

Efficacy and safety of antidiabetics agents in gestational diabetes mellitus (GDM): a literature review

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ABSTRACT

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One of the most common metabolic diseases during pregnancy period is gestational diabetes mellitus (GDM). It is associated with several perinatal complications, especially in those who have risk factors such as obesity, polycystic ovary syndrome, and a family history of type 2 diabetes mellitus (DM). Some research has shown that physical exercise and medical nutrition treatment can give beneficial effects to control glycemic and body weight for GDM affected women. Furthermore, pharmacological agents such as insulin and a specific oral antidiabetic can be prescribed safely during pregnancy to decrease maternal glucose blood. Therapy of GDM is needed to control blood for the wellness of the patient during and after the pregnancy. The main treatment therapy for GDM is lifestyle modification, which includes medical nutritional therapy and daily physical exercise. In the special case of disorder glucose level, drug therapy will be given to the patient. Insulin is the chosen drug because it is safe and does not cross the placenta. It is the gold standard pharmacological agent for GDM treatment. However, it still has some disadvantages such as the difficulties of how to use it, how many doses must be given, and the price that tends to be expensive. Consequently, the alternative drug may have to substitute it. Insulin can be substituted by metformin and glyburide (glibenclamide) in the form of oral antidiabetic. They are equal in terms of efficacy and safety compare to insulin as a treatment for GDM. Besides, they are also cheaper, and easy to use.

ABSTRAK

Diabetes melitus pada kehamilan (DMK) merupakan salah satu penyakit metabolik kehamilan yang paling umum, berhubungan dengan beberapa komplikasi perinatal, terutama yang memiliki faktor risiko seperti obesitas, sindrom ovarium polikistik, dan riwayat keluarga dengan diabetes melitus (DM) tipe 2. Beberapa penelitian telah menunjukkan efek yang bermanfaat dari olahraga dan terapi nutrisi medis terhadap kontrol glikemik dan berat badan pada wanita yang terkena GDM. Selain itu, agen farmakologis, seperti insulin dan agen anti-diabetik oral tertentu dapat diberikan dengan aman selama kehamilan, menurunkan glukosa darah maternal dan, dengan demikian, berisiko terhadap perinatal. Terapi GDM diperlukan untuk mengontrol kadar gula darah karena akan meningkatkan risiko baik selama kehamilan maupun setelah kehamilan. Modifikasi gaya hidup merupakan tatalaksana awal GDM yang meliputi terapi nutrisi medis dan latihan fisik harian. Jika kadar glukosa tidak terkontrol dengan modifikasi gaya hidup, maka perlu diberikan terapi obat. Insulin menjadi obat pilihan karena relatif aman dan tidak melewati plasenta. Walaupun insulin merupakan agen farmakologis unggulan untuk pengobatan GDM, namun terdapat kesulitan dalam penggunaan insulin antara lain cara penggunaannya, dosis yang diberikan, dan harga yang cenderung mahal. Oleh karena itu, diberikan alternatif berupa antidiabetik oral, seperti metformin dan gliburid (glibenklamid) karena cenderung lebih murah, mudah digunakan, dan berpotensi meningkatkan kepatuhan pasien. Kedua agen tersebut dapat menjadi alternatif, sebab menunjukkan kesetaraan dalam aspek efikasi dan keamanannya jika dibandingkan dengan insulin sebagai pengobatan GDM.

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INTRODUCTION

Gestational diabetes mellitus (GDM) is a common disease characterized by glucose intolerance caused by insulin resistance and the inability of pancreatic β -cells to compensate for the increase in insulin resistance that occurs during pregnancy.¹⁻³ American Diabetes Association (ADA) defines GDM as the type of carbohydrate metabolism impairment that occurs after the first trimester of pregnancy and it is not pre-existing diabetes.⁴ Gestational diabetes mellitus is associated with a high risk of maternal and fetal/neonatal complications which is commonly encountered during pregnancy that can be experienced by almost 15% of pregnant women worldwide.² Uncontrolled GDM can cause several complications such as the increased risk of macrosomia, neonatal hypoglycemia, hypertension in pregnancy, idiopathic respiratory distress syndrome, hyperbilirubinemia, and even dead infant.^{2,3,5}

The prevalence of GDM has increased in recent years along with the increase in the incidence of diabetes mellitus (DM).⁶ From the GDM prevalence, shows considerable heterogeneity among studies, as it depends on a wide spectrum of factors, including ethnicity, study design, methodology, and country. In addition, GDM prevalence varies according to the criteria applied for its definition.^{7,8}

