%), confirmed by repeat testing, as sufficient to diagnose diabetes in the presence or absence of pregnancy [10].

5.3.2. Gestational diabetes mellitus

As per the recommendation of the IADPSG (2010) and WHO (2013), the diagnosis of GDM is made using a single-step 75-g OGTT when one or more of the following results are recorded during routine testing specifically between weeks 24 and 28 of pregnancy or at any other time during the course of pregnancy:

(1) Fasting plasma glucose 5.1–6.9 mmol/L (92–125 mg/dL);
(2) 1-hour post 75-g oral glucose load ≥10 mmol/L (180 mg/dL);
(3) 2-hour post 75-g oral glucose load 8.5–11.0 mmol/L (153–199 mg/dL)

- FIGO adopts the WHO (2013) criteria for diagnosis of diabetes mellitus in pregnancy.
- FIGO adopts the WHO (2013) and IADPSG (2010) criteria for diagnosis of gestational diabetes mellitus. Given the resource constraints in many low-resource countries, other strategies described herein are considered equally acceptable.

FIGO suggests various options for diagnosis of GDM based on resource settings in Table 4.

5.3.3. Resource-based approach to diagnosis

Implementation of guidelines is a constant challenge. The reality is that most low-resource countries around the world are unable to implement a GDM detection program based on a universal 75-g OGTT or rely on just high-risk women undergoing a 75-g OGTT. These challenges and barriers have been reviewed extensively [28]. The applicability of the IADPSG cut-off value for fasting glucose to diagnose GDM, especially in the first trimester has been contested in a recent study from China [29].

Recommendations that are rigid and impractical in real-life settings are unlikely to be implemented and hence may produce little or no impact. On the other hand, pragmatic but less than ideal recommendations may produce significant impact owing to more widespread implementation.

The FIGO approach is three pronged: (1) to promote, encourage, and advocate ideal evidence-based guidance; (2) to offer pragmatic options for resource-constrained situations based on local experience backed by less than optimal evidence; and (3) to promote research aimed at improving the evidence base in both well-resourced and resource-constrained contexts.

FIGO recommendations are based on available resources at country level and evidence of local practice. Countries worldwide fall into four resource categories. There are also variations seen within any country. An affluent country may have pockets of poorly funded care and conversely, a low- or middle-resource country may have state-of-the art care in the private sector for a selected few.

High-resource countries: countries or regions such as Canada, Western Europe, Japan, South Korea, USA, etc.

Upper middle-resource countries: countries such as Brazil, China, Colombia, Hungary, Malaysia, Mexico, Romania, South Africa, Turkey, etc.

Low middle-resource countries: countries such as India, Indonesia, Pakistan, Nigeria, Egypt, Vietnam, etc.

Low-resource countries: countries such as Bangladesh, Nepal, Cambodia, Kenya, Tanzania, Uganda, Ethiopia, Congo, etc.

5.3.4. Risk models

If a country cannot afford any laboratory testing, risk models are available. Many have been advocated from studies in Canada [12], Denmark [30], Thailand [31], and Vietnam [32]. They use a permutation of various clinical risk factors, including age, BMI, family history of diabetes mellitus, GDM in past pregnancies, LGA newborns, and glycosuria. Their widespread applicability in large settings in low-resource countries has not been tested and is not recommended by FIGO.

Eight low- and middle-resource countries—India, China, Nigeria, Pakistan, Indonesia, Bangladesh, Brazil, and Mexico—account for 55% of the global live births (70 million live births annually) as well as 55% of the global burden of diabetes (209.5 million) and should be key targets for any focused strategy on addressing the global burden of GDM pregnancies.

A few examples of current approaches to diagnoses of GDM in different parts of the world, particularly from the large burden countries where systematic testing for GDM is being implemented, are provided in Appendix 1. These examples have inspired FIGO's pragmatic options and guidance for resource-constrained situations.

5.4. Cost-effectiveness of GDM testing and management

Apart from infrastructure and capacity constraints, implementation of universal testing for GDM is challenged by lack of good evidence to support cost-effectiveness in both the high- and low-resource countries. To facilitate decision-making, countries need reliable information on the cost and cost-effectiveness of GDM screening and treatment. Almost all cost-effectiveness analyses have assessed only short-term complications [33], omitting consideration of reductions in long-term T2DM. A recent study from the USA evaluated the potential cost-effectiveness of new GDM screening criteria for both time periods [34]. Another study, based on the Gestational Diabetes Formulas for Cost-Effectiveness or GeDiForCE Model [35] described in Appendix 2, showed that the interventions are "highly cost-effective" in both Indian and Israeli settings when long-term effects are taken into account [36].

- All countries have an obligation to implement the best GDM testing and management practices they can.
- FIGO acknowledges that for global progress to be made, India, China, Nigeria, Pakistan, Indonesia, Bangladesh, Brazil, and Mexico must be key targets for focused GDM attention

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Table 4
Options for diagnosis of gestational diabetes mellitus based on resource settings.

	Strategy			
Setting	Who to test and when	Diagnostic test	Interpretation[a]	Grade
Fully resourced settings	All women at booking/first trimester	Measure FPG, RBG, or HbA1c to detect diabetes in pregnancy		1|⊕⊕⊕○
	24–28 weeks	If negative: perform 75-g 2-hour OGTT		
Fully resourced settings serving ethnic populations at high risk[b]	All women at booking/first trimester	Perform 75-g 2-hour OGTT to detect diabetes in pregnancy		2|⊕○○○
	24–28 weeks	If negative: perform 75-g 2-hour OGTT		
Any setting (basic); particularly medium- to low-resource settings serving ethnic populations at risk	All women between 24 and 28 weeks	Perform 75-g 2-hour OGTT		1|⊕⊕⊕○
Alternative strategies as currently used in specified countries				
China: Medium- to low-resource settings serving populations at high risk	All women at booking/first trimester	Measure FPG to detect diabetes in pregnancy	>7.0 mmol/L or >126 mg/dL. FPG values between 5.6 and 6.9 mmol/L, (100–125 mg/dL) consider as GDM [18]	2|⊕○○○
	24–28 weeks	If negative: perform 75-g 2-hour OGTT *Or* To reduce number of OGTTs measure FPG. Only in women with values between 4.5 mmol/L and 5.0 mmol/L (81–90 mg/dL) perform 75-g 2-hour OGTT	 Value >5.1 mmol/L or >92 mg/dL diagnostic of GDM	1|⊕⊕⊕○ 2|⊕○○○
Indian subcontinent: Medium- to low-resource settings serving rural/semi-urban/urban ethnic populations at high risk	All women at booking/first trimester	Measure fasting or nonfasting 2-hour value after 75-g OGTT	Reading between 7.8 and 11.0 mmol/L or 140 and 199 mg/dL indicates GDM [19,20][c]	2|⊕○○○
	24–28 weeks	If negative: repeat test		
Latin America: Medium- to low-resource settings	All women at booking/first trimester	Measure FPG to detect diabetes in pregnancy	>7.0 mmol/L or >126 mg/dL. FPG values between 5.6 and 6.9 mmol/L (100–125 mg/dL), consider as GDM	2|⊕○○○
	24–28 weeks	If negative: perform 75-g 2-hour OGTT	75-g 2-hour glucose value >7.8 mmol/L or >140 mg/dL is diagnostic of GDM[d]	
UK: all settings	Selected women at booking/as soon as possible[e]	Perform 75-g 2-hour OGTT	FPG of 5.6 mmol/L or above or 2-hour plasma glucose of 7.8 mmol/L or above is diagnostic[g]	
	24–28 weeks	If negative: perform 75-g 2-hour OGTT		
	Offered also to other women with risk factors for GDM[f]			

Abbreviations: FPG, fasting plasma glucose; RBG, random blood glucose; HbA1c, glycosylated hemoglobin; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test.
[a] Interpret as per IADPSG/WHO/IDF guidelines unless stated otherwise.
[b] Asians are at high risk of hyperglycemia during pregnancy, which may include previously undiagnosed diabetes. The proportion of previously undiagnosed diabetes is highest in the youngest age group particularly among women [22]. In Asian populations, FPG and HbA1c have much lower sensitivity to diagnose diabetes than the 2-hour post-glucose value [23]. In a study of 11 Asian cohorts, more than half of the diabetic subjects had isolated postchallenge hyperglycemia [24]. In a study in China, 46.6% of the participants with undiagnosed diabetes (44.1% of the men and 50.2% of the women) had isolated increased 2-hour plasma glucose levels after an OGTT [25]. Therefore, the need to identify postprandial hyperglycemia seems especially relevant in Asian populations.
[c] Diabetes in Pregnancy Study Group in India (DIPSI) Guideline [8].
[d] Latin America Study Group [26].
[e] Women with a past history of GDM or women with glycosuria of 2+ or above on one occasion or of 1+ or above on two or more occasions (as detected by reagent strip testing during routine prenatal care in the current pregnancy).
[f] BMI above 30 (calculated as weight in kilograms divided by height in meters squared), previous macrosomic baby weighing 4.5 kg or above, family history of diabetes, first-degree relative with diabetes, minority ethnic family origin with a high prevalence of diabetes.
[g] National Institute for Health and Care Excellence (NICE) [27].

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6. Glucose measurement: Technical considerations in laboratory and point-of-care testing

Glucose levels are generally measured from serum, plasma, or whole blood. Today, most glucose measurements in laboratories are performed on serum or plasma. The glucose concentration in whole blood is approximately 15% lower than the glucose concentration in serum or plasma. Serum or plasma must be refrigerated and separated from the cells quickly to prevent substantial metabolism of glucose by the cellular fraction. The requirement that serum samples must be allowed to clot before serum glucose is tested significantly increases turnaround time for glucose results compared with plasma results. Thus, faster laboratory turnaround time is one reason that plasma has become the gold standard for glucose measurement. However, in most laboratory panels (i.e. the comprehensive metabolic panel), serum is the most suitable sample for all other laboratory tests performed, and so a "panel" glucose is usually a serum glucose. If plasma is used, the rapid separation of the red blood cells from the plasma by centrifugation is a critical element, because it is estimated that plasma glucose levels are reduced by approximately 10 mg/dL per hour by consumption of glucose in the red blood cell's glycolytic pathway.

Previously, sodium fluoride (gray-top tubes) was often used as an anticoagulant and preservative of whole blood, particularly when analysis was delayed. A recent study showed that citrate buffer inhibited in vitro glycolysis far more effectively than fluoride [1]. Lately, citrate buffer has been advocated as a rapidly effective glycolysis inhibitor. The mean glucose concentration in samples stored at 37°C decreased by only 0.3% at 2 hours and 1.2% at 24 hours when blood was drawn into tubes containing citrate buffer, sodium fluoride, and ethylenediaminetetraacetic acid (EDTA). The use of these blood collection tubes appears to offer a practical solution to the glycolysis problem [2]. Plasma from blood collected in fluoride tubes is generally unsuitable for measuring other laboratory parameters.

