Gestational Diabetes Mellitus

CHI Formulary Indication Review

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June 2023

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Abbreviations

GDM: Gestational Diabetes Mellitus
IADPSG: International Association of Diabetes and Pregnancy Study Groups
WHO: World Health Organization
DM: Diabetes Mellitus
IADPSG: International Association of Diabetes and Pregnancy Study Group
T2DM: Type 2 Diabetes Mellitus
GoR: Grade of Recommendation
LoE: Level of Evidence
SoA: Strength of Agreement
CHI: Council of Health Insurance
HTA: Health Technology Assessment
NICE: National Institute for Health and Care Excellence
HAS: Haute Autorité de Santé
IQWIG: Institute for Quality and Efficiency in Healthcare
PBAC: Pharmaceutical Benefits Advisory Committee
SNDC: Saudi National Diabetes Center
OGTT: Oral Glucose Tolerance Test
ADA: American Diabetes Association
RCTs: Randomized Controlled Trial
IGT: Impaired Glucose Tolerance
GWG: Gestational Weight Gain
PCOS: Polycystic Ovary Syndrome
FPG: Fasting Plasma Glucose
GCT: Glucose Challenge Test
HAPO: Hyperglycemia and Adverse Pregnancy Outcome
LGA: Large-for-gestational-age
CPG: Clinical Practice Guidelines
BMI: Body Mass Index
SMBG: Self-Monitoring of Blood Glucose
CGMS: Continuous Glucose Monitoring System
MDI: Multiple Daily Injections
NPH: Neutral Protamine Hagedorn
AC: Abdominal Circumference
ICT: Intensified Conventional Therapy
IFG: Impaired Fasting Glucose
IGT: Impaired Glucose Tolerance After 2 Hours

RID: Relative Infant Dose
DKA: Diabetic Ketoacidosis
NICU: Neonatal Intensive Care Unit
DCEC: Diabetes Canada Expert Committee
BG: Blood Glucose
OB: Obstetrician
HIP: hyperglycemia in pregnancy

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Executive Summary

The International Association of Diabetes and Pregnancy Study Groups (IADPSG) categorizes hyperglycemia detected during pregnancy as either "overt diabetes" or "gestational diabetes mellitus (GDM)."

The early detection of hyperglycemia during pregnancy is classified according to World Health Organization (WHO) since 2013 as Diabetes Mellitus in pregnancy or gestational diabetes mellites (GDM).

GDM is hyperglycemia first detected at any time in the second or third trimester of pregnancy and does not meet the criteria of overt diabetes.

The prevalence of GDM is on the rise globally. According to WHO criteria, it is estimated that approximately 16.9% (equivalent to 21.4 million live births in 2013) of pregnancies are affected by hyperglycemia.

The prevalence of GDM varies between 1% and 20% and is increasing globally, in line with the rise in obesity and type 2 diabetes mellitus (T2DM). The prevalence of GDM correlates with the prevalence of T2DM in a population or ethnic group. African, Hispanic, Indian, and Asian women have higher rates of GDM compared to Caucasian women. Recently, the prevalence of GDM has increased by 2-3 times, ranging from 8.9% to 53.4%. This increase is primarily due to the adoption of new screening and diagnostic criteria proposed by the IADPSG.

According to Saudi Medical Journal 2020 “The **prevalence of GDM** in Saudi Arabia is high compared to other countries. Advanced maternal age and higher BMI values were associated with increased prevalence of GDM. Thus, early prevention and management of GDM is vital to minimize the risks to both the mother and fetus”.(Alsaedi et al. 2020)

GDM is a type of diabetes that occurs during pregnancy. It is characterized by high blood sugar levels that develop or are first recognized during pregnancy in women who previously did not have diabetes. GDM typically arises due to hormonal changes and increased insulin resistance during pregnancy.

During pregnancy, the placenta produces several hormones that can interfere with the action of insulin, a hormone that regulates blood sugar levels. As a result, the body may require more insulin than usual to maintain normal blood sugar levels. If the body cannot produce enough insulin to compensate for this increased demand, gestational diabetes can develop.

GDM usually occurs in the later stages of pregnancy, around the 24th to 28th week, and tends to resolve after delivery.

GDM can impose various burdens on both the mother and the healthcare system. Here are some **key aspects** of the burden associated with GDM:

Maternal health risks: GDM increases the risk of complications for the mother during pregnancy and delivery. These complications can include high blood pressure, preeclampsia (a potentially serious condition characterized by high blood pressure and organ damage), cesarean section delivery, and the need for induced labor. These complications can have physical, emotional, and financial implications for the mother.

Neonatal health risks: Babies born to mothers with GDM are at an increased risk of certain health problems. They may experience excessive growth (macrosomia), which can increase the likelihood of birth injuries, such as shoulder dystocia (when the baby's shoulder gets stuck during delivery). There is also an increased risk of low blood sugar levels (hypoglycemia) in the newborn shortly after birth. Babies born to mothers with GDM may also have a higher risk of developing obesity and type 2 diabetes later in life.

Long-term health risks: Women who have had GDM are at a higher risk of developing type 2 diabetes in the future. Studies have shown that about 50% of women with GDM develop type 2 diabetes within 5 to 10 years after pregnancy. This increases the risk of various long-term health complications associated with diabetes, such as cardiovascular disease, kidney disease, and eye problems.

Healthcare system costs: GDM imposes economic burdens on the healthcare system. The costs include prenatal care, additional monitoring and testing, medications (if required), specialized healthcare visits, and potential hospitalization for the management of GDM-related complications. The long-term costs also extend to the management of type 2 diabetes in women who develop it after GDM.

Emotional and psychological impact: GDM can also have emotional and psychological effects on women. The diagnosis of GDM may cause anxiety and stress during pregnancy. Women may worry about the health of their baby and the long-term implications of GDM. They may also experience guilt or frustration if they feel they are not able to manage their blood sugar levels effectively.

To mitigate the burden of GDM, early detection, proper management, and ongoing support are essential. This includes regular prenatal care, education on healthy lifestyle modifications, close monitoring of blood sugar levels, and timely intervention with medication or insulin therapy when necessary. By effectively managing GDM, the associated risks and burdens can be minimized for both the mother and the baby.

The management of GDM involves a multidisciplinary approach. Section 3 provides a full description of treatment regimen options for the management of GDM on the global market. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of GDM.

This report compiles all clinical and economic evidence related to GDM according to the relevant sources. The ultimate objective of issuing GDM guidelines by the Council of Health Insurance is to update the Insurance Drug Formulary (IDF) (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to GDM patients in Saudi Arabia**. The focus of the review was on Saudi, North American and European guidelines issued within the last five years in addition to recent systematic reviews and Meta-Analysis.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in GDM were reviewed and summarized. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health, Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC). Section 2.0 provides a full description of each pharmacological agent with final statements on the placement of therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of SLE.

Major recommendations for suggested drug therapies are summarized in the table below:

Medication	Indication	Line of Therapy	Recommendations	Evidence
Insulin Aspart	GDM	1st Line	A	I
Insulin Lispro	GDM	1st Line	A	I
Insulin Detemir	GDM	1st Line	A	I
Oral hypoglycemic **Glibenclamide**	GDM	1st Line when use of insulin is challenging	A	I
		2nd Line	A	I
Oral hypoglycemic **Metformin**	GDM	2nd Line	A	I

The report concludes with the addition of a key recommendation synthesis section, which emphasizes the GDM therapeutic management pathway.

1.0 Summary of Reviewed Clinical Guidelines & Evidence

1.1 KSA Guidelines

The most recent Saudi guidelines for the definition, diagnosis and management of GDM were published in the Saudi Medical Journal in 2020(Alsaedi et al. 2020), and in the Saudi National Diabetes Center (SNDC)(First Edition 2021)(Saudi Diabetes Clinical Practice Guidelines (SDCPG) Saudi National Diabetes Center (SNDC) n.d.).

The below recommendations were made:

GDM is the most prevalent medical complication that can occur during pregnancy and is linked to adverse outcomes for both mothers and newborns. Maintaining proper blood glucose levels in GDM is crucial for reducing health complications. However, there is a lack of consistent global strategies for screening and diagnosing GDM. This review focuses on the latest advancements in diagnosing and managing GDM.

1.1.1 Screening

Typically, screening for GDM is performed during the 24th to 28th week of pregnancy. However, if a patient is considered high risk for developing GDM, screening may be initiated during the first antenatal visit (Alsaedi et al. 2020).

Screening for GDM can be performed using different tests, including the non-fasting 50g 1-hour glucose challenge test (1-h GCT), the 100g 3-hour oral glucose tolerance test (3-h OGTT), and the 75g 2-hour oral glucose tolerance test (2-h OGTT).

Globally, there is a lack of standardized approaches for screening and diagnosing GDM (**Figure 1**)(Alfadhli 2015)

Table 1 - Commonly used guidelines by different study groups for gestational diabetes mellitus (GDM).

Criteria, year	Approach	Number of required abnormal value(s)	Fasting mmol/L (mg/dL)	One hour mmol/L (mg/dL)	2-hour mmol/L (mg/dL)	3-hour mmol/L (mg/dL)
IADPSG, 2010[3]	One-step, 75 g load	1	5.1 (92)	10.0 (180)	8.5 (153)	-
WHO, 1999[28]	One-step, 75 g load	1	7.0 (126)	-	7.8 (140)	-
WHO, 2013[4]	One-step, 75 g load (for diagnosis of GDM)	1	5.1 - 6.9 (92 - 125)	10.0 (180)	8.5-11.0 (153-199)	-
	One-step, 75 g load (for diagnosis of diabetes of pregnancy)	1	≥7.0 (126)	-	≥11.1 (200)	-
ACOG, 2001-2013[29]	2-step, 100 g load	2	5.3 (95)	10.0 (180)	8.6 (155)	7.8 (140)
CDA, 2003-2008[32]	2-step, 75 g load	2	5.3 (95)	10.6 (191)	8.9 (160)	-

IADPSG - International Association of Diabetes in Pregnancy Study Groups, WHO - World Health Organization, ACOG - American College of Obstetricians and Gynecologists, CDA - Canadian Diabetes Association

Figure 1. Commonly used guidelines by different study groups for gestational diabetes mellitus (GDM)

1.1.2 Management

The initial treatment approach for GDM typically involves dietary adjustments and regular exercise. If these methods fail to achieve desired blood sugar levels, insulin therapy is recommended. Insulin analogs, which closely mimic the body's natural insulin, are preferred over human insulin due to their lower risk of hypoglycemia and potential for better glycemic control. Insulin lispro, aspart, and detemir are approved for use during pregnancy, while insulin glargine, though not officially approved, has shown no contraindications in existing studies. Since Insulin detemir has been subject to more extensive studies during pregnancy, it is preferred over insulin glargine. Notably, detemir can be administered twice per day with greater predictability compared to glargine (GDM-glucose-management-maternal-prognosis-uptodate-2023 n.d.)

Additionally, the oral hypoglycemic agents glibenclamide and metformin can be effective in some patients with GDM, they are associated high failure rate in addition to some safety concerns, hence insulin the preferred intervention.