It is proven that GDM treatment reduces the risk of gestational and perinatal complications.^{9,10} The multidisciplinary approach includes lifestyle modifications (nutritional modifications and physical exercise) besides pharmacological treatment and seems to be more effective than the standard care (diet, pharmacological therapy).^{4,11} Lifestyle modifications, which include medical nutrition therapy and daily exercise, are considered the primary therapeutic strategy for GDM.¹²⁻¹⁴ They are associated with lower weight gain during pregnancy, thus improving

glycemic control and reducing the risk of complications in both uncomplicated and GDM pregnancies.^{11,15,16} Exercise in pregnancy, on top of preventing adverse maternal and fetal complications, provides a long-term improvement in cardiovascular fitness.¹⁷ Women who do not achieve the glycemic therapeutic goals with lifestyle modifications only have to be additionally treated with pharmacological agents. Almost 30% of pregnant women require drug therapy for GDM.⁵ The gold standard is insulin therapy, with oral antidiabetic agents, such as metformin and glyburide (glibenclamide).¹² The beneficial effect of multidisciplinary treatment of GDM can be partly attributed to an increase in insulin sensitivity caused by metformin and physical exercise and to a direct effect on adipose tissue by all the therapeutic components.¹⁸

The main purpose of this article was to compare the options available to treat DM during the period of pregnancy. Our main concerns were the safety, whether or not the drugs potentially cause harm to fetus/neonates and pregnant mothers; and the efficacy of each treatment.

DISCUSSION

Gestational diabetes mellitus (GDM)

A normal pregnancy is usually identified by pancreatic β -cell hyperplasia resulting in higher fasting and postprandial insulin levels. In pregnant women, the increased secretion of placental hormones leads to increasing insulin resistance throughout the third trimester. In case of a condition of glucose intolerance, which may occur during pregnancy can be defined as GDM. Gestational diabetes mellitus occurs when β -cell is insufficient in overcoming insulin resistance.¹⁹ The incidence of GDM around the world is ranged from 1% to > 30%. However, this result could not be verified due to the lack of data and consensus on GDM diagnosis criteria. The Middle East and Northern Africa have the highest GDM

prevalence of all regions, with a median of 15.2%, followed by Southeast Asia with a median of 15%, western Pacific with a median of 10.3%, Central and Southern America with a median of 11.2%, Sub-Saharan Africa with a median of 10.8%, and Northern America and the Caribbean with a median of 7.0%. The lowest prevalence of GDM is observed in Europe (median 6.1%) although there were many variabilities in median GDM calculations.²⁰

Pathophysiology

During a healthy pregnancy, a woman will increase the production of basal endogenous glucose production (mainly hepatic) by 30%, to meet their fasting energy needs. An increase in plasma volume in early pregnancy and the increased glucose utilization led to decreasing circulating fasting glucose concentrations. Peripheral insulin sensitivity (the ability of insulin to increase glucose uptake in skeletal muscle and adipose tissue) decreases by 50% near the end of gestation. Women with normal glucose tolerance will have their insulin secretion increased between 2-3-fold in response to decreased insulin sensitivity which maintains blood glucose level.²¹

There is evidence of decreased peripheral insulin sensitivity before conception in women who are normoglycemic before pregnancy but go on to develop GDM in late gestation.²² These women initially adaptively maintain normoglycemia in early pregnancy because their β -cells increase their insulin response. During late pregnancy, however, insulin resistance increases and the response becomes inadequate. This defect in β -cell function exists before pregnancy in most cases but only clinically manifests with the increased insulin resistance of pregnancy, resulting in hyperglycemia.²³ In non-pregnant women with normal

glucose, the binding of insulin to the cell surface receptor in peripheral tissues such as skeletal muscle, results in glucose uptake by cells. Autophosphorylation by the tyrosine kinase domain of the insulin receptor β -subunit (IR β) then activates a signaling cascade that induces redistribution of glucose transporter type 4 (GLUT4) to the cell surface to enable glucose uptake by the cell. In pregnant women who developed GDM, there is a decrease in sensitivity before and as the pregnancy advances.²⁴ In late pregnancy, skeletal muscle content of insulin receptor substrate 1 (IRS1), signaling molecules, are lower than in non-pregnant women. Along with the lowering of IRS1 level, autophosphorylation of IR β is also lower with women in GDM than in pregnant women with normal glucose tolerance, which results in 25% lower glucose uptake in biopsied skeletal muscle.²¹