Glucose levels also vary depending on the source of the blood sample used for analysis, i.e. arterial, capillary, or venous. The variation is attributed to variation in glucose extraction by tissues, perfusion, oxygenation, pH, and temperature. On average, arterial glucose concentrations at normal partial pressure of oxygen are 5 mg/dL higher than capillary blood and approximately 10 mg/dL greater than venous concentrations. Except in intensive care situations plasma glucose is normally measured from venous or capillary blood.

Glucose measurements are based on enzymatic reactions involving one of the four enzymes: glucose oxidase (GO), glucose 1-dehydrogenase (GD), glucokinase (GK), or hexokinase (HK). The most widely used methods of glucose analysis use the enzymes GO, GK, or HK. GO is the most specific enzyme reacting only with D-glucose. The GK or HK method is considered more accurate than the GO method.

For point-of-care devices, GO or GD are the classic methodologies. GK and HK are the basis for many central laboratory methods.

Additional variability in glucose measurement may occur because of differences in different assays, collection and storage of samples, and quality of reagents (storage of test strips) etc.

Point-of-care blood glucose measurement is based on capillary whole blood, while laboratory-based measurements are usually based on venous plasma.

6.1. Laboratory testing

An array of instruments, from the simplest to the most sophisticated, are capable of measuring plasma glucose. Ideally, only accredited laboratories should be allowed to report any patients' results, since they account for major medical decisions. The minimum quality specifications are documented by accrediting bodies such as the College of American Pathologists (CAP) and the International Organization for Standards (ISO) 15189, etc.

Due to constraints of resources or available expertise, more often than not, results are reported by unaccredited laboratories. However, even low-resource countries can produce excellent laboratory results; conversely an overabundance of resources does not guarantee good quality. What is required is meticulous application of procedures. It is obligatory that every laboratory meticulously document: (1) reproducibility (precision) by recording internal quality control daily and calculating the Coefficient of Variation (CV%) monthly; and (2) accuracy (bias) by comparing its results through proficiency testing or comparing its results to an accredited laboratory. Once minimum requirements of precision are met by good laboratory practices, the bias can be addressed. For plasma glucose, the imprecision should be less than 2.9%, the accuracy (bias) less than 2.2%, and a total error less than 6.9%, based on biological variation of glucose [3].

6.2. Near patient or point-of-care testing

Ideally, the results of handheld glucose meters should match those of laboratory analyzers of an accredited laboratory. Furthermore, the targets for screening of diabetes, self-monitoring of glucose, and acute hospital critical care settings are not the same.

No universal criteria for the analytical performance of glucose meters exist. Generally, the performance of the glucometer is considered satisfactory if 95% of glucometer values fall within a specified percentage of simultaneously measured patient plasma glucose on laboratory analyzers. Current glucometer recommendations (compared with laboratory methods) range widely from ±5% to ±20% [3]. In January 2014, the US Food and Drug Administration recommended quality requirements; however, they are too stringent and have thus been criticized by most professional bodies [4].

When using a glucometer it is important to know what value is being reported, i.e. whether it is whole blood or plasma-correlated glucose. "Plasma correlated" refers to glucose concentrations measured in samples of whole blood but are converted to values that would be expected of plasma measurements. The site of blood collection may create additional variability. In general, blood samples for glucometer reading should be collected from the fingertips. The technique of glucometer use is usually responsible for more inaccuracy than the glucometer itself. Technical errors result from improper calibration and inadequate maintenance, in addition to the specific techniques used to measure glucose: photometric versus electrochemical, as well as the type of enzyme used (HK vs GO vs GD) [5].

Ideally, for diagnosis of GDM, reliable test results should be based on venous plasma samples properly collected and transported prior to laboratory testing. However, this ideal situation may not be present in many primary care settings, particularly in low-income countries where proper facilities for collection, transport, storage or testing may not exist. In this situation FIGO recommends that it is acceptable to use a plasma calibrated hand held glucometer with properly stored test strips to measure plasma glucose. Regular calibration should be undertaken with standard test solutions (usually supplied by the glucose meter manufacturer). Using a glucose

meter in this situation may be more reliable than laboratory tests done on samples that have been inadequately handled and transported.

- GDM diagnosis should be ideally based on blood tests done in an accredited laboratory on properly collected and transported venous plasma samples.
- FIGO recommends the use of a plasma-calibrated handheld glucometer with properly stored test strips to measure plasma glucose in primary care settings, particularly in low-resource countries, where a close-by laboratory or facilities for proper storage and transport of blood samples to a distant laboratory may not exist. This may be more convenient and reliable than tests done on inadequately handled and transported blood samples in a laboratory. It is recommended that from time to time a few samples are parallel tested in an accredited laboratory to document the variability.
- FIGO recommends that all laboratories and clinical services document their baseline quality and work toward improvement irrespective of the resources available.

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7. Management of hyperglycemia during pregnancy

Fetal and maternal outcomes are directly correlated with the degree of maternal glycemic control. The primary goal of treatment for pregnancies complicated by diabetes is to ensure as close to normal outcome as possible for the mother and offspring by controlling maternal hyperglycemia.

- FIGO recognizes that management of diabetes in pregnancy should be made in accord with available national resources and infrastructure, even without high-quality evidence, as it is preferable to the alternative of no or poor care.

7.1. Prenatal supervision

There is no evidence to support a particular protocol of prenatal care and monitoring for women with diabetes. The recommendations in Box 1 are based on the ACOG practice bulletin [1], as well as consensus on clinical practice.

7.1.1. Fetal sonographic assessment

Monitoring fetal growth is both challenging and inaccurate, with a ±15% error margin. Since fetal macrosomia is the most frequent complication of diabetes, special effort should be directed toward its diagnosis and prevention. Recommendations for fetal growth assessment are shown in Box 2.

7.1.2. Fetal well-being

Fetal assessment can be achieved by a fetal kick count, biophysical profile, and cardiotocography (nonstress test). There is no high-quality evidence to support a particular follow-up protocol. However, it is assumed that with reassuring fetal well-being, pregnancy prolongation to term can be achieved [1]. Recommendations for assessment of fetal well-being are shown in Box 3.

7.1.3. Timing and mode of delivery

Maternal hyperglycemia and macrosomia are associated with increased risk of intrauterine fetal death and other adverse outcomes. Therefore, induction of labor may be considered at 38–39 weeks, although there is no good-quality evidence to support such an approach. Thus, some guidelines suggest that a pregnancy with good glycemic control and a seemingly appropriate estimated weight for gestational age fetus ought to continue until 40–41 weeks [2–4]. Given the significantly greater risk of shoulder dystocia at any birthweight above 3750 g for babies of women with diabetes, consideration may be given to elective cesarean delivery when the best estimate of fetal weight exceeds 4000 g [5–10] (Figure 4). Recommendations for timing and mode of delivery in women with GDM are shown in Box 4.

Box 1
Recommendations for prenatal supervision in women with gestational diabetes mellitus.

Recommendations	Resource setting	Strength of recommendation and quality of evidence
Routine prenatal care should include visits to: • Healthcare professionals skilled in care of women with diabetes in pregnancy (obstetrician, perinatologist, diabetologist, diabetes educator, nutritionist etc): 1–3 weeks as needed • Nurse: Weight, blood pressure, dipstick urine protein: 1-2 weeks as needed	High	1|⊕○○○
Prenatal follow-up determined locally according to available resource: • A minimum of monthly check-ups with a healthcare provider knowledgeable in diabetes in pregnancy	Mid and Low	2|⊕○○○

Box 2
Recommendations for fetal growth assessment in women with gestational diabetes mellitus.

Recommendations	Resource setting	Strength of recommendation and quality of evidence
Clinical and sonographic growth assessments every 2–4 weeks from diagnosis until term	High	1|⊕○○○
Periodic clinical and sonographic growth assessments from diagnosis until term	Mid and Low	2|⊕○○○

Box 3
Recommendations for fetal well-being surveillance in women with gestational diabetes mellitus.

Recommendations	Resource setting	Strength of recommendation and quality of evidence
Use cardiotocography and/or biophysical profile or kick-count as indicated according to local protocol	All	1|⊕○○○

7.2. Glucose measurements

Blood glucose control can be evaluated in one of three ways: glycosylated hemoglobin (HbA1c), self-monitoring of blood glucose, or continuous glucose monitoring.

7.2.1. HbA1c

This test reflects the average glucose level in the three months prior to measurement. It is correlated with the risk of congenital malformations, not to any other adverse pregnancy outcomes. It is best used for pregnancy planning and prenatal follow-up in cases of diabetes in pregnancy. HbA1c does not replace the OGTT for the diagnosis of GDM. However, in women with GDM, HbA1c may be used to verify the reliability of their self-monitored glucose reports [11,12].

7.2.2. Self-monitoring of blood glucose

Self-monitoring of capillary glucose is achieved by multiple daily measurements of capillary blood glucose with a handheld glucometer. It only provides glucose values at the time of measurement and misses in between hyper/hypoglycemic events. Multiple studies have shown the utility of self-monitoring of blood glucose in achieving tight glycemic control to reduce pregnancy complications [13–16].

7.2.3. Continuous glucose monitoring

The device consists of a subcutaneous enzymatic sensor attached to a nonimplanted transmitter that sends readings to a receiver and provides numerous automated readings of interstitial tissue glucose, calibrated to reflect plasma glucose. The continuous measurement enables detection of virtually all glucose fluctuations and helps modify treatment [17–19]. Continuous glucose monitoring may help achieve a small HbA1c reduction in a nonpregnant population [20,21]. It can detect high postprandial blood glucose levels and nocturnal hypoglycemia [22,23]. However, no clear maternal or neonatal benefits have been reported during pregnancy in women with GDM [24,25].

7.2.4. Recommendations for glucose monitoring in women with GDM

The issue of the optimal daily frequency and timing in relationship to a meal for checking blood glucose in women with GDM remains unresolved. There is no "evidence" from a randomized controlled trial (RCT) to support any specific frequency. In the two RCTs for the management of GDM, the study by Landon et al. [26] stated that patients were instructed to test themselves fasting and 2 hours postprandial, without stating how often they should test throughout the day; the ACHOIS study [27] recommended that patients should monitor their home blood glucose levels initially four times a day and then used "daily

Box 4

Recommendations for timing and mode of delivery in women with gestational diabetes mellitus.