1.2 North American Guidelines

1.2.1 American guidelines(2. Classification and diagnosis of diabetes: Standards of medical care in diabetesd2019 2019)

1.2.1.1 Definition

The American Diabetes Association defines Gestational diabetes mellitus (GDM) as a form of diabetes that is initially detected during the second or third trimester of pregnancy and is not definitively classified as preexisting type 1 or type 2 diabetes.

1.2.1.2 Screening

Diabetes without pregnancy can be diagnosed using plasma glucose criteria, which includes evaluating either the fasting plasma glucose (FPG) level or the 2-hour plasma glucose (2-h PG) level during a 75-gram oral glucose tolerance test (OGTT), or by considering A1C criteria (Davidson et al. 2021) (Figure 2)

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).
*In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Figure 2. Criteria for the diagnosis of diabetes

According to ADA The diagnosis of gestational diabetes mellitus (GDM) can be achieved through two different approaches (**Figure 3**):

1. The "one-step" strategy, which involves a 75-gram oral glucose tolerance test (OGTT).
2. The "two-step" approach, which begins with a 50-gram nonfasting screening test, followed by a 100-gram OGTT for those who test positive on the screening test.

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes.

If the plasma glucose level measured 1 h after the load is ≥130 mg/dL, 135 mg/dL, or 140 mg/dL (7.2 mmol/L, 7.5 mmol/L, or 7.8 mmol/L, respectively), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made if at least two* of the following four plasma glucose levels (measured fasting and 1 h, 2 h, 3 h during OGTT) are met or exceeded:

	Carpenter-Coustan (86)	or	NDDG (87)
• Fasting	95 mg/dL (5.3 mmol/L)		105 mg/dL (5.8 mmol/L)
• 1 h	180 mg/dL (10.0 mmol/L)		190 mg/dL (10.6 mmol/L)
• 2 h	155 mg/dL (8.6 mmol/L)		165 mg/dL (9.2 mmol/L)
• 3 h	140 mg/dL (7.8 mmol/L)		145 mg/dL (8.0 mmol/L)

Figure 3. Screening for and diagnosis of GDM

1.2.1.3 Future Considerations

The divergent recommendations from expert groups highlight the availability of data supporting each approach. A cost-benefit analysis comparing the two strategies determined that the one-step approach is cost-effective only when patients with GDM receive post-delivery counseling and care to prevent the onset of type 2 diabetes.

As The IADPSG criteria (“one-step strategy”) have been adopted internationally, more evidence has surfaced supporting improved pregnancy outcomes and cost savings, making it a potentially preferable approach.

Additionally, pregnancies affected by GDM according to the IADPSG criteria, but not identified as such using the more stringent two-step criteria, demonstrate similar outcomes. There is a consensus among experts that establishing a standardized approach for diagnosing GDM would benefit patients, healthcare providers, and policymakers. Currently, longer-term studies are in progress to further investigate the outcomes associated with these approaches.

1.2.1.4 Recommendations

- Test for undiagnosed diabetes at the first prenatal visit in those with risk factors using standard diagnostic criteria. (**Figure4**)
- Test for GDM at 24–28 weeks of gestation in pregnant women not previously known to have diabetes.
- Test women with GDM for prediabetes or diabetes at 4–12 weeks postpartum, using the 75-g OGTT.
- Women with GDM history should have lifelong screening for the development of diabetes or prediabetes at least every 3 years.
- Women with GDM history found to have prediabetes should receive intensive lifestyle interventions or metformin to prevent diabetes.

1.2.1.5 Management

GDM is associated with an increased risk of macrosomia and birth complications. Additionally, women diagnosed with GDM face an increased risk of developing type 2 diabetes following pregnancy.

Several randomized controlled trials (RCTs) indicate that the incidence of GDM can potentially be reduced through interventions such as dietary modifications, exercise, and lifestyle counseling. The effectiveness of these interventions appears to be more pronounced when initiated during the first or early second trimester of pregnancy (Management of diabetes in pregnancy: Standards of medical care in diabetes-2020 2020).

Lifestyle Management

Upon receiving a diagnosis, the initial course of treatment typically involves the implementation of medical nutrition therapy, physical activity, and weight management, which are tailored based on the individual's pregestational weight.

Lifestyle modification alone has shown promising results in controlling GDM in a significant portion, ranging from 70% to 85%, of women diagnosed with GDM using the Carpenter Coustan criteria, depending on the specific population studied.

Medical Nutrition Therapy

The management of GDM includes a personalized medical nutrition therapy plan developed collaboratively between the woman and a registered dietitian/registered diabetes nurse (RD/RDN) with expertise in GDM management. The nutrition plan aims to ensure sufficient calorie intake to support the health of both the fetus/neonate and the mother, achieve glycemic targets, and align with the weight gain recommendations outlined by the 2009 Institute of Medicine.

Pharmacologic Therapy

Although certain individual randomized controlled trials (RCTs) have shown some effectiveness of metformin and Glibenclamide in reducing glucose levels for GDM treatment, these agents are not recommended as first line treatment for GDM due to their ability to cross the placenta and potential long-term safety concerns for offspring (Davidson et al. 2021),.

Additionally, separate RCTs have revealed that both Glibenclamide and metformin were unable to achieve adequate glycemic control in 23% and 25-28% of women with GDM, respectively.

According to ADA and American Congress of Obstetricians and Gynecologists (ACOG) recommendations, insulin remains the preferred treatment for GDM.(Barbour et al. 2018)

Glibenclamide

Glibenclamide has the ability to cross the placenta, leading to increased instances of neonatal hypoglycemia. Concentrations of Glibenclamide in umbilical cord plasma are approximately 50-70% of maternal levels (Sénat et al. 2018).

Glibenclamide has shown comparable efficacy and greater convenience compared to insulin. However, it was associated with an increased risk of macrosomia compared to insulin and metformin.(Balsells M, GarcÃa-Patterson A, SolÃ I, RoquÃ© M, Gich I, Corcoy R et al. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis *BMJ* 2015; 350 :h102 doi:10.1136/bmj.h102). The typical daily doses of Glibenclamide range from 2.5 to 20 mg, administered once or twice per day(Glover et al. 2015).

Metformin(Barbour and Feig 2019)

Systematic reviews have indicated that metformin is associated with a reduced risk of neonatal hypoglycemia and less maternal weight gain compared to insulin.

However, metformin easily crosses the placenta, leading to umbilical cord blood levels of metformin that are as high as or even higher than the levels in the mother at the same time.

There may be certain women with GDM who require medical treatment but face challenges such as cost, language barriers, comprehension, or cultural influences, which may hinder their ability to safely and effectively use insulin during pregnancy. In such cases, oral agents could be considered as an alternative after discussing the known risks and the need for more long-term safety data regarding their impact on offspring.

Metformin should not be used in women with hypertension, preeclampsia, or those at risk for intrauterine growth restriction due to the potential for growth restriction or acidosis in the presence of placental insufficiency.

Insulin

Insulin is the preferred first line therapy for GDM. No evidence of superiority of a specific insulin regimen.

1.2.1.6 Postpartum Follow-up

The oral glucose tolerance test (OGTT) is recommended over A1C testing for postpartum diabetes screening between 4 to 12 weeks after delivery. A1c was found to have low sensitivity for diabetes diagnosis in the postpartum period. (Kim KS, Kim SK, Cho YW, Park SW. Diagnostic value of haemoglobin A1c in post-partum screening of women with gestational diabetes mellitus. Diabet Med. 2016 Dec;33(12):1668-1672. doi: 10.1111/dme.13119. Epub 2016 Apr 16.

Given the association of GDM with elevated maternal risk of developing diabetes throughout their lifetime, estimated at 50-70% within 15-25 years, it is advisable to conduct regular testing every 1-3 years following a normal 75-g OGTT performed between 4-12 weeks postpartum. This ongoing monitoring is crucial to ensure early detection of any potential onset of diabetes in women who previously had GDM.

1.2.2 Canadian guidelines(Feig et al. 2018)

1.2.2.1 Prevention and risk factors(Canada 2018)

According to the Canadian Diabetes Association, between 3- 20% of pregnant women develop GDM, depending on their risk factors

The increasing prevalence of GDM can be attributed to a greater number of women starting pregnancy at an older age and/or with obesity. Other factors contributing to the rise include modifications in screening methods and diagnostic criteria. It is crucial to develop an effective and well-received intervention that can prevent the onset of GDM. Implementing such an approach holds the potential to enhance the health outcomes of both mothers and children while generating substantial cost savings within the healthcare system.

Understanding the pathophysiology of GDM and its risk factors is important for the development of preventive strategies.

The population of women with GDM is diverse, encompassing individuals with distinct metabolic profiles influenced by pregnancy hormones. Different presentations of GDM include:

- Hyperglycemia that likely existed prior to pregnancy, such as impaired glucose tolerance (IGT), elevated fasting glucose in the first trimester, overt diabetes in pregnancy, or monogenic diabetes.

- Declining insulin secretion capacity or reduced insulin secretory function, which may indicate the development of type 1 diabetes.
- Significant insulin resistance occurring early in pregnancy, often associated with conditions like polycystic ovary syndrome, overweight or obesity, and certain ethnic groups.
- Combinations of factors, including a family history of diabetes, previous history of GDM, and genetic predisposition for GDM or type 2 diabetes.

Due to the significant decrease in insulin sensitivity during pregnancy, it is not possible to prevent all cases of GDM. Therefore, studies should aim to identify specific groups of women who can benefit from preventive interventions and develop strategies tailored to their individual conditions. This includes exploring the timing of interventions (preconception vs. during pregnancy) and considering factors such as obesity or leanness in women. Given the heterogeneity of GDM, it is evident that personalized recommendations will need to be developed for each identified group of women at risk.

The available evidence is limited, but current literature suggests that the most effective preventive measure for GDM in early pregnancy, particularly in high-risk women, including those with obesity, is adopting a healthy diet and closely monitoring weight gain to prevent excessive gestational weight gain (GWG). Some promising results have been observed with nutritional supplements like probiotics and myo-inositol, but larger randomized trials are needed to confirm these findings. It is crucial to conduct further studies using consistent diagnostic criteria and focusing on specific populations, such as women with obesity, prior GDM and/or polycystic ovary syndrome (PCOS), and those with excessive GWG. This approach will enable the development of targeted preventive interventions tailored for these high-risk populations, ultimately reducing the prevalence of GDM.

1.2.2.2 Screening and Diagnosis

The selection of an appropriate screening test for early detection should prioritize its ability to predict adverse obstetrical outcomes, which can potentially be modified through lifestyle or pharmacological interventions. There are two approaches for assessing glucose levels in early pregnancy: utilizing non-pregnancy-recommended screening tests such as fasting plasma glucose (FPG) or A1C, or following the conventional gestational diabetes screening criteria (e.g., 50g glucose challenge test [GCT] and/or 75g oral glucose tolerance test [OGTT]) typically conducted between 24 to 28 weeks of gestation. It is important to note that applying non-pregnant FPG or A1C criteria in early pregnancy fails to account for their natural decrease during this period, potentially leading to underdiagnosis in women with pre-existing diabetes.

The determination of appropriate glucose thresholds to define GDM remains a topic of debate due to the absence of a clear threshold that correlates with improved pregnancy outcomes through glycemic management.

To address this, IADPSG Consensus Panel devised new diagnostic thresholds for GDM based on findings from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study.