Risk factors

The number of GDM risk factors are determined by several epidemiological studies, such as the history of GDM and family history of type 2 diabetes mellitus (T2DM), ethnicity, age, women >40-year-old women have twice the risk of increasing GDM compared to women <30 years of age (prevalence 9.8% versus 4.1%, respectively). Women carrying a male fetus appear to have a higher risk of developing GDM, and some reports suggest that twin pregnancies had a higher risk of GDM, although this study is not a universal finding.²⁰ Obesity or being overweight [body mass index (BMI) ≥ 25 kg m⁻²] before pregnancy is the most significant GDM risk factor, cigarette smoking by pregnant women, and a history of smoking parents also contribute to an increased risk of GDM. Low plasma levels of vitamin D and C in early pregnancy and increased dietary fat intake during pregnancy increases the risk of developing GDM.^{25,26}

TABLE1. Risk Factors for Gestational Diabetes Mellitus (GDM)¹⁹

Risk factor	Adjusted OR or RR
GDM in previous pregnancy	OR = 13.2
BMI > 25 kg per m ²	OR = 3.2
Diabetes in first degree relative	RR = 1.7
Weight gain of > 5 kg since 18 years of age	RR = 1.7
Maternal age older than 35 years	RR = 1.6
Gestational weight gain in excess of Institute of Medicine Guidelines	OR = 1.4
Macrosomia in previous pregnancy	OR = 1.4

Clinical consequences

Short-term consequences associated with GDM include pre-eclampsia, polyhydramnios, operative delivery, shoulder dystocia, birth canal lacerations, fetal overgrowth (macrosomia), neonatal hypoglycemia, jaundice, and in some studies of untreated GDM, perinatal mortality also may occur.²⁷⁻³² The risk of developing diabetes (mostly T2DM) in pregnant women with GDM may increase risk seven times worse compared to normoglycemic pregnancy.³³ Furthermore, there is also an increased risk of metabolic syndromes such as cardiovascular, kidney, liver, and retinal disease in women with a history of GDM.³⁴

Screening and diagnosis of GDM

A one-step 75 g oral glucose tolerance test is advised for all women whose diabetes is not confirmed yet, at 24-28 weeks of their pregnancy, per the suggestion of The International Association of Diabetes and Pregnancy Study Groups (IADPSG). Gestational diabetes mellitus is confirmed when one or more of the parameter values are exceeded (fasting ≥ 5.1 mmol/L, 1-hour ≥ 10.0 mmol/L, 2-hour ≥ 8.5 mmol/L).³⁵

Management of GDM

Several randomized controlled trials (RCTs) and a Cochrane review suggest that the risk of GDM may be reduced by diet, physical exercise, and lifestyle counseling. Particularly when

interventions are started during the first or early in the second trimester. There are no intervention trials in the offspring of mothers with GDM. A meta-analysis of 11 RCTs demonstrated that metformin treatment in pregnancy does not reduce the risk of GDM in high-risk women with obesity, polycystic ovary syndrome (PCOS), or pre-existing insulin resistance. A meta-analysis of 32 RCTs evaluating the effectiveness of telehealth visits for GDM demonstrated a reduction of incidences of cesarean delivery, neonatal hypoglycemia, premature rupture of membranes, macrosomia, pregnancy-induced hypertension or preeclampsia, preterm birth, neonatal asphyxia, and polyhydramnios compared with standard in-person care.³⁶

The primary goal of GDM management is to prevent fetal overgrowth and complications during pregnancy. Several methods are used to achieve this outcome, such as dietary modification, promotion of physical activities, and pharmacological treatment, which is required by a minority of pregnant women. American Diabetes Association (ADA) recommends self-monitoring of fasting and postprandial glucose in both GDM and preexisting diabetic pregnant women to achieve optimal glucose levels.³⁷

Non-pharmacologic therapy: lifestyle intervention

Other than insulin therapy, a lifestyle behavior change is an option in the management of GDM, and as the pieces

of evidence suggest, often suffice for the treatments of many women.³⁶ Physical activities or exercises such as walking, cycling, and swimming is recommended as a part of lifestyle intervention.³⁷ Diet and physical activity are sufficient in controlling glycemic status in ~70-85% with GDM.^{38,39} A systematic review concluded that regular exercises (20–50 min/d, 2–7 d/wk of moderate-intensity) either aerobic training or resistance training, or both, will improve glucose control and reduce the need for insulin dose.³⁶ Daily nutrition intake for women with GDM should be based on the dietary reference intakes (DRI) nutrition assessment. A minimum of 175 g of carbohydrate, a minimum of 71 g of protein, and 28 g of fiber were suggested by the DRI. The diet should emphasize monounsaturated and polyunsaturated fats, limit saturated fats and avoid trans-fat.³⁷