Recommendations	Resource setting	Strength of recommendation and quality of evidence
As per local protocol or as suggested in Figure 4	All	2|⊕○○○

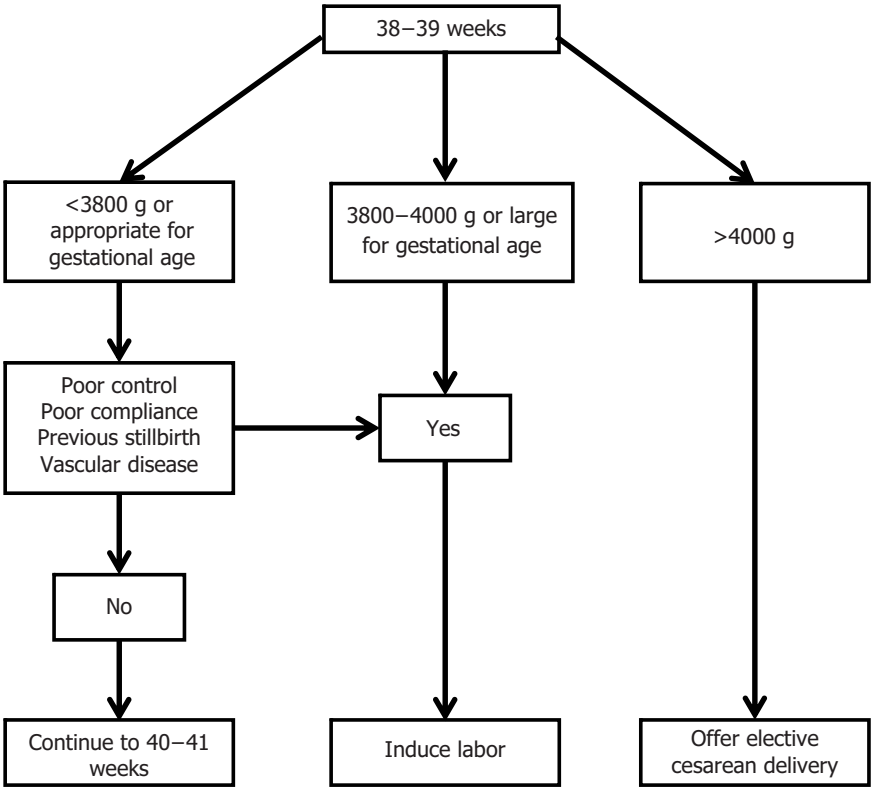

Figure 4 Timing of delivery in women with gestational diabetes mellitus and diabetes in pregnancy.

monitoring at rotating times." In an observational study, Langer et al. [28] requested patients to test themselves seven times a day (although they actually tested themselves at a mean of 4.2 times a day). Guidelines are also equivocal. The National Institute for Health and Care Excellence (NICE) suggests that personnel should "advise women who need intensification of hypoglycemic therapy to increase the frequency of self-monitoring to include fasting and a mixture of pre- and post-prandial levels" [29]. ACOG states [1] "There is insufficient evidence concerning the optimal frequency of blood glucose testing of GDM. Based on the data available the general recommendation is four-times daily glucose monitoring performed at fasting and either at 1-hour or 2-hour intervals after each meal. Once the patient's glucose levels are well-controlled by her diet, the frequency of glucose monitoring can be modified." In its 2015 clinical practice recommendations, the ADA encourages pre- and postprandial monitoring of blood glucose but does not recommend a specific frequency of testing [30].

The recommendations for glucose monitoring in women with GDM are shown in Box 5.

7.3. Targets of therapy

The main goal for treatment of GDM is to prevent adverse effects on the mother and fetus; the most important and proven factor to achieve this goal is reduction of glucose levels without undue hypoglycemia. This should be achieved throughout pregnancy and during labor and delivery. Attempts must be made to achieve glucose levels as close as possible to those seen in normal pregnancy.

7.3.1. Glucose control during pregnancy

Elevated glucose values, specifically postprandial glucose levels, are associated with adverse pregnancy outcomes in patients with hyperglycemia in pregnancy [31–33]. Data suggest that postprandial glucose levels are more closely associated with macrosomia than fasting glucose levels [34,35]. No controlled study has, as yet, established the optimal plasma glucose level(s) to prevent increased fetal risk.

7.3.2. Glucose control during labor and delivery

Neonatal hypoglycemia develops as a consequence of the heightened fetal insulin response to cope with transplacental transfer of high maternal glucose. After delivery, the sudden decrease in glucose supply to the newborn in the midst of high insulin levels of fetal origin results in hypoglycemia [35,36]. Several observational trials have studied the correlation between glucose levels during labor and neonatal outcomes [37–43]. There is general agreement that maternal hyperglycemia during labor and delivery is associated with neonatal hypoglycemia, in both GDM [37] and T2DM [38–41]. Other reports show that maternal hyperglycemia during labor is also associated with birth asphyxia and nonreassuring fetal heart rate tracings [42,43]. In women with type 1 diabetes (T1DM) it has been shown that targeting maternal glucose levels in the range of 4.0–7.0 mmol/L (72–126 mg/dL) during labor is associated with a lower risk of maternal hypoglycemia than lower target levels [44]. In addition, these levels during labor and delivery are helpful in reducing the incidence of neonatal hypoglycemia, birth asphyxia, and nonreassuring heart rate tracings. Glycemic targets for women with GDM are given in Box 6.

7.3.3. Weight gain

The epidemic of obesity adversely affects the health of an entire population, but has important consequences for pregnancy and postpartum outcomes [45]. Overweight and obese women before pregnancy are at an increased risk for pregnancy complications including diabetes, hypertensive complications, stillbirth, and increased risk for cesarean delivery. The Institute of Medicine (IOM) has published recommendations for weight gain during pregnancy, based on prepregnancy body mass index [46]. There is no evidence for recommendations for weight gain specific to pregnancies complicated by diabetes. According to IOM guidelines for weight-appropriate and underweight women, to ensure normal infant birth weight a recommended weight gain with no restriction in caloric intake is recommended. For overweight and obese women there is no consensus regarding caloric intake and weight gain during pregnancy. Some evidence suggests that weight reduction may be appropriate [47], whereas other studies indicate that in overweight and obese women, weight loss or gain of less than or equal to 5 kg during pregnancy is associated with an increased risk of SGA and decreased neonatal fat mass, lean mass, and head circumference [48]. Recommendations for weight gain during pregnancy and during pregnancy in women with GDM are given in Boxes 7 and 8.

7.4. Lifestyle modification

7.4.1. Nutritional therapy

Nutritional therapy includes an individualized food plan to optimize glycemic control. It should be based on personal and cultural eating habits, physical activity, blood glucose measurements, and the expected physiological effects of pregnancy on the woman and her fetus. Medical nutritional therapy in pregnancy can be described as "a carbohydrate-controlled meal plan that promotes adequate nutrition with appropriate weight gain,

Box 5
Recommendations for glucose monitoring in women with gestational diabetes mellitus.

Recommendations	Resource setting	Strength of recommendation and quality of evidence
Self-monitoring of blood glucose is recommended for all pregnant women with diabetes, 3–4 times a day: • Fasting: once daily, following at least 8 hours of overnight fasting • Postprandial: 2-3 times daily, 1 or 2 hours after the onset of meals, rotating meals on different days of the week	All	2|⊕⊕○○
Self-monitoring of blood glucose is recommended for all pregnant women with diabetes at least once daily, with documented relation to timing of meal	Low	2|⊕○○○

Box 6
Recommendations for glycemic targets for gestational diabetes mellitus.[a]

Recommendations	Resource setting	Strength of recommendation and quality of evidence
Targets for glucose control during pregnancy: • Fasting glucose <5.3 mmol/L (95 mg/dL) • 1-hour postprandial <7.8 mmol/L (140 mg/dL) • 2-hour postprandial <6.7 mmol/L (120 mg/dL)	All	1|⊕⊕○○
Educate to recognize and treat signs of hypoglycemia: • Ingest 15 g of simple carbohydrate (sugar, rapidly absorbed tablets, sweetened liquids)	All	1|⊕⊕⊕⊕
Teach family members how to use the glucometer	All	2|⊕⊕○○
Target for glucose control during labor and delivery: • 4–7 mmol/L (72−126 mg/dL)	All	1|⊕⊕⊕⊕

[a] Source: American Diabetes Association [30].

normoglycemia, and the absence of ketosis" [49]. Nutritional intervention for diabetes, specifically pregnancy complicated with diabetes, is consistently considered a fundamental treatment modality [50–53]. It is the first-line therapy in all women diagnosed with GDM [54–55]. However, there is paucity of data to provide evidence-based recommendations for most of the nutrition interventions. Studies that have examined the impact of nutritional practice guidelines demonstrate improved metabolic control for T1DM and T2DM [56,57], as well as a positive impact on the metabolic goals of GDM [58].

7.4.2. Calories

Restricting calories has been a strategy for controlling weight gain, glucose levels, and avoiding macrosomia in women with GDM and their babies. Successful pregnancy outcomes have been reported within a wide range of caloric intake ranging from 1500−2800 calories per day [59–64]. However, most studies were small sized, uncontrolled, and relied on self-reported dietary intakes. Existing data suggest that severe caloric restriction (less than 1500 calories/day or 50% restriction) increases ketonemia. This is of particular significance in women with T1DM in pregnancy where high levels of third trimester ketone bodies may impair mental development of the offspring [60]. Modest caloric restriction (1600−1800 calories/day, 33% reduction) does not lead to ketosis [65,66]. Daily energy intake of approximately 2050 calories in all BMI categories in women with GDM was reported to reduce weight gain, maintain euglycemia, avoid ketonuria, and achieve average birth weights of 3542 g [67,68].

Box 7
Institute of Medicine recommendations for weight gain during pregnancy.[a]

Prepregnancy body mass index[b]	Total weight gain, Kg	Mean (range) rates of weight gain at the second and third trimester, kg/weeks)
Underweight <18.5	12.5−18	0.51 (0.44−0.58)
Normal weight 18.5−24.9	11.5−16	0.42 (0.35−0.50)
Overweight 25.0−29.9	7−11.5	0.28 (0.23−0.33)
Obese ≥30.0	5−9	0.22 (0.17−0.27)

[a] Source: Institute of Medicine [46].
[b] BMI calculated as weight in kilograms divided by the height in meters squared.

Box 8
Recommendations for weight gain during pregnancy with diabetes.[a]

Recommendations	Resource setting	Strength of recommendation and quality of evidence
Institute of Medicine revised guidelines for weight gain during pregnancy	All	2|⊕⊕○○
Weight reduction for obese and overweight women prior to pregnancy	All	1|⊕⊕⊕⊕

[a] Source: Institute of Medicine [46].