These IADPSG thresholds were established by identifying maternal glucose values from HAPO that were associated with a 1.75-fold increase in factors such as large-for-gestational-age (LGA), elevated C-peptide, high neonatal body fat, or a combination of these indicators, in comparison to the average maternal blood glucose levels observed in women included in the HAPO study.

Given the current limited availability of high-quality research comparing the "preferred" and "alternative" approaches for GDM screening and diagnosis as outlined in the 2013 Clinical Practice Guidelines (CPG), it was determined by the committee that maintaining the same diagnostic criteria introduced in the 2013 CPG is the most appropriate course of action. It is acknowledged that further high-quality evidence is necessary to ascertain whether maternal body mass index (BMI) and other clinical risk factors should influence the selection of diagnostic thresholds. Cost analysis evaluations generally support a sequential screening approach for GDM.

The 2018 Diabetes Canada Expert Committee (DCEC) recognizes the limitations associated with having different diagnostic strategies and thresholds for the same 75 g oral glucose tolerance test (OGTT), but currently, there is insufficient evidence to favor one strategy over the other. Consequently, well-designed prospective studies with sufficient participant numbers are needed to compare these two approaches.

1.2.2.3 Management

Weight gain: The 2009 Institute of Medicine (IOM) guidelines for weight gain during pregnancy were developed for a general healthy population, and there is limited information on optimal weight gain specifically for women with GDM. Further research is needed to establish weight gain guidelines for GDM patients and to determine the safety of weight gain below the IOM guidelines or weight loss during pregnancy. In the absence of this data, women with GDM should be encouraged to follow the IOM guidelines for weight gain based on their BMI category to minimize adverse outcomes for both the mother and baby and to prevent postpartum weight retention.

Nutrition therapy: Nutrition therapy is a fundamental component of GDM management. All women at risk for or diagnosed with GDM should undergo assessment, counseling, and follow-up by a registered dietitian whenever possible. The goal of nutrition therapy is to ensure adequate nutritional intake without ketosis, achieve glycemic targets, promote appropriate fetal growth, and manage maternal

weight gain. Guidelines for nutrition best practices and a comprehensive review of the role of nutrition therapy in GDM management are available for reference.

Meal planning advice for women with GDM should prioritize a healthy diet during pregnancy, with a minimum carbohydrate intake of 175 g/day distributed over three moderate-sized meals and two or more snacks (including one at bedtime). Additionally, replacing high-glycemic index (GI) foods with low-GI alternatives should be emphasized.

Physical activity: When combined with nutritional intervention, physical activity has shown to be beneficial for GDM management, although its effectiveness in preventing GDM is not as well-established. Unless contraindicated by obstetric factors, physical activity should be encouraged as an integral component of GDM management.

Glycemic control: Current evidence suggests that targeting a reduced fasting blood glucose (FBG) level of ≤5.0 mmol/L for women with GDM may help reduce the rates of large for gestational age (LGA) and other perinatal complications. However, well-designed randomized controlled trials comparing different blood glucose targets are needed to determine optimal FBG and postprandial blood glucose targets. These studies should also assess the risk of maternal hypoglycemia, small for gestational age (SGA) infants, insulin use, and the cost-effectiveness of such modifications.

Monitoring: Regular self-monitoring of blood glucose (SMBG) is crucial for guiding GDM therapy. Both fasting and postprandial blood glucose testing are recommended to optimize therapy and improve fetal outcomes. Continuous glucose monitoring systems (CGMS) have shown utility in detecting previously undetected hyperglycemia, but their cost-effectiveness compared to SMBG is yet to be established.

eHealth medicine: The adoption of telehomecare and emerging technologies for glucose monitoring and healthy behavior interventions is on the rise. These innovative approaches, including the use of web-based platforms, are being increasingly utilized in Canada and globally for monitoring blood glucose levels in pregnant women with diabetes. They enable interactive communication between women and healthcare providers, allowing real-time transmission of blood glucose results for timely feedback. Studies have shown that integrating telehomecare with standard care has led to a significant reduction in face-to-face medical visits ranging from 38.0% to 82.7%. Moreover, the use of telehomecare has been associated with decreased insulin requirements in pregnant women, without an increase in maternal or perinatal complications.

Pharmacological therapy:

Insulin is recommended if women with GDM do not achieve their blood glucose targets within two weeks of initiating nutritional therapy and exercise. The use of

insulin has been demonstrated to reduce fetal and maternal morbidity by achieving glycemic control. Various protocols have been utilized, with multiple daily injections (MDI) being the most effective approach. Continuous adjustment of insulin dosage is typically necessary to attain the desired glycemic targets.

While rapid-acting bolus analogues such as **aspart** and **lispro** can help achieve postprandial targets without causing severe hypoglycemia, their use has not shown improvements in fetal outcomes compared to regular insulin.

Glargine and **detemir** have mainly been studied in women with pre-existing diabetes during pregnancy. Randomized trial evidence suggests that **detemir** is safe and may result in less maternal hypoglycemia compared to neutral protamine hagedorn (NPH), while observational studies suggest that glargine, although potentially less preferable in theory, is also considered safe.

Other antihyperglycemic agents:

Metformin has been studied in several meta-analyses of randomized trials to compare its use with insulin in women with GDM. Weight gain and incidence of pregnancy-induced hypertension were lower with women treated with metformin compared to those treated with insulin. Infants born to mothers using metformin had a lower gestational age and a lower occurrence of neonatal hypoglycemia.

While metformin appears to be a safe alternative to insulin therapy, it does cross the placenta.

Long-term monitoring conducted over a period of 18 months to 2 years suggests that exposure to metformin in utero does not appear to have harmful effects on early motor, linguistic, social, metabolic, and neurodevelopmental outcomes. However, extended follow-up data beyond this timeframe are currently unavailable.

Glibenclamide**.** Glibenclamide has demonstrated the ability to pass through the placenta. Two meta-analyses of randomized trials investigating the use of Glibenclamide versus insulin in women with GDM have shown that Glibenclamide is associated with increased birthweight, macrosomia, and neonatal hypoglycemia when compared to insulin. Additionally, compared to metformin, Glibenclamide use has been linked to higher maternal weight gain, birthweight, macrosomia, and neonatal hypoglycemia. As a result, Glibenclamide is not recommended as the primary or secondary treatment option during pregnancy. It may be considered as a third-line treatment if the mother declines insulin and either declines or experiences inadequate glycemic control with metformin.

Acarbose. Limited data is available on the use of acarbose in women with GDM, with only one small randomized trial conducted. This trial did not find any significant

differences in maternal or fetal outcomes when compared to insulin, although there was an increase in gastrointestinal side effects.

Other antihyperglycemic agents. There is currently no human data available regarding the use of DPP-4 inhibitors, GLP-1 receptor agonists, or SGLT2 inhibitors during pregnancy. As a result, the use of these non-insulin antihyperglycemic agents is not recommended during pregnancy.

1.3 European Guidelines

According to the German Diabetes Association, the GDM prevalence in Germany in the perinatal statistics was 5.97% in 2017 (an increase of 14.6% compared to 2016).

The GDM diagnosis is established using a 75g oral glucose tolerance test (OGTT) conducted under standardized conditions, with glucose levels accurately measured from venous plasma to ensure quality assurance (Schafer-Graf et al. 2021)(Pilszyk et al. 2022).

1.3.1 Prevention

Strategies for GDM have been extensively explored in various studies, primarily focusing on lifestyle modifications such as dietary changes, increased physical activity, and the use of supplements like myoinositol, vitamin D, probiotics, and fish oil. However, the outcomes of these interventions have not provided clear and definitive results.

Nevertheless, it is recommended that women who are overweight or obese take proactive measures to reduce their weight by adopting a healthy lifestyle. This approach should be initiated as early as the planning stage of pregnancy and continued throughout the entire pregnancy period to mitigate the risk of developing GDM.

1.3.2 Screening and Diagnostics

1.3.2.1 Screening for risk of diabetes at first medical appointment in pregnancy

During the initial medical appointment in early pregnancy, which occurs before the 24th week, it is crucial to conduct screening for pregnant women who are at an increased risk of developing diabetes (**Figure 4**). The objective is to identify the presence of a glucose tolerance disorder or preexisting, previously undetected diabetes mellitus (type 1 or type 2).

If pregnant women exhibit symptoms specific to diabetes, such as polyuria, polydipsia, or significant glucosuria in spontaneous urine, further tests should be conducted to ascertain the presence of pre-conception diabetes mellitus that may have gone undiagnosed.

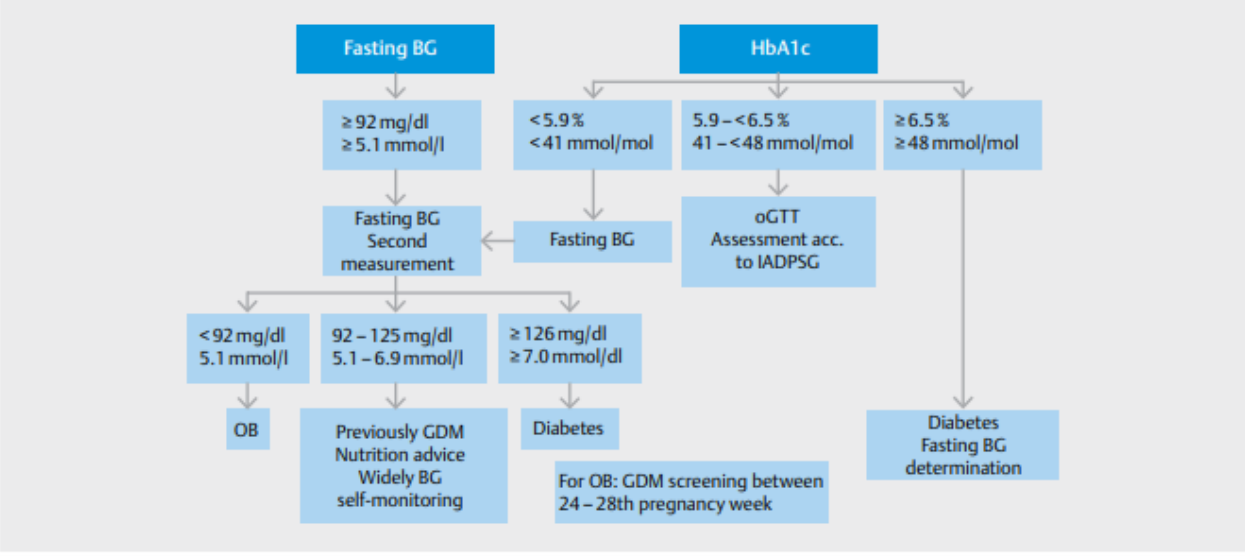
	OR	95%CI
Pregnancies with GDM		
previous GDM	50.4	42.1–60.3
Weight (>69 kg)	1.02	1.01–1.03
Pregnancies without GDM		
No GDM in previous pregnancy	0.45	0.4–0.5
Age (compared to 35 years)	1.08	1.07–1.09
Weight (>69 kg)	1.03	1.03–1.04
Height (>1.64 m)	0.94	0.93–0.95
1st degree relatives with diabetes	2.5	2.2–2.8
2nd degree relatives with diabetes	1.7	1.4–2.1
Ovulation induction	1.6	1.1–2.3
Origin: East Asian region	2.9	2.2–3.8
Origin: South Asian region	2.3	1.8–2.8
Z-score of birth weight of former children	1.25	1.1–1.3

Figure 4. Independent risk factors for the emergence of GDM in the course of pregnancy

There are two potential methods for screening, as illustrated in **Figure 5**:

1. **Fasting glucose measurement**: Blood glucose(BC) levels in venous plasma of ≤ 92mg/dl (5.1mmol/l) can exclude the presence of diabetes mellitus and GDM. If the fasting blood glucose level in venous plasma is ≥ 92mg/dl (5.1mmol/l), a second measurement is conducted on a different day, adhering to laboratory standards. The second measurement must surpass the designated cut-off value for a diagnosis of GDM. As per the recommendations of IAPDSG and WHO, blood glucose values ranging from 92–125mg/dl (5.1–6.9mmol/l) indicate GDM in early pregnancy. Nutritional counseling and blood glucose self-monitoring are advisable. Plasma glucose levels ≥ 126mg/dL (7.0mmol/l) indicate the presence of diabetes mellitus, likely pre-conception diabetes mellitus.
2. **HbA1c measurement**: An HbA1c value of ≤ 5.9% excludes diabetes mellitus but not early GDM. Therefore, an additional fasting blood glucose determination is required. For HbA1c values ranging from 5.9% to 6.4%, an oral glucose tolerance test (OGTT) is recommended to further clarify the situation, following the assessment guidelines provided by IADPSG and WHO. Values ≥ 6.5% indicate diabetes.

If the screening results are negative in early pregnancy, regular GDM screening, as per maternity guidelines, is conducted between the 24th week + 0 and 27th week + 6, preferably using a 75g oral glucose tolerance test (75-g-oGTT) (**Figure 5**).



BG: Blood Glucose, oGTT: Oral Glucose Tolerance Test, OB: Obstetrician

Figure 5. Diabetes screening in early pregnancy at risk for DM (HbA1c) or GDM (HbA1c)

1.3.2.2 Screening for GDM in the period 24th week + 0 to 27th week + 6

As per the guidelines in Germany for maternity care, initial screening for GDM can be conducted using a 50-g Glucose Challenge Test (GCT), as shown in **Figure 3**. The 50-g GCT is performed without the requirement of fasting, irrespective of the time of day or food intake. A solution containing 50g of glucose in 200 ml of water is consumed. If the blood glucose level in venous plasma reaches or exceeds 135 mg/dl (7.5 mmol/l) after one hour, it is considered a positive result, necessitating a subsequent diagnostic 75-g oral glucose tolerance test (75-g-oGTT). A blood glucose level in venous plasma of ≥ 200 mg/dl (11.2 mmol/l) confirms the diagnosis of GDM, and the 75-g-oGTT is not performed.

Based on findings from the HAPO study, it was observed that 33% of women with GDM had an increase in fasting blood glucose levels that were not detected by the 50-g GCT. However, since fasting blood glucose levels have a strong correlation with adverse pregnancy outcomes, it is recommended to additionally measure fasting

blood glucose in case the 50-g GCT yields a negative result, specifically between the 24th week + 0 and 27th week + 6 of gestation.

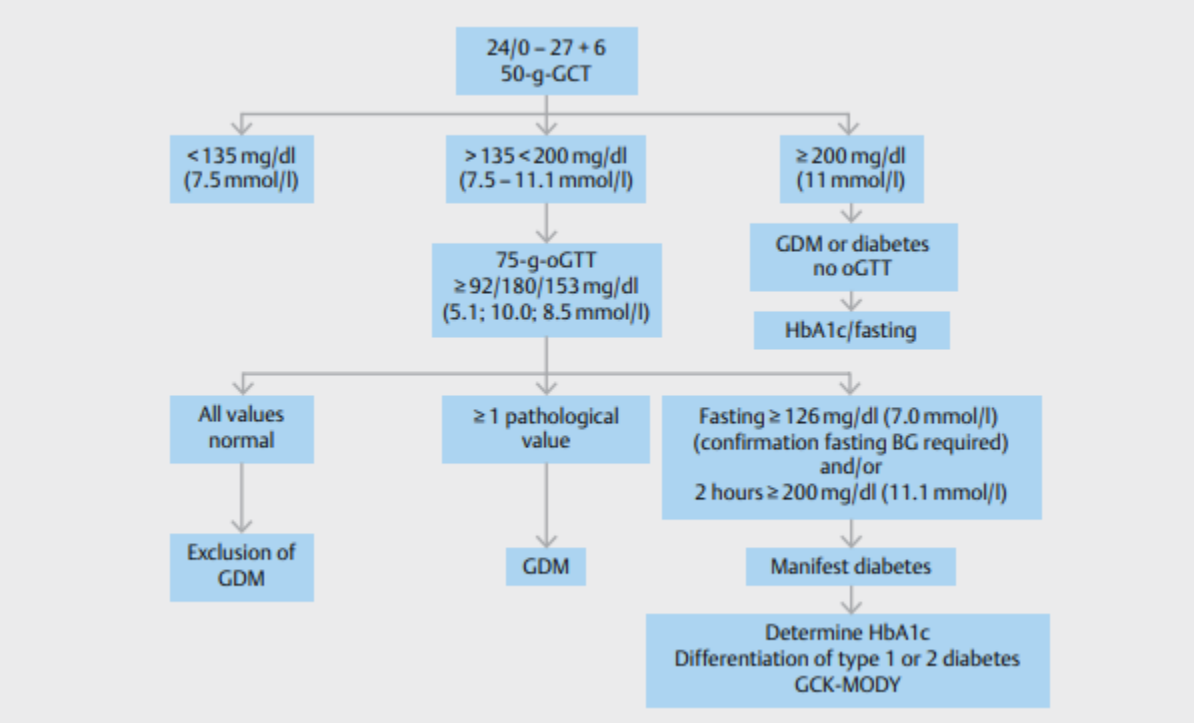


Figure 6. Screening for gestational diabetes in the 3rd trimester according to German maternity guidelines

GDM screening procedures such as urine glucose, fasting glucose, casual plasma glucose or HbA1c are not recommended in German Diabetes Association guideline.

1.3.2.3 Diagnostics of GDM by means of 75g-oGTT

The 75-g oral glucose tolerance test (75-g-oGTT) is conducted in the morning, following standard conditions, and on an empty stomach. If the recommended time window between the 24th week + 0 and 27th week + 6 is exceeded, the test can be performed at a later time as directed by the healthcare team. In situations where there are indications of GDM, such as polyhydramnios, macrosomia (with the abdominal circumference greater than the head circumference), or significant glucosuria, it is advisable to repeat the diagnostic 75-g-oGTT for GDM in the third trimester, particularly if the initial screening during the 24-28 weeks of gestation yielded a negative result.

The diagnostic threshold values for interpreting the test results of the 75-g oral glucose tolerance test (75-g-oGTT) are determined by the IADPSG criteria, which are consistently utilized as per the maternity guidelines. If any one of the three predefined limits in venous plasma is reached or surpassed, a diagnosis of GDM is made (**Figure 7**).

A fasting blood glucose value of ≥ 126 mg/dl (7.0 mmol/l) is indicative of manifest diabetes mellitus. To confirm this diagnosis, a second measurement of fasting blood glucose on a different day, along with an HbA1c measurement, is recommended. The diagnosis of manifest diabetes mellitus is confirmed if both blood glucose values are ≥ 126 mg/dl. In such cases, continuation of the 75-g-oGTT is not necessary.

Additionally, if the blood glucose value after two hours reaches or exceeds ≥ 200 mg/dl (11.1 mmol/l), it confirms the diagnosis of diabetes mellitus. In such instances, an additional HbA1c measurement proves useful. Subsequent management aligns with the approach for pre-conception type 1 or type 2 diabetes that was already known.

According to the HAPO study, if the OGTT is limited to a duration of one hour (measurement conducted on an empty stomach and after one hour), approximately 2.1% of pregnant women with GDM may go undetected (**Figure 7**).

Time point 24th week + 0 to 27th week + 6	Cut-off values IADPSG venous plasma (mg/dl)	(mmol/l)
Fasting	92	5.1
After 1 hour	180	10.0
After 2 hours	153	8.5

Figure 7. Cut-off values in venous plasma according to IADPSG consensus recommendation

1.3.3 Management

1.3.3.1 First medical consultation after GDM diagnosis

The key components of the initial structured medical consultation encompass:

1. Emphasizing the significance of the diagnosis for both the child and the mother.
2. Defining the timeframe for implementing measures and outlining the structure of medical care.
3. Referring to outpatient therapy guidelines as the primary source of guidance.
4. Explaining the purpose of blood glucose self-monitoring.
5. Highlighting the potential need for nutritional modifications and establishing weight development goals based on Institute of Medicine recommendations.
6. Outlining the benefits of regular exercise in terms of increasing insulin sensitivity.
7. Discussing the potential use of off-label pharmacotherapy options such as insulin or metformin and the rationale behind their consideration.

8. Concluding the session with an open discussion that encourages questions about concerns, worries, and fears.

1.3.3.2 Physical activity

It is recommended to engage in brisk walking, a basic and equipment-free form of physical exercise, for a minimum of 30 minutes, at least three times a week. Alternatively, daily exercise involving the use of an elastic band can also be considered. Initiating physical activity/training ideally begins prior to conception or during the initial trimester. Additionally, incorporating short exercise sessions within the first hour after main meals can provide notable benefits (Koivusalo et al. 2016).

1.3.3.3 Nutritional advice

The dietary plan should be adjusted to meet the specific nutrient demands of pregnancy while ensuring sufficient caloric intake. The suggested nutrient distribution is as follows:

- Carbohydrates: 40-50% of the total calorie intake.
- Protein: 20% of the total calorie intake.
- Fat: 30-35% of the total calorie intake.

1.3.3.4 Recommended weight gain

Pregnant women are advised to regularly monitor and record their weight on a weekly basis. This should be done in the morning, without clothing, and on an empty stomach at home. (**Figure 8**)

Preconceptual BMI (kg/m²/WHO)	Total weight gain during pregnancy (kg)	Weight gain/week 2nd and 3rd Trimester[1] (kg)
18.5	12.5–18	0.5–0.6
18.5–24.9	11.5–16	0.4–0.5
25.0–29.9	7–11.5	0.2–0.3
≥30	5–9	0.2–0.3
[1] A weight gain of 0.5–2 kg in the first trimester is assumed.		

Figure 8. Recommended range of weight gain during pregnancy

1.3.3.5 Blood glucose monitoring

Individual blood glucose measurements

- At the beginning: For 1-2 weeks, a 4-point profile is recommended. This includes fasting measurements in the morning and 1 or 2 hours after the initiation of main meals.
- If all values remain within the target range during the first 2 weeks, the frequency can be reduced to a single daily measurement on a rotating basis or a 4-point profile twice a week.

Continuous glucose monitoring system (CGMS)

- CGMS is not part of the routine care of pregnant women with GDM and does not improve the outcome of the pregnancy

HbA1c

- Within the scope of early screening (≤24th week), the HbA1c value is used to diagnose a pre-existing glucose metabolism disorder/ manifest diabetes mellitus.

Blood glucose target values

- **Figure 9** displays the target blood glucose values derived from plasma-calibrated self-monitoring devices.