7.4.3. Carbohydrates

Focusing on total amount, quality, and distribution of carbohydrate intake helps achieve metabolic control in all patients with diabetes. The total amount of carbohydrates, distribution of carbohydrates in different meals and snacks, type of carbohydrates, and the glycemic index (GI) of foods can all be modified without affecting the total caloric intake [69]. Carbohydrates should be distributed throughout the day in three small- to moderate-sized meals and 2–4 snacks. An evening snack may be needed to prevent accelerated ketosis overnight. A minimum of 175 g carbohydrates/day should be provided, which is higher than the 130 g/day recommended for nonpregnant women [70].

7.4.4. Glycemic index

The glycemic index of a food is defined as the area under the two-hour blood glucose curve (AUC) following a 12-hour fast and ingestion of a food with a certain quantity of available carbohydrate (usually 50 g). The AUC of the test food is divided by the AUC of the standard (either glucose or white bread, giving two different definitions) and multiplied by 100. The average GI value is calculated from data collected in 10 human subjects. Both the standard and test food must contain an equal amount of available carbohydrate and usually ranges between 50 and 100. The GI of foods is also an important factor, as food with a low GI may reduce postmeal glycemic excursion and flatten the glucose curve. Foods with a high GI (>70) may show higher postprandial values, while low GI diets in nonpregnant patients with diabetes lead to an additional 0.4% reduction in hemoglobin A1c [71]. Low GI diet has been shown to reduce birth weight [72–74] and cause a two-fold increase in rates of underweight for gestational age babies in nondiabetic women [74]. By extrapolation, this may provide an advantage in reducing macrosomia in women with GDM and diabetes in pregnancy. Low GI diets are associated with less frequent insulin use and lower birth weight than in control diets, suggesting that it is the most appropriate dietary intervention to be prescribed to patients with GDM [75]. Pregnancy does not change the GI values of specific foods. However, due to the wide interindividual variability in the GI, each woman needs to determine which foods to avoid or consume in smaller portions at all meals or during specific times of the day, for the duration of her pregnancy [76].

7.4.5. Fiber

Fiber intake, particularly soluble fiber, is beneficial in lowering serum lipid levels and reducing glucose excursions. Low GI foods often have higher fiber content. While good quality studies are not available to determine the benefits of fiber-rich diets in pregnant women with diabetes, preference should be given to foods rich in fiber. Up to 28 g fiber intake per day is recommended for pregnant women [77]. Fiber also helps reduce constipation, which is a common problem in pregnancy.

7.4.6. Nutritional education

While providing individual diet counseling is the ideal option, it is most often not feasible because of lack of resources. Women with GDM and DIP must receive practical education that empowers them to choose the right quantity and quality of food. This can be achieved through teaching portion sizes or using the plate model and a culturally appropriate food pyramid or color coding of food. Nutritional education should emphasize healthier cooking methods and reduction or moderation in consumption of processed, high sugar, high fat, high salt, and low fiber foods. It is important to highlight that women with GDM be advised (repeatedly during pregnancy) to continue the same healthy eating habits even after delivery to reduce the risk of future T2DM and metabolic syndrome. Recommendations for nutrition therapy in women with GDM are given in Box 9.

7.4.7. Physical activity

Physical activity in nonpregnant patients with diabetes has been shown to improve metabolic control, reduce insulin resistance, reduce cardiovascular risk, and improve weight control and overall well-being [78]. Women with GDM may achieve reduced glucose levels (up to 1.3 mmol/L [23 mg/dL]) with 30 minutes of physical activity [79]. A recent meta-analysis suggested that physical activity in pregnancy provided a slight protective effect against the development of GDM. Studies evaluating type, timing, duration, and compliance with physical activity regimens are warranted to best inform obstetric guidelines [80]. Regular aerobic exercise with proper warm-up and cool-down has been shown to lower fasting and postprandial glucose concentrations in several small studies of previously sedentary women with GDM. Safety of prescribed exercises for glucose management has not been demonstrated; therefore, women should be advised to monitor fetal activity and blood glucose levels before and after exercise. Increased physical activity postpartum in women with history of GDM is associated with significantly lower risk of progression to T2DM [81,82]. Recommendations for physical activity in women with GDM are given in Box 10.

- FIGO recognizes that nutrition counseling and physical activity are the primary tools in the management of GDM.
- FIGO recommends that women with GDM receive practical nutrition education and counseling that empowers them to choose the right quantity and quality of food.
- Women with GDM must be repeatedly advised to continue the same healthy eating habits after delivery to reduce the risk of future T2DM.

7.5. Medical therapy

7.5.1. Oral antidiabetic agents

Traditionally, when dietary therapy was insufficient to maintain normoglycemia in women with GDM, insulin was the only available medical therapy [83–85]. In the past, oral antidiabetic agents (OAD) were not recommended during pregnancy owing to the fear of potential adverse fetal effects including teratogenicity and neonatal hypoglycemia [86–90]. Earlier evidence in support of OAD was weak and principally based on case series involving the use of first-generation sulfonylureas [86–88,91–95]. Although neither glyburide nor metformin are approved for use in pregnancy, their use as an adjunct therapy in GDM has been considered by several organizations. For example, glyburide has been acknowledged in the Fifth International Workshop-Conference on Gestational Diabetes Mellitus [96] and both are considered in the NICE guidance [97] and ACOG practice bulletin [1]. Use of oral agents is increasing, and in some settings they are the first option when drug treatment is required for women with GDM. In a large nationwide retrospective cohort study in the USA, including 10 778 women with drug-treated GDM, use of glyburide increased from 7.4% in 2000 to 64.5% in 2011, becoming the most common treatment since 2007 [98].

Box 9
Recommendations for nutrition therapy in women with gestational diabetes mellitus.

Recommendations	Resource setting	Strength of recommendation and quality of evidence
We recommend that the following principles should be adhered for all pregnant women with diabetes: • Design an appropriate diet with respect to prepregnancy BMI, desired body weight, physical activity, habits, and personal and cultural preferences. • Provide routine follow-up and diet adjustments throughout pregnancy to achieve and maintain treatment goals. • Offer training, education, support, and follow-up by a qualified dietician experienced in care of women with diabetes. Issues for discussion include: weight control, food records, carbohydrate counting, prevention of hypoglycemia, healthy foods, and physical activity.	All	1|⊕⊕○○
We suggest that caloric intake be calculated based on prepregnancy BMI and desirable weight gain as follows: • 35−40 kcal/kg desirable body weight for underweight women • 30−35 kcal/kg desirable body weight for normal weight women • 25−30 kcal/kg desirable body weight for overweight women	All	2|⊕⊕○○
We recommend limiting carbohydrate intake to 35%–45% of total calories, with a minimum of 175 g carbohydrate per day, distributed in three small-to-moderate sized meals and 2−4 snacks.	All	1|⊕⊕⊕○
For obese women, caloric intake may be reduced by 30%, but not below 1600−1800 kcal/d	All	2|⊕⊕○○
For women with diabetic nephropathy, protein may be lowered to 0.6−0.8 g/kg ideal body weight	All	2|⊕○○○

Box 10
Recommendations for physical activity in women with gestational diabetes mellitus.

Recommendations	Resource setting	Strength of recommendation and quality of evidence
We suggest that appropriate, personally adapted, physical activity be recommended for all women with diabetes: • Planned physical activity of 30 min/day • Brisk walking or arm exercises while seated in a chair for 10 min after each meal. • Women physically active prior to pregnancy should be encouraged to continue their previous exercise routine.	All	2|⊕⊕○○

7.5.1.1. Glyburide

This is a second generation sulfonylurea. Its transfer across the placental barrier was first evaluated in single-cotyledon placental models, wherein no significant transfer of glyburide was found, even when maternal glyburide concentrations were much higher than the therapeutic concentrations [99,100]. Following these observations, Langer et al. [101] conducted an RCT to compare the efficacy and safety of glyburide (n=201) and insulin (n=203) in the management of women with GDM. This study found no differences in the rate of maternal and neonatal adverse outcomes between the glyburide and insulin treated groups, as well as no detection of glyburide in cord blood. Furthermore, glycemic control and pregnancy outcomes were comparable.

Other studies [102,103] suggested that glyburide may be actively transported from fetus to mother and that the fetus may be exposed to about 9%−70% of the maternal concentration. Subsequently, these observations were confirmed in a series of clinical studies evaluating the outcome of infants born to mothers receiving glyburide during the second and third trimesters for GDM [104–107] as well as for T2DM [108]. A recent systematic review and meta-analysis [109] shows that comparing glyburide treatment with insulin results in about 100 g higher birth weight, two-fold higher neonatal hypoglycemia, and more than two-fold higher macrosomia in the glyburide group. The magnitude of the difference in these outcomes is relevant for clinical practice.

In head-to-head comparison between metformin and glyburide, the former was associated with less maternal weight gain (pooled mean difference −2.06 kg [95% CI, −3.98 to −0.14]), lower birth weight (pooled mean difference −209 g [95% CI, −314 to −104]), less macrosomia (pooled risk ratio 0.33 [95% CI, 0.13 to 0.81]), and fewer LGA newborns (pooled risk ratio 0.44 [95% CI, 0.21 to 0.92]). The average treatment failure was 26.8% (48/179)

in the metformin group versus 23.5% (40/170) in the glyburide group. Metformin was associated with higher fasting blood glucose during treatment (pooled mean difference 0.15 mmol/L (0.00 to 0.30).

7.5.1.2. Metformin

Metformin has been shown to freely cross the placental barrier [110], reaching concentrations in fetal circulation of 50% or more of those measured in maternal serum. The fetus can be exposed to concentrations as high as or even higher than those measured in maternal serum [111]. Several studies have reported outcomes in women, mainly women with PCOS exposed to metformin at the time of conception and during early pregnancy [112–114]. The rates of adverse outcomes, including congenital malformations and neonatal hypoglycemia, were similar to those reported in the general population [112].

In the Metformin in Gestational Diabetes (MiG) trial, the largest RCT comparing metformin with insulin, Rowan et al. [115] randomized 751 women with GDM at 20–33 weeks to treatment with either metformin or insulin. Metformin was associated with a significantly lower rate of neonatal hypoglycemia (3.3% vs 8.1%; $P<0.008$), but with a higher rate of preterm birth (12.1% vs 7.6%; $P=0.04$) than insulin. There were no differences between the groups with regard to the rate of congenital anomalies or other serious maternal and neonatal adverse events. In a two-year follow-up of offspring from the MiG trial, offspring of mothers treated with metformin had more subcutaneous fat in the shoulder and upper arm regions compared with those where the initial medical treatment was insulin [116]. A one-year follow-up of women and offspring from an RCT of women with PCOS treated with or without metformin during pregnancy [117], found that although women in the metformin group gained less weight during pregnancy, they had a higher BMI one year postpartum and that the offspring in the metformin group were significantly heavier (0.5 kg) at 1 year of age. Another similar but smaller study from the same authors found significantly higher fasting glucose in 8-year-old offspring of women treated with metformin [118].