Time	plasma equivalent	
	mg/dl	mmol/l
Fasting, preprandial	65–95	3.6–5.3
1 h postprandial	<140	<7.8
2 h postprandial	<120	<6.7

Figure 9. Blood glucose setting targets based on pharma-calibrated self-monitoring device

1.3.3.6 Insulin therapy

General indication for insulin therapy

If the desired metabolic objectives cannot be achieved despite employing lifestyle measures to their maximum extent (such as nutritional therapy and physical activity), the utilization of insulin therapy becomes warranted.

It is challenging to significantly influence fasting blood glucose levels of 110mg/dL (6.1mmol/L) or higher through dietary modifications during pregnancy. Therefore, if fasting glucose values consistently exceed 110mg/dL (6.1mmol/L), prompt consideration should be given to initiating insulin therapy. It is worth noting that approximately 20-30% of pregnant women with GDM may require insulin treatment.

Insulin therapy with consideration of fetal growth in ultrasound

In cases of asymmetric macrosomia, characterized by a fetal abdominal circumference (AC) equal to or exceeding the 75th percentile, it is advisable to initiate insulin therapy promptly and strive for slightly lower target blood glucose values. This approach becomes particularly important when additional risk factors for fetal macrosomia are present, such as a BMI exceeding 30 kg/m², previous delivery of a large-for-gestational-age (LGA) newborn, or fasting blood glucose exceeding 110mg/dL in the initial profile upon commencing therapy.

Implementation of insulin therapy

Insulin therapy should be implemented following the ICT (intensified conventional therapy) principle, where either basal or short-acting insulin may be necessary. If postprandial blood glucose levels cannot be adequately controlled with appropriate dosage of short-acting human insulins, switching to insulin aspart or lispro is worth considering. Both rapid-acting and long-acting insulin analogues can also be predominantly employed. It is advisable to initiate insulin adjustment in an outpatient setting, involving experienced diabetologists and perinatal physicians who possess the necessary expertise in caring for pregnant women with diabetes.

1.3.3.7 Oral antidiabetics and GLP-1 agonist

Following a comprehensive assessment of off-label use, the consideration of metformin administration is possible for GDM.

Serum creatinine and creatinine clearance must be evaluated prior to initiating metformin.

It is recommended to avoid exceeding a daily metformin dosage of 2.0 g.

Alpha-glucosidase inhibitors, glitazones, glinides, DPP-4 inhibitors, and GLP-1 agonists should not be prescribed to pregnant women with GDM due to lack of evidence (Barbour and Feig 2019) .

1.3.4 Postpartum Support

Glucose control of the mother during birth and in the postpartum phase

- In cases of induced birth, the use of short-acting insulins is recommended to achieve improved glucose control.
- The target range for capillary plasma glucose during labor is set between 90 and 140mg/dL (4.4-7.2mmol/L).
- If the maternal nutritional therapy is appropriately adjusted, routine monitoring of maternal blood glucose during labor is not necessary.

Insulin therapy for GDM:

Blood glucose levels for GDM patients on insulin should be measured every two hours, with individual adjustment of time intervals as necessary.

During labor, the need for insulin therapy in GDM cases is rare.

Insulin therapy is discontinued after childbirth.

Postpartum, blood glucose control is maintained by conducting a 4-point daily profile on the second day. Diabetologists should be informed if consistently high values are observed.

The same thresholds as for non-pregnant women apply for blood glucose limits.

Postpartum insulin administration is indicated for blood glucose levels of 200mg/dL (11.1mmol/L) or higher, or in the presence of hyperglycemic symptoms.

Postpartum care for the mother:

- In approximately 13-40% of cases, the glucose tolerance disorder observed during pregnancy does not resolve after childbirth.
- Women who have experienced gestational diabetes mellitus (GDM) face a 7- to 8-fold higher risk of developing diabetes.
- The risk of developing diabetes is particularly elevated in women with pre-conceptional obesity, a positive family history of diabetes mellitus, a higher insulin requirement during GDM, advanced age, and among Asian and black African women.

Postpartum 75 g oral glucose tolerance test (OGTT):

Normal blood glucose levels in the postpartum period are assessed 6-12 weeks after childbirth using a 75 g OGTT, regardless of breastfeeding.

Normal values for the OGTT are determined based on non-pregnancy guidelines established by the World Health Organization (WHO), involving fasting blood glucose measurements and blood glucose levels 2 hours after eating:

Normal range: Fasting < 100mg/dL (5.6mmol/L), 2 hours after eating < 140mg/dL (7.8mmol/L).

Diabetes mellitus: Fasting ≥ 126mg/dL (7.0mmol/L) and/or 2 hours after eating ≥ 200mg/dL (11.1mmol/L).

Impaired fasting glucose (IFG): 100-125mg/dL (5.6-6.9mmol/L).

Impaired glucose tolerance after 2 hours (IGT): 140-199mg/dL (7.8-11.05mmol/L).

The primary determination of HbA1c 6-12 weeks after childbirth is not recommended for diagnostic purposes. Fasting glucose measurement alone is also insufficient.

In cases of impaired glucose tolerance or other risk factors like pre-conception obesity or GDM insulin therapy, women receive comprehensive advice on lifestyle measures to reduce the risk of developing diabetes in the future.

1.4 South Asia guidelines: Chinese Guidelines on Diagnosis and Management of Hyperglycemia in Pregnancy (2023)(Wang, Juan, and Yang 2023)

1.4.1- Diagnosis of GDM

The diagnosis of GDM is determined by a "one-step" 75-gram oral glucose tolerance test (OGTT) conducted between 24 and 28 weeks of gestation. This diagnostic approach entails assessing plasma glucose levels at various time points: fasting, 1 hour, and 2 hours after the OGTT. The established threshold values for plasma glucose are 5.1 mmol/L for fasting, 10.0 mmol/L for 1 hour, and 8.5 mmol/L for 2 hours. If any of these values are equal to or higher than the respective thresholds, the diagnosis of GDM should be confirmed.

1.4.2- Management of GDM

Nutritional therapy

Pregnant women with hyperglycemia in pregnancy (HIP) are advised to regulate their daily calorie intake. In the early stages of gestation, it is recommended that daily caloric intake does not dip below 1600 kcal/day (1 kcal = 4.184 kJ). However, during the middle and late stages of pregnancy, a caloric intake ranging from 1800 to 2200 kcal/day is considered appropriate. In the case of women who are obese prior to pregnancy, it is recommended to reduce their energy intake while ensuring it does not fall below 1600 kcal/day in the first trimester. Subsequently, a moderate increase in energy intake is suggested for the second and third trimesters.

Physical activity

Incorporating consistent physical activity both prior to and during pregnancy can substantially decrease the likelihood of GDM in expectant mothers, particularly in those who are overweight or obese before conceiving. A randomized controlled trial conducted in China revealed that overweight and obese pregnant women experienced a remarkable 45.8% reduction in GDM risk when they engaged in cycling sessions three times per week from the early stages of pregnancy.

Medical therapy

In cases where pregnant women with GDM fail to achieve target blood glucose levels through diet and/or physical activity, or experience starvation ketosis despite dietary control, timely initiation of insulin therapy is recommended.

During pregnancy, the following forms of insulin are considered safe: ultra-rapid-acting insulin, rapid-acting insulin, medium-acting insulin, and long-acting insulin.

The formulation of insulin regimen should be based on blood glucose monitoring results during pregnancy.

Individualization of insulin regimen is crucial and should be guided by each patient's blood glucose monitoring results. Adjustments should follow the principle that every 2-4 units of insulin can reduce blood glucose by 1 mmol/L.

Metformin has demonstrated comparable efficacy and short-term safety to insulin during pregnancy. It can be used as an alternative when pregnant women are unable or unwilling to use insulin. (Grade A)

Although metformin crosses the placental barrier and reaches fetal circulation, no significant adverse effects on offspring have been observed. (Grade B)

1.5 Systematic reviews/ Meta-analysis

Table. Results of Systemic Reviews and Meta-Analyses

Table 1. Results of Systemic Reviews and Meta-Analyses

Study	Author (year)	Primary Objective	Outcomes	Results
1	(Oliveira et al. 2022)	Efficacy of metformin vs Glibenclamide in treatment and control of GDM	Safety and Efficacy: - Weight gain - Risk of caesarian section - Gestational Age at birth Neonatal outcomes: -Birth weight -Neonatal hypoglycemia -risk of Neonatal Intensive Care Unit NICU admissions	-No significant differences in terms of safety and efficacy in the administration of metformin and Glibenclamide - Metformin caused lower neonatal weights, due to its ability to decrease insulin concentration by crossing the placental barrier. - Glibenclamide caused increased birth weight

2	(He et al. 2022)	The efficacy and safety of metformin alone or as an add-on therapy to insulin in pregnancy with GDM	<u>Maternal outcomes</u>: - Weight gain - Risk of caesarian section - Gestational Age at birth <u>Neonatal outcomes</u>: -Birth weight -Neonatal hypoglycemia -risk of Neonatal Intensive Care Unit NICU admissions	-When compared with insulin, Metformin had a much lower level of maternal weight gain, risk of caesarian section and gestational age at birth -When compared with insulin, Metformin significantly decreased the birth weight, the risk of neonatal hypoglycemia as well as the risk of NICU admissions

1.6 Secondary and tertiary resources

The international guidelines detailed above being newly updated (as recently as March 2023), a detailed search of secondary and tertiary resources for additional guidelines, such as Google Scholar, the Ovid Health Technology Assessment Database, the National Institute for Health and Care Research Journals Library, and UpToDate did not yield any additional data that hasn't already been described.

2.0 Drug Therapy

2.1 Insulin

2.1.1Insulin Aspart

(Jacobs et al. n.d.)(Insulin Aspart Anatomic Therapeutic Chemical (ATC) Classification 2023)(Your responsibility 2023)

SCIENTIFIC NAME - INSULIN ASPART	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes off label
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	Z79. 4
Drug Class	Rapid acting insulin analogue
ATC Code	A10AB05
Pharmacological Class (ASHP)	Rapid-acting Insulins
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Subcutaneous use
Dose (Adult) [DDD]*	N.A / Individualize the dosage of Insulin Aspart based on the patient's metabolic needs, blood glucose monitoring results and glycemic control goal

Maximum Daily Dose Adults*	Total daily insulin requirement is generally between 0.4 to 1 unit/kg/day (current pregnant weight)
Dose (pediatrics)	Insulin doses should be individualized based on patient needs; changes in physical activity, meal patterns, acute illness, or with changes in renal or hepatic function.
Maximum Daily Dose Pediatrics*	Total daily insulin requirement is generally between 0.4 to 1 unit/kg/day
Adjustment	**Dosing: Altered Kidney Function:** no dosage adjustments needed. **Dosing: Hepatic Impairment:** no dosage adjustments needed.
Prescribing edits*	ST, MD, Age
AGE (Age Edit): Not to be given to patients less than 6 months old	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians experienced in diabetes mellitus therapy and management should prescribe insulin Aspart.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Recommended as first-line treatment for GDM.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	