In a meta-analysis of 10 studies that assessed the effect of exposure to metformin, the rate of congenital anomalies and neonatal mortality was not increased [119]. A prospective study of 126 infants of mothers treated with metformin for PCOS during pregnancy reported no adverse effects on the infants' weight, length, motor activity, or behavior at the age of 18 months [120]. In the MiG trial [115], the rate of composite neonatal morbidity (neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5-minute Apgar score <7, or prematurity) was comparable in the metformin and the insulin groups. In addition, there were no differences in the degree of glycemic control and in umbilical cord insulin levels between the metformin and insulin groups. Metformin was associated with a lower weight gain during pregnancy (0.4 ± 2.9 vs 2 ± 3.3 kg; $P<0.001$). Furthermore, the majority of women in the metformin group stated that they would choose to receive their assigned treatment again (76.6% vs 27.2%; $P<0.001$). Nevertheless, metformin was associated with a failure rate of 46.3% (defined as a requirement for additional insulin).

In a smaller and more recent randomized study comparing metformin with glyburide, Moore et al. [121] assigned 149 women with GDM who had failed diet treatment to either metformin or glyburide. The failure rate in achieving adequate glycemic control in the metformin group was 34.7%, which was more than two-fold higher than in the glyburide group (16.2%; $P=0.01$). In another recent RCT [122], 72 women with GDM were randomized for treatment with metformin or glyburide; the failure rate of metformin and glyburide was 25% and 23.8%, respectively.

Recently, Dhulkotia et al. [123] conducted a systematic review and meta-analysis of RCTs comparing the effects of oral hypoglycemic agents (glyburide and metformin) with insulin in GDM patients. Six studies comprising 1388 subjects were included in the analysis. There were no significant differences between the OAD and insulin groups with regard to maternal fasting or postprandial glycemic control, rate of neonatal hypoglycemia, birth weight, or rate of LGA infants. The authors concluded that glycemic control and pregnancy outcomes were similar for oral hypoglycemic agents and insulin. Moreover, they suggested that glyburide and metformin should be used as the first-line agents in GDM management. Furthermore, as oral hypoglycemic agents are considerably more convenient and less expensive than insulin [124] and do not require intensive education regarding their use at the time of therapy initiation; they are clearly preferred by most patients [125,126] and thus enhance treatment adherence. These advantages are particularly beneficial in situations where insulin is not readily available or when patients refuse insulin therapy.

Additionally, metformin may also significantly reduce several adverse maternal and neonatal outcomes, including pregnancy induced hypertension, neonatal hypoglycemia, and the need for NICU admission [119]. Treatment of GDM with metformin, compared with insulin, is associated with significantly lower weight gain, and lower incidence of pregnancy induced hypertension, but with a higher rate of preterm labor [127]. In the meta-analysis by Balsells et al. [109], metformin—when compared with insulin—was associated with less maternal weight gain (pooled mean difference −1.14 kg [95% CI, −2.22 to −0.06]), lower gestational age at delivery (pooled mean difference −0.16 weeks [95% CI, −0.30 to −0.02]), and more preterm births (pooled risk ratio 1.50 [95% CI, 1.04 to 2.16]). A trend was observed toward a lower rate of any neonatal hypoglycemia (pooled risk ratio 0.78 [95% CI, 0.60 to 1.01]); the average treatment failure in the metformin group was 33.8% (229/678). For secondary outcomes, metformin was associated with lower postprandial blood glucose (pooled mean difference −0.14 mmol/L [95% CI, −0.22 to −0.05]), less maternal weight gain since study entry (pooled mean difference −1.23 kg [95% CI, −1.72 to −0.73]), less pregnancy induced hypertension (pooled risk ratio 0.53 [95% CI, 0.31 to 0.90]), and less severe neonatal hypoglycemia (pooled risk ratio 0.62 [95% CI, 0.42 to 0.94]) [109].

7.5.1.3. Recommendations for pharmacological treatment

In the short term, in women with GDM requiring drug treatment, glyburide seems inferior to both insulin and metformin, while metformin (plus insulin when required) performs slightly better than insulin [109]. Recommendations for pharmacological treatment in women with GDM are given in Box 11.

It is important to note that there is no long-term evidence on the safety of OADs.

7.5.2. Insulin therapy

When blood glucose targets cannot be reached by diet and/or OADs, insulin is required. There is no evidence supporting the advantages of any one type of insulin or regimen of insulin over another. Thus, insulin type and regimens should be individualized [128–131]. It is beneficial to pair rapid-acting with intermediate or long-acting insulin, in order to simulate the physiologic insulin secretion throughout the day. In women with diabetes, insulin requirements gradually increase throughout pregnancy: 0.7 units/kg/day in the first trimester; 0.8 units/kg/day from week 18; 0.9 units/kg/day from week 26; and 1.0 units/kg/day from week 36 until delivery. In some instances lower doses may suffice.

Box 11
Recommendations for pharmacological treatment in women with gestational diabetes mellitus.

Recommendations	Resource setting	Strength of recommendation and quality of evidence
Insulin, glyburide, and metformin are safe and effective therapies for GDM during the second and third trimesters, and may be initiated as first-line treatment after failing to achieve glucose control with lifestyle modification. Among OADs, metformin may be a better choice than glyburide [109].	All	2|⊕⊕○○
Insulin should be considered as the first-line treatment in women with GDM who are at high risk of failing on OAD therapy, including some of the following factors [129]: • Diagnosis of diabetes <20 weeks of gestation • Need for pharmacologic therapy >30 weeks • Fasting plasma glucose levels >110 mg/dL • 1-hour postprandial glucose >140 mg/dL • Pregnancy weight gain >12 kg	High	2|⊕⊕○○

Box 12
Recommendations for insulin treatment in women with gestational diabetes mellitus.

Recommendations	Resource setting	Strength of recommendation and quality of evidence
The following insulins may be considered safe and effective treatment during pregnancy: regular insulin, NPH, lispro, aspart and detemir.	All	1|⊕⊕⊕○

Regular soluble human insulin and neutral protamine Hagedorn (NPH) human insulin are commonly used for treating diabetes during pregnancy. However, the action of regular human insulin is too slow to control peak postprandial blood glucose. However, lower postprandial maternal glucose concentrations with rapid-acting insulin analogs have not been associated with a diminution in adverse maternal, fetal, or perinatal outcomes. Although NPH is considered as intermediate acting insulin [132], its basal insulin action in pregnant women may require 2–3 daily injections. Consequently, the risk of hypoglycemia is increased, particularly at night. These disadvantages in human insulin can be overcome by the use of short-acting (lispro and aspart) and long-acting (detemir and glargine) insulin analogues, or continuous insulin infusion in a pump.

7.5.2.1. Insulin lispro

Transplacental transport of lispro appears to be minimal [133–135], and without documented teratogenic effects [136] or adverse maternal outcome [137,138]. Women receiving lispro were reported to have a significantly lower area under the curve for glucose, insulin, and C-peptide compared with women treated with regular human insulin [139–142] and similar pregnancy outcomes [143,144].

7.5.2.2. Insulin aspart

Pettitt et al. [145] were the first to compare the efficacy of insulin aspart with that of regular human insulin in 15 women with GDM, demonstrating improved glycemic control with insulin aspart. The Insulin Aspart Pregnancy Study Group conducted the largest evaluation to date of insulin aspart use in pregnancy. A total of 322 women with T1DM were randomized to receive either insulin aspart or regular insulin. The rates of major congenital malformations [146], maternal and cord blood levels of insulin antibodies [147], hypoglycemic events, and pregnancy outcomes were comparable, while glycemic control was improved in the group receiving insulin aspart [148]. Based on the results of this study, the FDA changed the pregnancy use warning from category C to category B.

7.5.2.3. Insulin detemir

Insulin detemir is a long-acting insulin analogue that was first evaluated in pregnancy involving 10 women with T1DM treated throughout pregnancy [149]. No adverse maternal or neonatal effects were documented. Several RCTs in nonpregnant women have shown that, compared with NPH insulin, detemir is associated with a lower rate of hypoglycemia and less weight gain [150–152]. In 2014, a large RCT compared insulin detemir with human NPH insulin, and demonstrated its efficacy and safety during pregnancy in women with T1DM [153]. No specific safety issues were identified [154]. Use in GDM has not been specifically investigated but is expected to have the same efficacy and safety as demonstrated in pregnant women with T1DM [155].

7.5.2.4. Insulin glargine

There is paucity of data on the use of insulin glargine during pregnancy. From the limited studies, however, it appears to be safe and well tolerated [156,157].

7.5.2.5. Recommendations for insulin treatment

Recommendations for insulin treatment in women with GDM are given in Box 12.

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8. Postpartum management

The postpartum period is crucial, not only in terms of addressing the immediate perinatal problems, but also in the long term for establishing the basis for early preventive health for both mother and child, who are at a heightened risk for future obesity, metabolic syndrome, diabetes, hypertension, and cardiovascular disorders.

- FIGO supports the concept that the postpartum period in women with GDM provides an important platform to initiate early preventive health for both the mother and the child who are both at a heightened risk for future obesity, metabolic syndrome, diabetes, hypertension, and cardiovascular disorders.

8.1. Immediate postpartum period

8.1.1. Infections

Mothers with diabetes have an increased risk of infection and thus require extra attention in order to detect early signs of genitourinary, uterine, and surgical site infections (episiotomy and cesarean delivery), particularly if the delivery has been prolonged or required operative intervention. Women with diabetes in pregnancy are at a higher risk compared with women with GDM. The large-sized offspring of diabetic mothers do not suckle well; this may lead to milk retention and higher risk of breast abscess. Apart from neonates with infant respiratory distress syndrome or those with aspiration during birth, the risk of infection in the offspring of diabetic mothers is no higher than in the offspring of nondiabetic women [1].

8.1.2. Breastfeeding

Mothers with GDM and diabetes in pregnancy should be encouraged and supported in initiating and maintaining breastfeeding. Breastfeeding has been shown to be protective against the occurrence of infant and maternal complications [2], including reduction in childhood obesity, T2DM, and even T1DM [3–6]. Moreover, breastfeeding helps postpartum weight loss. Treatment with insulin or commonly used OADs, such as glyburide and metformin, is not a contraindication to breastfeeding as levels of OAD medications in breast milk are negligible and do not cause hypoglycemia in the baby.

8.1.3. Contraception

Women with GDM and diabetes should be encouraged to space their pregnancies in order to maintain and achieve optimal health between pregnancies. This also helps reduce the risk of GDM or diabetes in a subsequent pregnancy. In women with diabetes, pregnancy planning helps ensure that conception can occur when the mother's metabolic health is optimal to reduce risks of spontaneous abortions or congenital malformations. These women must have access to and should receive advice about safe and effective methods of contraception [7,8]. With advances in contraceptive technology, clinicians can now offer their patients a relatively large range of options ensuring efficacy, efficiency, and satisfaction with regard to individual preferences.

8.1.4. Postpartum glucose testing

For all women diagnosed with hyperglycemia for the first time during pregnancy (GDM and diabetes in pregnancy), the glycemic status should be re-evaluated with a 75-g oral OGTT at 6–12 weeks after delivery [9,10]. Diagnosis at that time should be based on the currently recommended WHO criteria for diabetes [11], impaired fasting glucose (IFG), and impaired glucose tolerance (IGT) in the nonpregnant state. Women who do not have diabetes or pre-diabetes, according to these definitions, are still at risk of progression to diabetes and other cardiovascular problems and require ongoing surveillance [10] according to local protocol. There is no clear guidance about the type of tests (should these women undergo annual OGTTs, or can fasting plasma glucose or HbA1c measurement suffice?) or the frequency and duration for ongoing surveillance. When guidance exists it is often glucose centric, missing out other important parameters but most importantly it is poorly implemented.

8.1.5. Reducing long-term risk of T2DM and cardiovascular disease

Irrespective of the glycemic status on early postpartum testing, it should be assumed that women with GDM have the same or a higher level of future risk of diabetes and cardiovascular disease as people with pre-diabetes and they should be advised to maintain a healthy lifestyle with an appropriate diet, regular exercise, and normal body weight. Furthermore, to ensure optimal health before attempting their next pregnancy they should seek consultation with healthcare providers knowledgeable about diabetes prevention prior to discontinuation of contraception.

Progression to diabetes is more common in women with a history of GDM compared with those without a GDM history. Both "intensive lifestyle" and metformin have been shown to be highly effective in delaying or preventing diabetes in women with IGT and a history of GDM [12]. Data from the Diabetes Prevention Program Outcomes Study (DPPOS) have been published [13] and show that the benefits of lifestyle intervention and metformin seen in the DPP study continue over a longer period. DPPOS is a long-term follow-up of the DPP participants to investigate whether the delay in the development of diabetes observed during DPP is sustained and to assess the long-term effects of the interventions on health. DPPOS followed participants from the DPP study for an additional 7 years, during which time the lifestyle and metformin groups were encouraged to continue those interventions, and all participants were offered group lifestyle classes. Over 10 years, women with history of GDM assigned to placebo had a 48% higher risk of developing overt diabetes compared with women without a history of GDM. In women with a history of GDM, "intensive lifestyle" and metformin reduced progression to diabetes compared with placebo by 35% and 40%, respectively. Among women without a history of GDM, "intensive lifestyle" reduced the progression to diabetes by 30%, while metformin did not reduce the progression to diabetes [13].

As part of the ongoing Diabetes and Women's Health Study, a cohort of 4554 women from the Nurses' Health Study II who had a history of GDM were followed up from 1991 to 2007. Compared with women who maintained their total physical activity levels, women who increased their total physical activity levels by 7.5 MET-h/wk or more (equivalent to 150 minutes per week of moderate intensity physical activity) had a 47% lower risk of T2DM (RR 0.53; 95% CI, 0.38–0.75); the association remained significant after additional adjustment for BMI [14]. Increasing physical activity might have lowered the risk of progression from GDM to T2DM.

Postpartum care is a critical area that should not be overlooked because of the long-term and intergenerational consequences. However, there are many barriers to achieving

this objective [15]. Following delivery, women with GDM seldom present with diabetes; and they are no longer pregnant therefore unlikely to visit physicians or obstetricians for check-ups. They are thus likely to be considered lost to follow-up. However, these women do visit health services focused on the well-being of their babies (for instance for the child's vaccination program and to monitor the child's growth and development) and are likely to do so at regular intervals for at least 5 years [16]. Obstetricians, family physicians, internists, pediatricians, and other healthcare providers must link postpartum follow-up of a GDM mother with the child's vaccination and routine pediatric care program, to ensure continued follow-up and engagement of the high-risk mother–child pair.

- FIGO encourages obstetricians to establish connections with family physicians, internists, pediatricians, and other healthcare providers to support postpartum follow-up of GDM mothers linked to the regular check-up and vaccination program of the child to ensure continued engagement of the high-risk mother–child pair.

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9. Preconception care

Preconception care is a set of assessment measures and interventions undertaken prior to conception. These are aimed at identifying and modifying medical, behavioral, and social risks to women's health during pregnancy, which may prevent or mitigate adverse pregnancy outcomes [1].

Pregnancies should be planned and maternal assessment with possible interventions should occur prior to conception to improve pregnancy outcome and maternal health [2]. This may not only improve immediate maternal, perinatal, and neonatal outcomes, but possibly may have long-term beneficial effects on both the mother and her baby, lasting well into adulthood and impacting next generation offspring, through epigenetic changes and intrauterine fetal programming. Key organizations have published extensive guidelines and recommendations for preconception care, including the American Academy of Pediatrics, ACOG, and the Centers for Disease Control and Prevention [3–5]. It is estimated that 30%–90% of women have at least one condition or risk factor, such as anemia, under nutrition, obesity, diabetes, hypertension, and thyroid disorders, etc. that may benefit from an appropriate preconception intervention [6,7]. However, only 30%–50% of pregnancies are planned and receive proper preconception care [7–14]. The key challenge is increasing awareness and acceptance of the concept of preconception counseling and to increase affordability and access to preconception services to women of reproductive age.

Universal preconception care, as a concept, is still a challenge in most parts of the world, where a significant proportion of women do not have access to prenatal care or receive only one or two prenatal visits, the concept of preconception care is a far-off goal but envisaged as an intervention that could dramatically change maternal and neonatal health and outcomes. Screening for conditions such as malnutrition, anemia, overweight and obesity, hypertension, diabetes, and thyroid dysfunction etc. may have a significant impact. For women with diabetes, preconception care is also cost-saving [15] and yet only half of the women with diabetes undergo appropriate preconception glycemic control [16].

Discussion on preconception care in the context of GDM not only has relevance in terms of ruling out pre-existing diabetes, but also in terms of identifying women who are at risk of GDM (as described earlier) and initiating treatment and preventive care. Only normalizing blood glucose levels in the preconception period and in early pregnancy will reduce the rate of congenital malformations seen with marked maternal hyperglycemia. In this context, postpartum care of GDM women is preconception care for a subsequent pregnancy. Preconception care as an opportunity for predicting and preventing noncommunicable diseases has been described in a review by Hader et al. [16]

- FIGO calls for public health measures to increase awareness and acceptance of preconception counseling and to increase affordability and access to preconception services to women of reproductive age, as this is likely to have both immediate and lasting benefits for maternal and child health.

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10. Research priorities

Pregnancy offers a window of opportunity to provide maternal care services in order to reduce traditional maternal and perinatal morbidity and mortality indicators and also to address intergenerational prevention of noncommunicable diseases, such as diabetes, hypertension, cardiovascular disease, and stroke. The relevance of GDM as a priority for maternal health and its impact on the future burden of noncommunicable diseases is no longer in doubt; but how best to deal with the issue remains relatively unclear as there are many unanswered questions. The available evidence is often not definitive, thorough, or based on optimum quality data. There are many gaps in this realm of knowledge. However, this should not be an excuse for inaction.

The FIGO Initiative on GDM is based on current available evidence and best practice, expert opinion, and consensus. FIGO acknowledges that there are major gaps in knowledge on how best to prevent, diagnose, and manage GDM to optimize care and outcomes, before, during, and after pregnancy for the immediate and long-term health of both a mother and her offspring. These questions can best be answered only through further research in pregnancy to ensure that the window of opportunity mentioned above is fully realized. FIGO encourages all relevant stakeholders to advocate, promote, support, carry out, and fund research to address the many knowledge gaps and research priorities identified and described in Appendix 3.

- FIGO encourages all relevant stakeholders to advocate, promote, support, carry out, and fund research to address the many knowledge gaps and research priorities in GDM.

11. Appendices

Appendix 1. Current approaches to GDM diagnosis in selected countries

Appendix 1a

Experience from India: The Diabetes in Pregnancy Study Group in India (DIPSI) test

Asian Indians are considered to be at the highest risk of gestational diabetes. Based on studies from India and keeping in mind the already high burden and rising prevalence of diabetes and the realities of resource constraints within the health system in India, as well as the high rate of deliveries (27 million each year), the Diabetes in Pregnancy Study Group in India (DIPSI) developed the following guideline for diagnosis of GDM in the community [1]. This guideline has been endorsed by the Ministry of Health, Government of India, the Federation of Obstetrics and Gynecological Societies of India (FOGSI), and the Association of Physicians of India (API).

Who to test? The target population

All pregnant women in the community should be tested for hyperglycemia during pregnancy, i.e. there should be universal testing.

When to test?

Testing for GDM is recommended twice during prenatal care. The first testing should be done during first prenatal contact as early as possible in pregnancy. The second testing should be done ideally during 24–28 weeks of pregnancy if the first test is negative. If women present beyond 28 weeks of pregnancy, only one test is to be done at the first point of contact.

How to test?

Test for diagnosis should be simple, economical, and feasible both within the resource challenged public health system as well as the equally overburdened and busy private practice.

The Single Step Test measures plasma glucose 2 hours after ingestion of 75 g glucose dissolved in approximately 300 mL water irrespective of the last meal (fasting or nonfasting). In the absence of available laboratory facilities a plasma standardized glucometer may be used to evaluate blood glucose. A glucose level of ≤7.8 mmol/L or ≤140 mg/dL is taken as the cut-off for diagnosis of GDM.

Advantages of the DIPSI test

- Single test: Serves as both screening and diagnostic procedure (universal testing is possible). Fasting values alone fail to detect many women with GDM particularly in the Asian setting.
- Convenient and feasible: Most women do not come fasting for the prenatal visit [2]. When asked to come back again in the fasting state for the test, the dropout rate is high [3,4] owing to travel time and cost; even if women do come fasting, their fasting gets unduly prolonged because of clinic schedules and high patient volume, causing discomfort and inconvenience. The nonfasting test increases convenience as well as implementation feasibility. Using the glucometer provides an opportunity to communicate results instantly and initiate counseling right away, avoiding the need for the patient to return for test result.