SAFETY	
Main Adverse Drug Reactions **(most common and most serious)**	**Most common:** Chest pain, Onychomycosis, dermatological disorder (5%), allergic skin rash, Vomiting, nausea, abdominal pain, diarrhea, Urinary tract infection, Hypersensitivity reaction **Most serious**: Severe hypoglycemia, Antibody development, Headache Hyporeflexia, Nasopharyngitis, viral respiratory tract infection, Accidental injury
Drug Interactions*	**Category X**: • Macimorelin • Rosiglitazone
Special Population	Hospitalized patients
Pregnancy	Rapid-acting insulin aspart is one of the preferred insulins for use in pregnancy
Lactation	Insulin Aspart is present in breast milk. Insulin Aspart is not systemically absorbed via breastmilk but may provide local benefits to the infant GI tract.
Contraindications	Known hypersensitivity to the product or its components.
Monitoring Requirements	Diabetes mellitus: Blood glucose (individualize frequency based on treatment regimen, hypoglycemia risk, and other patient-specific factors: electrolytes; renal function; hepatic function; weight. • GDM: Blood glucose 4 times daily (1 fasting and 3 postprandial) until

	glycemic targets are met, then as appropriate. • Hospitalized patients: In patients who are eating, monitor blood glucose before meals and at bedtime. HbA1C: Monitor at least twice yearly in patients who have stable glycemic control and are meeting treatment goals Diabetic ketoacidosis: Frequent monitoring (every 1 to 4 hours) of serum electrolytes
Precautions	-Glycemic control: The most common adverse effect of insulin is hypoglycemia -Hypersensitivity -Hypokalemia: If left untreated, it may result in respiratory paralysis, ventricular arrhythmia or death **Disease-related concerns:** • Bariatric surgery: – Type 2 diabetes, hypoglycemia -Weight gain: Insulin therapy is preferred if antidiabetic therapy is required during the perioperative period • Cardiac disease: Concurrent use with peroxisome proliferator-activated receptor (PPAR)-gamma agonists, including thiazolidinediones, may cause dose-related fluid retention and lead to or exacerbate heart failure -Hepatic impairment: Risk of hypoglycemia -Renal impairment: Risk of hypoglycemia -Patient education: Diabetes self-management education is essential to maximize the effectiveness of therapy.

Black Box Warning	**N.A**
REMS*	**N.A**

Health Technology Assessment (HTA):

The table below lists the HTA reviews and recommendations of GDM treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Aspart.**

Medication	Agency	Date – HTA Recommendation
Aspart	NICE	2023- The majority of pregnant women with GDM will need insulin or oral hypoglycemic agent -Rapid-acting insulin analogues (such as aspart and lispro) do not have any adverse effect on pregnancy or the baby's health.
	CADTH(COMPUS Optimal Therapy Recommendations for the Prescribing and Use of Insulin Analogues À l'appui des décisions éclairées 2009)	When a bolus insulin is required, human insulin or rapid-acting insulin analogues (insulin aspart and insulin lispro) are recommended
	HAS	Insulin use is recommended only in case of severe hypergylcemia
	IQWIG	No evidence available of a superiority of rapid-acting insulin analogues over

		human insulin in the treatment of adult patients with diabetes mellitus type 1
	PBAC(PBAC-insulin-aspart-psd-nov-2021 n.d.)	cost-effectiveness of Truvelog and Truvelog Solostar would be acceptable if they were cost-minimised to NovoRapid Penfill and NovoRapid Flexpen respectively

The use of Insulin Aspart is recommended as first-line therapy for the management of GDM. Its use is backed by numerous HTA recommendation supporting its benefit from an economic standpoint.

2.1.2 Insulin Lispro

(Insulin Lispro 2023)(Your responsibility 2023)

SCIENTIFIC NAME- INSULIN LISPRO	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	Z79. 84
Drug Class	Insulin
ATC Code	A10AB04
Pharmacological Class (ASHP)	rapid acting human insulin analog
DRUG INFORMATION	
Dosage Form	Solution for injection

Route of Administration	Subcutaneous use
Dose (Adult) [DDD]*	N.A / Individualize the dosage of Insulin Aspart based on the patient's metabolic needs, blood glucose monitoring results and glycemic control goal
Maximum Daily Dose Adults*	Total daily insulin requirement is generally between 0.4 to 1 unit/kg/day (current pregnant weight)
Dose (pediatrics)	Insulin doses should be individualized based on patient needs; changes in physical activity, meal patterns, acute illness, or with changes in renal or hepatic function.
Maximum Daily Dose Pediatrics*	Total daily insulin requirement is generally between 0.4 to 1 unit/kg/day
Adjustment	**Dosing: Altered Kidney Function:** no dosage adjustments needed. **Dosing: Hepatic Impairment:** no dosage adjustments needed.
Prescribing edits*	ST, MD , Age
AGE (Age Edit): Not to be given to patients less than 6 months old	
CU (Concurrent Use Edit): N/A.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians experienced in diabetes mellitus therapy and management should prescribe Insulin Lispro.	

PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Recommended as first-line treatment for GDM.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** , Infusion-site reaction, Headache, Cough, flu-like symptoms, nasopharyngitis, pharyngitis, rhinitis **Most serious**: Severe hypoglycemia, Antibody development
Drug Interactions*	**Category X**: • Macimorelin • Rosiglitazone
Special Population	Hospitalized patients
Pregnancy	Insulin lispro is one of the preferred insulins for use in pregnancy
Lactation	Insulin Lispro is present in breast milk. Insulin Lispro is not systemically absorbed via breastmilk but may provide local benefits to the infant GI tract
Contraindications	Known hypersensitivity to the product or its components
Monitoring Requirements	Diabetes mellitus: Blood glucose (individualize frequency based on treatment regimen,

	hypoglycemia risk, and other patient-specific factors: electrolytes; renal function; hepatic function; weight. • GDM: Blood glucose 4 times daily (1 fasting and 3 postprandial) until glycemic targets are met, then as appropriate. • Hospitalized patients: In patients who are eating, monitor blood glucose before meals and at bedtime. HbA1C: Monitor at least twice yearly in patients who have stable glycemic control and are meeting treatment goals Diabetic ketoacidosis: Frequent monitoring (every 1 to 4 hours) of serum electrolytes
Precautions	-Glycemic control: The most common adverse effect of insulin is hypoglycemia -Hypersensitivity -Hypokalemia: If left untreated, it may result in respiratory paralysis, ventricular arrhythmia or death **Disease-related concerns:** • Bariatric surgery: – Type 2 diabetes, hypoglycemia -Weight gain: Insulin therapy is preferred if antidiabetic therapy is required during the perioperative period

	• Cardiac disease: Concurrent use with peroxisome proliferator-activated receptor (PPAR)-gamma agonists, including thiazolidinediones, may cause dose-related fluid retention and lead to or exacerbate heart failure -Hepatic impairment: Risk of hypoglycemia -Renal impairment: Risk of hypoglycemia -Patient education: Diabetes self-management education is essential to maximize the effectiveness of therapy.
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA):

The table below lists the HTA reviews and recommendations of GDM treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Lispro.**

Medication	Agency	Date – HTA Recommendation
Lispro	NICE	Rapid-acting insulin analogues (such as aspart and lispro) do not have any adverse effect on pregnancy or the baby's health.

	CADTH	N/A
	HAS	Insulin use is recommended only in case of severe hypergylcemia
	IQWIG	No evidence available of a superiority of rapid-acting insulin analogues over human insulin in the treatment of adult patients with diabetes mellitus type 1
	PBAC	N/A

The use of Lispro is recommended as off-label for the management of GDM.

2.1.3 Insulin Detemir

(Detemir and English 2023)(SUMMARY OF PRODUCT CHARACTERISTICS 1 NAME OF THE MEDICINAL PRODUCT Levemir Penfill 100 units/ml solution for injection in cartridge. 2 QUALITATIVE AND QUANTITATIVE COMPOSITION n.d.)

SCIENTIFIC NAME - INSULIN DETEMIR	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	**Z79.4**
Drug Class	Long-Acting Insulin
ATC Code	A10AE05
Pharmacological Class (ASHP)	man-made long-acting insulin

DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Subcutaneous use
Dose (Adult) [DDD]*	N.A / Individualize the dosage of Insulin Detemir based on the patient's metabolic needs, blood glucose monitoring results and glycemic control goal
Maximum Daily Dose Adults*	Total daily insulin requirement is generally between 0.4 to 1 unit/kg/day (current pregnant weight)
Dose (pediatrics)	Insulin doses should be individualized based on patient needs; changes in physical activity, meal patterns, acute illness, or with changes in renal or hepatic function.
Maximum Daily Dose Pediatrics*	Total daily insulin requirement is generally between 0.4 to 1 unit/kg/day
Adjustment	**Dosing: Altered Kidney Function:** no dosage adjustments needed. **Dosing: Hepatic Impairment:** no dosage adjustments needed.
Prescribing edits*	ST, MD, Age
AGE (Age Edit): Not to be given to patients less than 6 months old	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	

MD (Physician Specialty Edit): Only physicians experienced in diabetes mellitus therapy and management should prescribe insulin Detemir.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): The use of Detemir is recommended as second-line therapy for the management of GDM when NPH insulin is not adequate.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions **(most common and most serious)**	**Most common:** Nausea, vomiting, Viral infection, Back pain, Bronchitis, cough, rhinitis, Fever **Most serious**: Hypoglycemia, Abdominal pain, gastroenteritis, Headache, Flu-like symptoms
Drug Interactions*	**Category X**: • Macimorelin • Rosiglitazone
Special Population	**Hospitalized patients**
Pregnancy	Insulin detemir can be detected in cord blood.
Lactation	
Contraindications	Known hypersensitivity to the product or its components
Monitoring Requirements	Diabetes mellitus: Blood glucose (individualize frequency based on

	treatment regimen,hypoglycemia risk, and other patient-specific factors • Gestational diabetes mellitus: Blood glucose 4 times daily (1 fasting and 3 postprandial) until well controlled Hospitalized patients: monitor blood glucose every 4 to 6 hours HbA 1C: Monitor at least twice yearly in patients who have stable glycemic control, monitor quarterly in patients in whom treatment goals have not been met.
Precautions	-Glycemic control: The most common adverse effect of insulin is hypoglycemia -Hypersensitivity -Hypokalemia: If left untreated, it may result in respiratory paralysis, ventricular arrhythmia or death **Disease-related concerns:** • Bariatric surgery: – Type 2 diabetes, hypoglycemia -Weight gain: Insulin therapy is preferred if antidiabetic therapy is required during the perioperative period • Cardiac disease: Concurrent use with peroxisome proliferator-activated receptor (PPAR)-gamma agonists, including thiazolidinediones, may cause dose-related fluid retention and lead to or exacerbate heart failure -Hepatic impairment: Risk of hypoglycemia

	-Renal impairment: Risk of hypoglycemia -Patient education: Diabetes self-management education is essential to maximize the effectiveness of therapy. Dosage forms specific issues: • Multiple dose injection pens: pen-shaped injection devices should never be used for more than one person/ risk of infection. Other warnings/precautions: • Administration: Insulin detemir, although a clear solution, is NOT intended for IV or IM administration. • Dosage adjustments: The duration of action of insulin detemir is dose-dependent • Patient education: Diabetes self-management education is essential to maximize the effectiveness of therapy.
Black Box Warning	Low blood sugar warning: Insulin detemir can cause hypoglycemia
REMS*	N.A

Health Technology Assessment (HTA):(Your responsibility 2023)

The table below lists the HTA reviews and recommendations of GDM treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable.