Why the diagnostic cut-off point of 2 hour 75 g ≥7.8 mmol/L (140 mg/dL)?

- DIPSI guidelines were initiated before the WHO accepted and endorsed the IADPSG guideline and have now been ratified by the Ministry of Health and other professional bodies. The DIPSI guideline follows the old WHO 2 hour cut-off value.
- A study to support the single nonfasting 2-hour 75-g test with a standard fasting 75-g OGTT was done using the ≥7.8 mmol/L (140 mg/dL) diagnostic cut-off, and demonstrated no statistically significant difference in the glycemic profile at 2 hours between the nonfasting and standard OGTT in the diagnosis of GDM [5,6].
- Given the positive relationship of poor pregnancy outcomes with increasing maternal plasma glucose values in short Asian Indian women with a relatively small pelvis, a cut-off value based on a lower odds ratio (1.5 of HAPO data) for macrosomia corresponding to a 2-hour value of 7.8 mmol/L or 140 mg/dL of the earlier WHO criteria is considered more appropriate to identify those at risk for macrosomia-related birth complications.
- Treatment of women with GDM identified with 2-hour post-75 g glucose cut-off values ≥7.8 mmol/L (140 mg/dL) is associated with reduced adverse pregnancy outcomes [7].

Appendix 1b

Experience from China: Using fasting plasma glucose values to reduce the number of OGTTs

China is facing a huge burden of diabetes. The overall prevalence of diabetes in the Chinese adult population is estimated to be 11.6%: 12.1% among men and 11.0% among women. The prevalence of pre-diabetes is 50.1% in Chinese adults: 52.1% in men and 48.1% in women. In approximately two-thirds of the cases, the condition had not previously been diagnosed [8]. Of the participants with undiagnosed diabetes (44.1% of men and 50.2% of women), 46.6% have isolated increased 2-hour plasma glucose levels after an OGTT and a fasting glucose level alone would have failed to identify these cases [9]. As age of onset of diabetes is decreasing, the risk that young women may have undiagnosed T2DM when they become pregnant is quite real as is the risk of GDM. GDM prevalence in China has been reported to be as high as 17.5% [10].

The Ministry of Health in China published its recommendations for testing and diagnosis of GDM in 2011 [11]. According to this, fasting plasma glucose measurement or 75-g 2-hour OGTT should be taken at first prenatal visit to rule out pre-existing diabetes. Fasting plasma glucose ≥7.0 mmol/L or ≥126 mg/dL, or 75-g 2-hour OGTT ≥11.1 mmol/L or ≥200 mg/dL, or random plasma glucose ≥11.1 mmol/L or ≥200 mg/dL are considered diagnostic of pre-existing diabetes.

The diagnosis of GDM is based on a single-step 75-g 2-hour OGTT done between 24 and 28 weeks of pregnancy. The cut-off points for diagnosis of GDM are 0 hour: 5.1 mmol/L or 92 mg/dL; 1 hour: 10 mmol/L or 180 mg/dL; and 2 hour: 8.5 mmol/L or 153 mg/dL.

To reduce the number of OGTTs to be done among all pregnant women at 24 and 28 weeks of pregnancy it has been suggested that the fasting plasma glucose test may be done first using a rule in/rule out approach. If the fasting plasma glucose value is

less than 4.4 mmol/L or 80 mg/dL, no further testing is needed [12]. For values above 5.1 mmol/L or 92 mg/dL no further testing is needed and GDM can be diagnosed without an OGTT. Pregnant women with fasting glucose values between 4.4 and 5.1 mmol/L must undergo a 75-g 2-hour OGTT to further confirm or rule out GDM. Using this strategy, only half of pregnant women would require a formal OGTT [12]. If plasma-standardized glucometers are used, women requiring an OGTT based on the results of the fasting value may be administered the 75-g glucose load and further testing can be continued in the same sitting.

A comprehensive study from China [10] also showed that in Chinese women, a fasting plasma glucose value ≥5.1 mmol/L or ≥92 mg/dL at first prenatal visit cannot be used to diagnose GDM. The study shows that less than one-third of women with a fasting plasma glucose value >5.1 mmol/L or ≥92 mg/dL at the first prenatal visit showed a fasting plasma glucose value >5.1 mmol/L or ≥92 mg/dL at 24–28 weeks of pregnancy. Only 38.9% of women with fasting plasma glucose between 5.1 and 6.09 mmol/L (92–109 mg/dL) at first prenatal visit went on to develop GDM at 24 to 28 weeks; whereas about two-thirds (66.2%) of pregnant women with fasting plasma glucose values between 6.1 and 7.0 mmol/L (110–125 mg/dL) at first prenatal visit develop GDM at 24 to 28 weeks. The study proposes that women with fasting plasma glucose values ≥6.1 mmol/L and <7.0 mmol/L (110–125 mg/dL) at first prenatal visit may be considered to have GDM and be treated with diet and exercise. They must undergo a 75-g OGTT between 24 and 28 weeks of pregnancy to confirm the diagnosis of GDM. Half of the women with fasting plasma glucose between 5.6 and 6.09 mmol/L (92–109 mg/dL) developed GDM and should therefore be considered as a high-risk group for GDM. Proper attention must be paid to their nutrition and exercise and they must undergo a formal 75-g 2-hour OGTT between 24 and 28 weeks of pregnancy.

Appendix 1c

Latin American practice

At the time of booking/first trimester, a fasting plasma glucose test is done to rule out overt diabetes (≥7 mmol/L or >126 mg/dL).

- Values under 5.6 mmol/L or 100 mg/dL are considered normal and a 75-g 2-hour OGTT is done between 24 and 28 weeks of pregnancy.
- Values between 5.6 and 6.9 mmol/L or 100 and 125 mg/dL are considered diagnostic for GDM.

Cut-off value for a 75-g 2-hour OGTT at 24 to 28 weeks:

- ≥7.8 mmol/L or ≥140 mg/dL is considered GDM.
- <140 mg/dL is normal. However, if the patient has risk factors, the test is repeated between 31 and 33 weeks.

The cut-off point 7.8 mmol/L or >140 mg/dL is supported by the ACHOIS trial [13] and the Brazilian Gestational Diabetes Study Group data [14] and other studies [15,16].

Preliminary data analysis from an ongoing multicenter study comparing maternal and neonatal outcomes in 4000 pregnant women in Latin America shows that the incidence of macrosomia among the offspring of mothers with fasting plasma glucose between 92 and 99 mg/dL and not receiving any treatment is similar to that of the whole population.

Appendix 1d

ADIPS consensus guidelines for the testing and diagnosis of hyperglycemia in pregnancy in Australia and New Zealand

The ADIPS consensus guidelines [17] recommend:

- Universal single-step testing with 75-g OGTT at 24–28 weeks of pregnancy for all pregnant women not previously known to have prepregnancy diabetes or hyperglycemia in pregnancy.
- Women with risk factors for hyperglycemia in pregnancy should be tested early in pregnancy. Some of these risk factors include: prepregnancy BMI >30; previous macrosomia (baby with birth weight >4500 g or >90th centile); previous hyperglycemia in pregnancy; age ≥40 years; Asian, Indian subcontinent, Aboriginal, Torres Strait Islander, Pacific Islander, Maori, Middle Eastern, non-white African ethnic background; family history of first degree relative with diabetes or a sister with hyperglycemia in pregnancy; PCOS etc. The method of testing must be based on clinical judgment, local healthcare policy, and possible risk stratification.
- The use of WHO 2013 recommendations for the classification and diagnosis of hyperglycemia first detected at any time during pregnancy.

Appendix 1e

National Institute for Health and Care Excellence (NICE) Guideline 3 (UK)

NICE published an update to its 2008 guidance on Diabetes in Pregnancy on February 25, 2015 [18]. By the time this document became available publically the FIGO GDM Initiative writing group had finalized its document and recommendations, and did not have time to fully review this document.

The key features of the NICE Recommendations are the following:

- NICE guidance does not recommend universal testing for GDM.
- NICE guidance recommends early testing (as soon as possible after booking, whether in the first or second trimester) with a 75-g 2-hour OGTT only for women with history of GDM in a previous pregnancy and for women with glycosuria of 2+ or above on 1 occasion or of 1+ or above on 2 or more occasions detected by reagent strip during routine prenatal care in current pregnancy.
- NICE guidance recommends testing for GDM with a 75-g 2-hour OGTT between 24 and 28 weeks of pregnancy only for women with the following risk factors:
  - BMI >30
  - Previous macrosomic baby weighing 4.5 kg or above
  - Previous GDM
  - Family history of diabetes (first-degree relative with diabetes)
  - Minority ethnic family origin with a high prevalence of diabetes
- Cut-off values for diagnosing GDM are:
  - Fasting plasma glucose ≥5.6 mmol/L or ≥100 mg/d
  - 2-hour plasma glucose ≥7.8 mmol/L or ≥140 mg/dL
- In deciding on the recommendation for risk factor based testing versus universal testing and the cut-off values, the NICE guidance, apart from other available evidence, also relied on the cost-effectiveness of different testing options (universal versus risk factor based) and cut-off values primarily using data from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study centers in the UK and Australia—representing the population of the UK.
- NICE guidance does not distinguish between diabetes first diagnosed during pregnancy and GDM. Any level of glycemia above the cut-off levels diagnosed for the first time during the index pregnancy is considered GDM.

Appendix 1f

Gestational diabetes: Situation in middle-eastern countries

The regional office of the WHO in Cairo lists 21 countries in the Eastern Mediterranean Region. They include countries that: (1) are affluent (e.g. Saudi Arabia, Qatar, UAE, Saudi Arabia, Oman, Kuwait); (2) have average income (Tunisia, Egypt, Syria, Lebanon, Morocco); and (3) have low income (Sudan, Somalia).

The prevalence of diabetes (and gestational diabetes) in the six richest countries in the Eastern Mediterranean Region is among the highest in the world, at approximately 20% [19]. The overall prevalence of GDM in all Eastern Mediterranean countries is 14.5% (3.5%–26.2%) using the WHO 1999 criteria. The follow-up after delivery that could potentially reduce the epidemic of diabetes mellitus in these high-risk populations is poor.

In general, information about GDM guidelines and criteria for diagnosis are sketchy and, when present, outdated. Among the websites of the countries examined, none—including the WHO regional office in Cairo [20]—mentioned the International Association of Diabetes in Pregnancy Study Groups (IADPSG)/WHO 2013 criteria.