The recommendations are for Detemir.

Medication	Agency	Date – HTA Recommendation
Detemir	NICE	-NPH insulin is the first choice for long-acting insulin during pregnancy -Long-acting insulin analogues use is considered off-label -For women with diabetes who have achieved satisfactory blood glucose control prior to pregnancy, it may be considered to maintain treatment with long-acting insulin analogues (such as insulin detemir)
	CADTH	N/A
	HAS	Insulin use is recommended only in case of severe hyperglycemia
	IQWIG	N/A
	PBAC	N/A

The use of Detemir is recommended as second-line therapy for the management of GDM when NPH insulin is not adequate.

2.2 Metformin

(Agent n.d.)(SFDA-metformin n.d.)

SCIENTIFIC NAME- MEFTORMIN	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	No not approved for GDM

EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	**Z79.84**
Drug Class	Antidiabetic agent
Drug Sub-class	Biguanide
ATC Code	A10BA02
Pharmacological Class (ASHP)	Non-sulfonylureas
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	GDM: Immediate release**: Oral:** Initial: 500 mg once or twice daily; increase dosage to meet glycemic targets, typically over 1 to 2 weeks
Maximum Daily Dose Adults*	up to a maximum of 2 to 2.5 g daily in 2 to 3 divided doses for GDM
Dose (pediatrics)	For pediatric patients 10 years of age and older is 500 mg orally twice a day, given with meals.
Maximum Daily Dose Pediatrics*	up to a maximum of 2 to 2.5 g daily in 2 to 3 divided doses
Adjustment	**Altered kidney function:** eGFR ≥60 mL/minute/1.73m: No dosage adjustment necessary eGFR >45 to <60 mL/minute/1.73m: No dosage adjustment necessary. Metformin plasma concentrations

	may be higher compared to patients with an eGFR ≥60 mL/minute/1.73m; increase monitoring of renal function (every 3 to 6 months) eGFR 30 to 45 mL/minute/1.73m: Initiation of therapy: Use generally not recommended Hepatic impairment prior to treatment: **Child-Turcotte-Pugh class A:** No dosage adjustment necessary **Child-Turcotte-Pugh class B:** 500 mg once daily; may increase by ≤500 mg/day **Child-Turcotte-Pugh class C**: Avoid use Hepatic impairment during treatment: **Progression from baseline to Child-Turcotte-Pugh class A:** No dosage adjustment necessary. **Progression from Child-Turcotte-Pugh class A to B:** No dosage adjustment necessary; however, a dose reduction may be required in patients at risk for lactic acid–producing events **Progression from Child-Turcotte-Pugh class B to C:** If tolerating with appropriate clinical endpoints, use with caution **Metformin-induced hepatotoxicity:** Permanently discontinue metformin therapy

Prescribing edits*	ST, AGE, MD
AGE (Age Edit): Metformin may be prescribed for pediatric patients who are 10 years of age or older.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians experienced in diabetes mellitus therapy and management should prescribe Metformin.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Metformin is recommended as a second line therapy for managing GDM in patients who are unable to safely or effectively utilize insulin.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** diarrhea, nausea, flatulence, dyspepsia, vomiting, and abdominal pain **Most serious**: Lactic acidosis, Vitamin B12 deficiency, Hemolytic anemia, Hepatic injury (cholestatic, hepatocellular, and mixed) Hypersensitivity: Fixed drug eruption, Encephalopathy
Drug Interactions*	**Category X**: Alcohol (Ethyl)

	Pacritinib
Special Population	**N.A**
Pregnancy	Metformin crosses the placenta, resulting in concentrations that may be similar to or even higher than those observed in the mother's bloodstream
Lactation	Metformin is present in breast milk Breastfeeding is considered acceptable when the Relative Infant Dose RID is <10%
Contraindications	Known hypersensitivity to the product or its components Canadian labeling: Additional contraindications (not in US labeling): End-stage renal disease, patients on dialysis, or when renal function is unknown
Monitoring Requirements	-Urine for glucose and ketones, plasma glucose (individualize frequency based on treatment regimen, hypoglycemia risk, and other patient-specific factors; some patients may be candidates for continuous glucose monitoring -Monitor renal function (eGFR) prior to therapy initiation and at least annually or at least every 3 to 6 months if eGFR is <60mL/minute/1.73 m or at least every 1 to 3 months in patients with hepatic impairment -HbA1C : Monitor at least twice yearly in patients who have stable glycemic control and are meeting treatment goals; monitor quarterly in patients in

	whom treatment goals have not been met, or with therapy change
Precautions	**Disease-related concerns:** • Bariatric surgery: Altered absorption: Use IR tablets or solution after surgery **Hepatic impairment**: Use cautiously in patients at risk for lactic acidosis **Renal impairment**: Metformin is substantially excreted by the kidney; dosing adjustments may be required. **Stress-related states:** It may be necessary to discontinue metformin and administer insulin if the patient is exposed to stress **Dosage form specific issues:** -ER tablet: Insoluble tablet shell (Glumetza 1,000 mg tablet) may remain intact and be visible in the stool -Propylene glycol: Some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated with hyperosmolality, lactic acidosis, seizures, and respiratory depression **Appropriate use**: Not indicated for use in patients with type 1 diabetes mellitus or with diabetic ketoacidosis.

	Iodinated contrast: Administration of iodinated contrast agents has been associated with postcontrast acute kidney injury **Surgical procedures**: Metformin-containing products should be withheld the day of surgery; restart after renal function is stable
Black Box Warning	• Lactic acidosis
REMS*	N.A

Health Technology Assessment (HTA):

The table below lists the HTA reviews and recommendations of GDM treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for metformin.**

Medication	Agency	Date – HTA Recommendation
Metformin	NICE	-If dietary and exercise modifications within a span of 1 to 2 weeks did not help to lower blood glucose level, metformin can be prescribed -During the preconception period and throughout pregnancy, women with GDM may receive recommendations to incorporate metformin as a supplementary or potential substitute for insulin.
	CADTH	N.A /Data available for diabetes type 2
	HAS	N/A

	IQWIG	N/A
	PBAC	N/A

Metformin is recommended as a second line therapy for managing GDM in patients who are unable to safely or effectively utilize insulin.

2.3 Glibenclamide

(Agent n.d.)(WHO Vision for Medicines Safety No country left behind: worldwide pharmacovigilance for safer medicines, safer patients 2019)

SCIENTIFIC NAME- GLIBENCLAMIDE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	Z79. 84
Drug Class	Antidiabetic Agent, Sulfonylurea
ATC Code	**A10BB01**
Pharmacological Class (ASHP)	Sulfonylureas
DRUG INFORMATION	
Dosage Form	**Tablet**
Route of Administration	Oral use
Dose (Adult) [DDD]*	**Oral:**

	-Initial: 1.25 to 5 mg once daily administered with the first main meal; in patients whose glycemic levels are close to goal, use lower initial doses (eg, 1.25 to 2.5 mg once daily) to reduce the risk of hypoglycemia **-Maintenance dose**: 2.5 to 10 mg/day in 1 or 2 divided doses
Maximum Daily Dose Adults*	**20mg/day**
Dose (pediatrics)	**N/A**
Maximum Daily Dose Pediatrics*	**N/A**
Adjustment	**Adjustment for renal impairment:** eGFR ≥60 mL/minute/1.73m: No dosage adjustment required eGFR <60 mL/minute/1.73m: Avoid use risk of hypoglycemia **Adjustment for hepatic impairment:** No dosage adjustment required
Prescribing edits*	ST, MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians experienced in diabetes mellitus therapy and management should prescribe Glibenclamide.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): The use of Glibenclamide is recommended as second-line therapy for the management of GDM.	

EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions **(most common and most serious)**	**Most common:** Epigastric fullness, heartburn, nausea, Diuresis, weight gain **Most serious**: Hypersensitivity, Hypoglycemia, hyponatremia, Hemolytic anemia, Cholestatic jaundice, hepatic failure, hepatitis Disulfiram-like reaction
Drug Interactions*	**Category X**: • Aminolevulinic Acid (Systemic) • Bosentan • Leniolisib • Mecamylamine • Mitiglinide
Special Population	-Hospitalized patients -Older adult: avoid use in older adults due to potential for severe hypoglycemia
Pregnancy	Glibenclamide crosses the placenta, Glibenclamide should not be recommended as an initial alternative therapy
Lactation	potential for hypoglycemia in the breastfeeding infant
Contraindications	-Hypersensitivity to Glibenclamide or any component of the formulation; type 1 diabetes mellitus or diabetic ketoacidosis, with or without coma; concomitant use with bosentan.

	-Canadian labeling: Additional contraindications (not in US labeling): Hypersensitivity to any sulfonylurea or sulfonamide; diabetic precoma or coma, stress conditions; liver disease or frank jaundice; renal impairment; pregnancy; breastfeeding.
Monitoring Requirements	-Signs and symptoms of hypoglycemia, urine glucose test, fasting blood glucose. -HbA1C : Monitor at least twice yearly in patients who have stable glycemic control; monitor quarterly in patients in whom treatment goals have not been met
Precautions	**Concerns related to adverse reactions:** • **Cardiovascular mortality:** In patients with established atherosclerotic cardiovascular disease (ASCVD), other agents are preferred -Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia - Sulfonamide ("sulfa") allergy **Disease-related concerns**: • Bariatric surgery: – Altered absorption: Use IR formulations after surgery to minimize the potential effects of bypassing stomach – Hypoglycemia: Use an antidiabetic agent without the potential for hypoglycemia

	– Weight gain: Consider alternative therapy after gastric bypass, sleeve gastrectomy, and gastric banding -Glucose-6-phosphate dehydrogenase deficiency: increased risk of sulfonylurea-induced hemolytic anemia -Renal impairment: not recommended in chronic kidney disease - Stress-related states: discontinue therapy and administer insulin if the patient is exposed to stress - **Special populations:** • Older adult: avoid use in older adults due to potential for severe hypoglycemia **Dosage form specific issues**: • Glibenclamide tablet formulations: Micronized Glibenclamide tablets are not bioequivalent to conventional Glibenclamidetablets; retitration should occur if patients are being transferred to a different Glibenclamide formulation or from other hypoglycemic agents. Other warnings/precautions: • Appropriate use: Not for use in patients with diabetic ketoacidosis (DKA) or patients with type 1 diabetes mellitus. • Hospitalized patients: Consider temporary discontinuation of noninsulin antidiabetic agents and initiation or continuation of insulin therapy during hospitalization
Black Box Warning	Lactic acidosis
REMS*	**N.A**

Health Technology Assessment (HTA):

The table below lists the HTA reviews and recommendations of GDM treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for** Glibenclamide.

Medication	Agency	Date – HTA Recommendation
Glibenclamide	NICE	N.A
	CADTH	CADTH considers sulfonylureas (Glibenclamide) as the most cost-effective option for second-line therapy of Diabetes but does not recommend Glibenclamide for GDM
	HAS	N.A
	IQWIG	2009. Use of Glibenclamide is recommended in GDM
	PBAC	**N.A**

The use of Glibenclamide is recommended as second-line therapy for the management of GDM.

3.0 Key Recommendations Synthesis

- GDM is increasingly prevalent worldwide, primarily influenced by epidemiological factors. These factors include the rising rates of obesity among women of reproductive age, the advancing maternal age during pregnancy, and the adoption of the updated criteria and diagnostic approaches for GDM by IADPSG. (Pilszyk et al. 2022)

- The absence of a global consensus regarding GDM diagnosis reflects its intricate historical development and the practical considerations related to antenatal resources, as GDM has now become one of the most prevalent complications during pregnancy. (**Figure 11)**

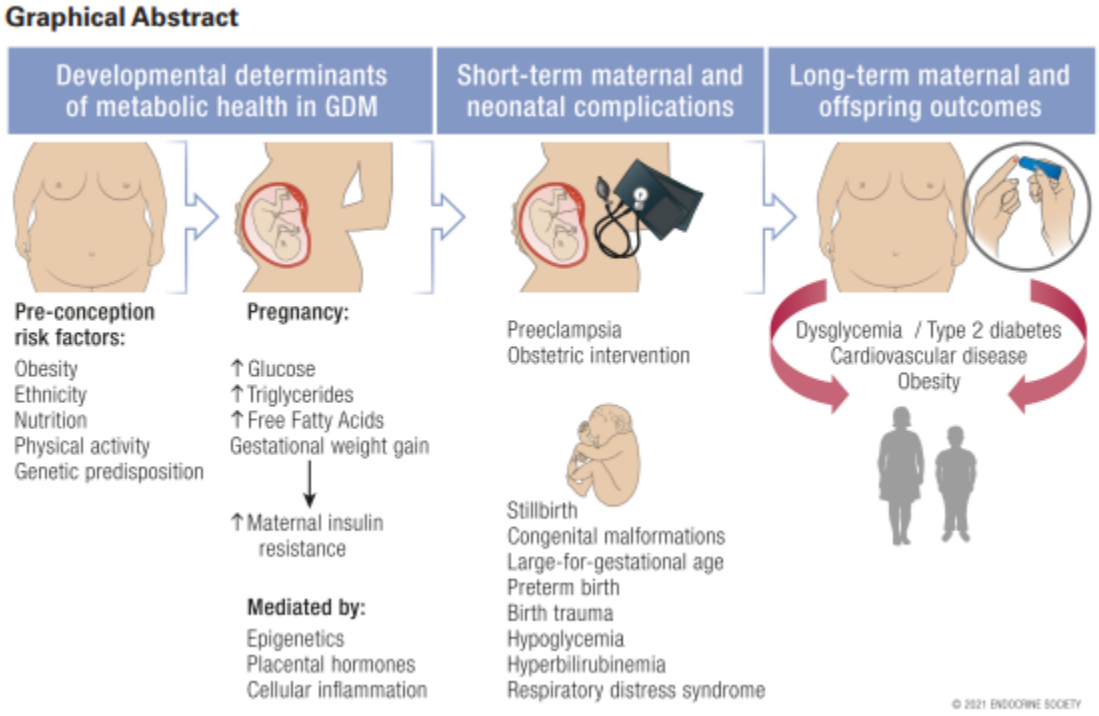


Figure 10. GDM Physiopathology, (Sweeting et al. 2022)

- The primary treatment strategy for GDM typically involves making **dietary adjustments and engaging in regular exercise** (figure 12). If these methods do not effectively achieve the desired blood sugar levels, **insulins are usually recommended as first line therapy**. Insulin analog, which closely resemble the body's natural insulin, are preferred over human insulin because they carry a lower risk of hypoglycemia and offer the potential for improved glycemic control.
- During pregnancy, **insulin lispro, aspart, NPH and detemir are approved for use,** while **insulin glargine and insulin degludec**, though not officially

approved, may be safe and effective based on data from patients with preexisting diabetes.

- Additionally, **glibenclamide and metformin**, which are oral hypoglycemic agents, have been deemed safe and effective during pregnancy, usually recommended as second line option and should not be offered as first line
- Figure 12 below illustrates GDM management while summarizing therapeutic options within treatment pathway.

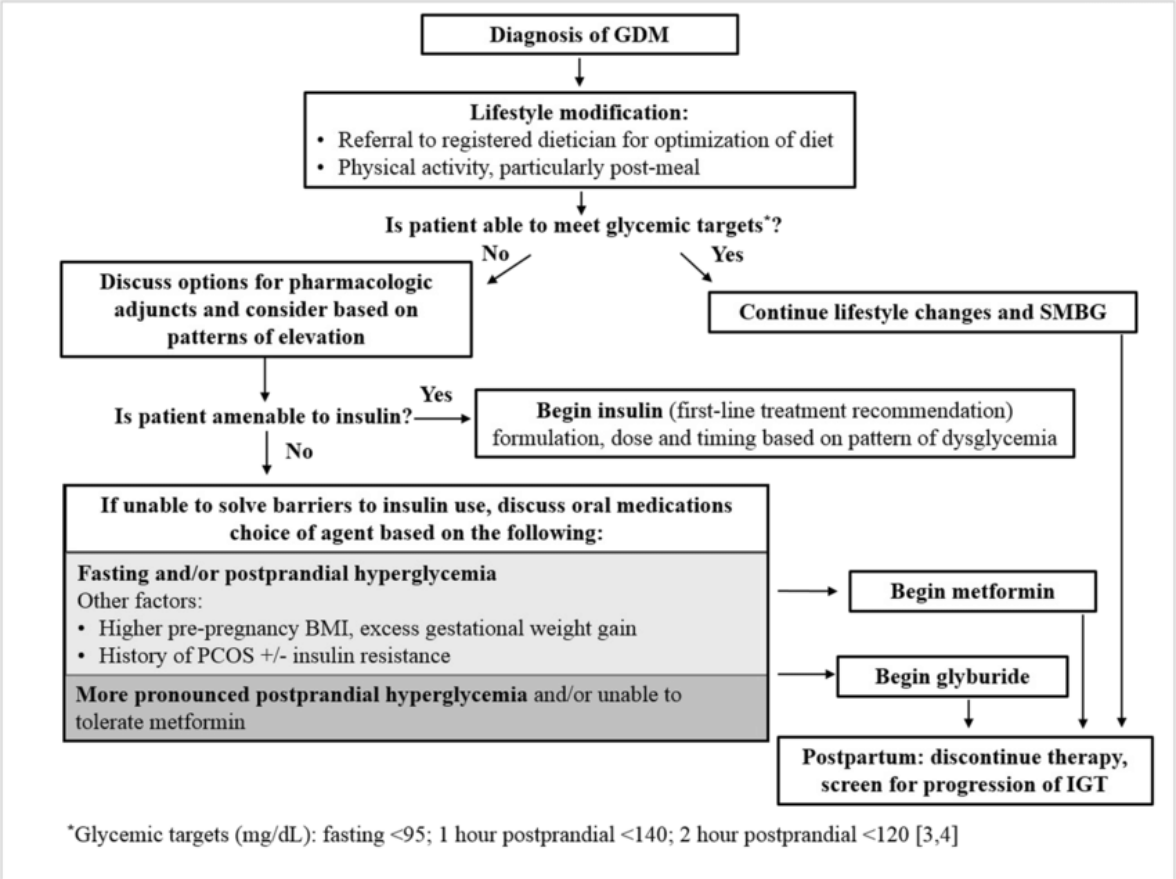


Figure 11. Management of GDM, (Blair, Rosenberg, and Palermo 2019)

4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of gestational diabetes mellitus.

These recommendations should be used to support and not supplant decisions in individual patient management.

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SUMMARY OF PRODUCT CHARACTERISTICS 1 NAME OF THE MEDICINAL PRODUCT Levemir Penfill 100 Units/Ml Solution for Injection in Cartridge. 2 QUALITATIVE AND QUANTITATIVE COMPOSITION.

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6.0 Appendices

Appendix A- Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B- Level of Evidence Description

I- Level of Evidence Adopted:

Grade of research	
A	Strongly recommend; good evidence
B	Recommend; at least fair evidence
C	No recommendation for or against; balance of benefits and harms too close to justify a recommendation
D	Recommend against; fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; evidence is lacking or of poor quality; benefits and harms cannot be determined
Level of evidence	

Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C- PubMed Search

The following is the result of the PubMed search conducted for gestational diabetes mellitus guideline search:

Query	Sort By	Filters	Search Details	Results
((((((Diabetes, Gestational[MeSH Terms]) OR (Diabetes, Pregnancy-Induced[Title/Abstract])) OR (Diabetes, Pregnancy Induced[Title/Abstract])) OR (Pregnancy-Induced Diabetes[Title/Abstract])) OR (Gestational Diabetes[Title/Abstract])) OR (Diabetes Mellitus, Gestational[Title/Abstract])) OR (Gestational Diabetes Mellitus[Title/Abstract])			"diabetes, gestational"[MeSH Terms] OR "diabetes pregnancy induced"[Title/Abstract] OR "diabetes pregnancy induced"[Title/Abstract] OR "pregnancy induced diabetes"[Title/Abstract] OR "gestational diabetes"[Title/Abstract] OR "diabetes mellitus gestational"[Title/Abstract] OR "gestational diabetes mellitus"[Title/Abstract]	25,137

Appendix D- Treatment Algorithm

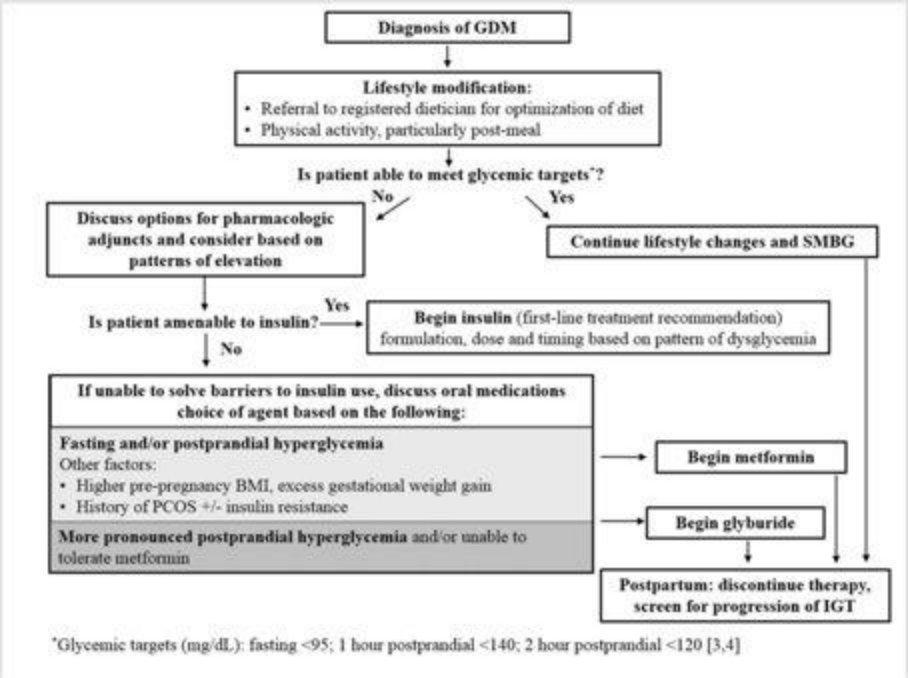

Figure 1: Management of gestational diabetes mellitus