A 2012 physician survey [21] assessed the current regional practices of screening, diagnosis, and follow-up of GDM and knowledge of HAPO and IADPSG within seven hospitals in UAE and one in Oman. Physicians used a multitude of criteria for GDM: National Diabetes Data Group (NDDG 1979), American Diabetes Association (ADA 2010), WHO 1999, Australasian Diabetes in Pregnancy Society (ADIPS 1998), and the New Zealand Society for Study of Diabetes (NZSSD 2011). There was no consistency within and between hospitals. Approximately 60% physicians were aware of HAPO or IADPSG. More awareness and education of caregivers would make the discordant approach to GDM (within and between hospitals) more harmonious.

Appendix 1g

The European Board and College of Obstetrics and Gynaecology (EBCOG) proposal on screening for gestational diabetes and on the management for obesity

Developing a consensus on screening for GDM in Europe is challenging owing to diversity of ethnic populations and healthcare delivery systems across Europe. After the WHO 2013 recommendations were released, many national societies within Europe have either revised or are considering revising their guidelines. However, most national societies in Europe do not recommend a universal one-step screening strategy with an OGTT, in part because of the associated workload and costs.

A steering committee, appointed by EBCOG, has developed a proposal for the use of uniform diagnostic criteria for GDM in Europe [22].

Screening for overt diabetes in early pregnancy

Since the frequency of obesity and T2DM in young adults is increasing in Europe and as the use of a simple screening test will lead to more women being timely diagnosed with overt diabetes, the steering group recommends screening for overt diabetes at preconception or at first prenatal contact, especially in high-risk groups using the cut-off values for diabetes outside pregnancy.

Due to the lack of clear evidence on which women would benefit most from screening and treatment of GDM in early pregnancy and which screening strategy for GDM should be used, the steering group has not made any recommendations on which diagnostic criteria for GDM should be used in early pregnancy.

Criteria for gestational diabetes in Europe at 24-28 weeks of pregnancy

In the belief that use of a uniform 2-hour 75-g OGTT in pregnancy with the same diagnostic criteria across Europe will lead to simplification and facilitate research on GDM within Europe, EBCOG has proposed the use of the 75-g OGTT and WHO 2013 diagnostic criteria for GDM at 24–28 weeks of pregnancy. However, owing to lack of consensus, no clear recommendation has been made on whether universal one-step, two-step, or a selective risk factor-based screening approach should be used.

Postpartum screening strategy for glucose intolerance in women with a history of GDM

The current EBCOG proposal is to screen women with a history of GDM at 6–12 weeks postpartum using the 2-hour 75-g OGTT with nonpregnancy diagnostic criteria. Women with a history of GDM should have lifelong screening for the development of diabetes or prediabetes, at least every 3 years. As currently there is insufficient evidence to recommend one test over the other; HbA1C, FPG, or 75-g 2-hour OGTT are all considered appropriate to test for diabetes and prediabetes in the postpartum period. Women with a history of GDM found to have prediabetes should receive specific lifestyle interventions with or without metformin to prevent diabetes. EBCOG has also developed standards of care for obese women [23] and recommends these be taken into account when providing postpartum care.

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Appendix 2. Gestational Diabetes Formulas for Cost-Effectiveness (GeDiForCE)

The GeDiForCE (Novo Nordisk, Denmark) model is an Excel-based (Microsoft, Redmond, USA) mathematical model developed to estimate the cost and health impact of various GDM screening and management choices [1]. The model aims to inform policy makers regarding GDM screening strategies and guidelines. GeDiForCE can compare alternative screening algorithms, prenatal interventions, and postpartum preventive lifestyle interventions. It estimates the cost per year of screening and interventions, perinatal complications, and cases of T2DM. It also calculates averted disability-adjusted life-years (DALYs).

The model is structured using a decision tree flowing from testing, to prenatal interventions and perinatal outcomes, to postpartum interventions and long-term T2DM outcomes. Key inputs include test sensitivity and specificity, health outcome risks, and intervention efficacy in reducing those risks—all derived from literature. A previously developed diabetes model, the CORE model [2], is used to assess the costs and health effects related to T2DM that occur after pregnancy in the mother and her offspring.

For every use, the GeDiForCE model will be populated with setting-specific data on GDM prevalence and cost of GDM screening and management. The model has been piloted in five different healthcare facilities in India and Israel. An analysis of the cost-effectiveness of GDM screening in urban China was presented at the Diabetes in Pregnancy (DIP) Symposium in Berlin, April 2015, concluding that GDM screening and interventions are cost-saving in an urban Chinese setting by IADPSG standards [3].

Development of GeDiForCE

The model was developed by health economic experts and the overall design of the model was reviewed by a group of international experts in mathematical modelling, health economics, gestational diabetes risk and management, and public health, in Stockholm, September 2010, and at workshops held at the Diabetes in Pregnancy (DIP) symposia in 2011 and 2013. The model was subsequently modified according to the inputs received.

The development of the GeDiForCE model was funded by Novo Nordisk A/S. The model is made available for use free of charge and can be downloaded at: www.changingdiabetesaccess.com

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Appendix 3. Research priorities in gestational diabetes

Needs, capacity, and resource assessment

It is acknowledged that the increased prevalence of hyperglycemia in pregnancy, even with potential revised models of care, will have resource implications. FIGO calls for action by national associations in collaboration with other stakeholders to support and undertake comprehensive national review of capacity, training needs, and obstetric and neonatal resource allocations relating to hyperglycemia in pregnancy.

Options for risk stratification

Not all cited risk factors for hyperglycemia in pregnancy are likely to be of equivalent predictive value and further research is required to determine whether some risk factors could be designated "high." The ability and accuracy of obstetric care providers to conduct early pregnancy testing for hyperglycemia in pregnancy based on the potential stratification of risk factors will require evaluation and will be influenced by the frequency of abnormal glucose tolerance in the local population.

Point of care testing and alternatives to glucose tolerance tests (GTT)

Given constraints of access, resources and capacity, and the need for travel, time, and costs of laboratory-based testing for GDM in many parts of the world, the current strategies are unlikely to achieve the objective of universal testing for GDM. There is a pressing need to develop alternative convenient, reliable, quick, low cost, nonfasting testing strategies to detect GDM at the point of care or close to home, e.g. more evidence on the use of handheld glucometers that can be used by community health workers, or noninvasive glucose testing, or use of glycated serum proteins as surrogate marker for hyperglycemia.

Prospective observational studies in low-resource countries to estimate the impact of universal GDM testing, diagnosis, and care on pregnancy outcomes and maternal and perinatal morbidity and mortality

Despite that GDM is one of the most common medical disorders of pregnancy that increases the risk for other pregnancy-associated medical disorders, such as pregnancy-induced hypertension, pre-eclampsia, etc—all contributing to poor outcomes—screening for GDM in most low-resource countries is an exception rather than the rule. Its overall negative impact on maternal outcomes is therefore perhaps underestimated.

Studies looking at pregnancy outcomes in centers in low-resource countries with similar clinical settings randomized to either implement a universal GDM testing, diagnosis, and standard treatment protocol, or the current status-quo approach, would help determine the true direct and indirect impact of hyperglycemia in pregnancy on poor pregnancy outcomes. These studies will help advocate for more resources and build evidence for action.

Treatment targets

Well-designed intervention studies for determining optimal glucose control for best treatment outcomes.

Fetal well-being and growth assessment

Intensity of therapy is adjusted depending on the results of ultrasonographic assessment of fetal growth (in particular measurements of fetal abdominal circumference). Research is required to see if this is a viable option in different resource settings and populations, and what other tools can be used in the absence of ultrasound services. Similarly, in the absence of a nonstress test and biophysical profile, what other measures, such as kick counts, can be used to assess fetal well-being?

Prediction and early testing

Hyperglycemia in pregnancy is generally diagnosed in the late second or early third trimester. Prepregnancy prediction may help address prevention and early detection, and treatment may potentially improve outcomes. However, there is no or limited evidence in this area. Well-designed studies to determine the most appropriate means of prepregnancy prediction and testing for gestational diabetes in early pregnancy and exploring outcomes of early treatment interventions are needed.

Long-term observational cohort studies

While there are studies to show that maternal GDM or diabetes in pregnancy is associated with higher risk of obesity, early onset T2DM, and metabolic syndrome in the offspring, there is currently limited or no evidence to show that good glycemic control during pregnancy results in reduced risk to offspring. Similarly, it is well known that GDM increases the risk of progression to T2DM but there are no studies to show whether the quality of metabolic control during pregnancy influences the level of risk or speed of progression to T2DM in mothers with GDM.

How to improve postpartum follow-up and preventive care

The biggest economic benefit of GDM diagnosis and care emerges from the ability to prevent future diabetes and metabolic syndrome in both mother and child through postpartum follow-up and preventive care. Unfortunately, 75%–80% of women are lost to follow-up. Operational research is advocated to ascertain if the follow-up can be linked to the child's vaccination program and well-baby clinics by identifying the mother and child high-risk pair for more intensive counselling and follow-up.

Cost-effectiveness studies

Existing published cost/benefit analyses based on modelling suggested that testing women for GDM and providing care are cost-effective in improving pregnancy outcomes and longer-term maternal health. However, no large-scale long-term prospective cohort studies were done using actual costs and outcomes to assess cost-effectiveness of the different testing, treatment, and follow-up regimens. In the absence of such studies it may be useful to use local input costs data to populate available models such as GeDiForCE to develop cost-effectiveness estimates for different countries and regions.

Metabolomics, microbiome, and micro RNAs

Studies to search for metabolomic signatures in women with GDM and their newborns can help better understand the mechanisms of many congenital abnormalities as well as help develop diagnostic and prognostic tests to detect these changes and take preventive and corrective actions.

The role of gut microbiome in influencing host metabolism is only starting to be revealed now. Early studies show that changes

in gut microbial ecology can cause metabolic abnormalities leading to obesity and diabetes. Studies on the effect of pregnancy on gut microbes and its impact on metabolism leading to gestational diabetes and hypertension could offer solutions for prevention and management of these conditions. Similarly, the influence of maternal gut microbiome on the colonization of the offspring's gut and its consequent long-term impact on their metabolism is an area for study that may open up opportunities for prevention.

The evidence implicating micro RNAs (miRNAs) in the pathophysiology of human diseases has triggered great interest in developing diagnostic tests as well as modalities to inhibit or restore miRNA function. The recognition that specific miRNAs are induced by hypoxia and are commonly dysregulated in pre-eclampsia raises the possibility that such miRNAs mediate the adverse effects of placental hypoxia in pre-eclampsia. The connection between miRNAs, adipose tissue, and insulin resistance may have a role in GDM pathophysiology as well. These miRNAs present in maternal blood may have the potential to be used as biomarkers, as they are relatively stable and tissue specific.

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