Pharmacological therapy

Lifestyle changes are an option for gestational diabetes therapy; however, it is not sufficient to control the patient's glycemic level. Consequently, additional pharmacological therapy is needed to support the effectiveness of therapy. There are only a few drugs that are safe to use for pregnant women. The most recommended drug is insulin, due to its inability to cross the placenta. In addition to insulin, two drugs that can be used for pregnant women are metformin and glyburide, unfortunately, they tend to cross the placenta and several RCT studies suggest that monotherapy of metformin or glyburide are inadequate to achieve controlled glycemic levels.³⁶

Insulin

Lifestyle and insulin treatment improves perinatal outcomes of women with GDM.⁴⁰ Insulin is recommended as the first-line agent for GDM, while some studies recommend Metformin and glyburide are known to cross the placenta and to provide adequate glycemic control in two separate RCTs

(23% and 25-28% of women with GDM, respectively).⁴¹⁻⁴⁵ An initial dose of 0.3 IU per kg BW per 24 h of insulin can be used to initiate the treatment, up to 1 IU per kg BW.⁴⁶ The use of multiple daily insulin injections and continuous subcutaneous insulin infusions are reasonable delivery strategies, and neither has been shown to be superior to the others during pregnancy. Insulin should be used for the management of type 1 diabetes mellitus (T1DM) in pregnancy, and it is also the preferred agent for the management of T2DM in pregnancy. In a pregnancy complicated by T1DM, the use of multiple daily injections or insulin pump technology is recommended.³⁶

The use of insulin as part is associated with its superior ability to lower postprandial blood glucose levels and has no reported adverse events on newborns and teratogenicity. Therefore, insulin is widely used as the first choice in therapy for women with GDM, it is often combined with metformin in GDM patients with CH to achieve a better result. Dual-use of insulin and metformin is associated with a lower incidence of puerperal infection and neonatal respiratory distress compared to patients on a monotherapy regimen. The combination of metformin and insulin also contributes to lowering blood pressure with certain clinical significance.⁴⁷

Insulin in T1DM

In the first trimester, women with T1DM will have an increased risk of hypoglycemia and also will have altered counterregulatory response in pregnancy which will be resulting in a decreased hypoglycemia awareness. Therefore, it is important to educate both patients and family members about the prevention, recognition, and treatment of hypoglycemia before, during, and after pregnancy to prevent and manage the risks of hypoglycemia in the future since insulin resistance drops rapidly after delivery. Besides hypoglycemia, pregnant women with T1DM are at

risk for diabetic ketoacidosis (DKA) at lower blood glucose levels compared to the non-pregnant state. These patients should be prescribed ketone strips and receive education about DKA prevention and detection because DKA has a high risk of stillbirth. If women in DKA are unable to eat, a 10% dextrose infusion with an insulin drip might be indicated to adequately meet the higher carbohydrate demands of the placenta and fetus in the third trimester to resolve their ketosis. Another concern is retinopathy. Worsening of retinopathy is associated with rapid implementation of euglycemia in the setting of retinopathy.³⁶

Insulin in T2DM

Since T2DM is often associated with obesity, the recommendations for weight gain in overweight women are 15–25 lbs and 10–20 lbs for obese women. No adequate data are available on optimal weight gain versus weight maintenance in women with BMI >35 kg/m². Women with T2DM have a good prognosis, but they might require higher doses of insulin, and sometimes concentrated insulin formulations are necessary. Similar to type 1 diabetes treatment, insulin is also the preferred treatment for type 2 diabetes in pregnancy.³⁶ Because insulin effects are minimal in patients with insulin-resistant GDM (T2DM), its combination with metformin is capable of regulating glucose metabolism, and it is one of the important therapeutic agents to improve *in vivo* insulin sensitivity. The use of a two-drug combination in patients with GDM is common in a clinical setting, due to its ability to reduce the incidence of adverse maternal and neonate outcomes, such as premature rupture of membranes, neonatal jaundice, and macrosomia, especially in GDM patients with CH.⁴⁷ Compared to women with T1DM in their first trimester, pregnancy loss appears to be more prevalent in women with T2DM during the third trimester. The risk for associated hypertension and other comorbidities may be as high or higher

with T2DM as with T1DM.

Oral anti-diabetic agents (OAAs)

Sulfonylureas (glyburide/glibenclamide)

Sulfonylureas are used in treating women with GDM and are known to cross the placenta, causing neonatal hypoglycemia. It is approximately 50–70% of the maternal level of glyburide is in the plasma of the umbilical cord. A higher rate of neonatal hypoglycemia, macrosomia, and increased neonatal abdominal circumference is observed in GDM patients who use glyburide compared to insulin or metformin.⁴⁸ There is no long-term safety data for offspring exposed to glyburide.³⁶

Biguanide (metformin)

Lower risk of neonatal hypoglycemia and less maternal weight gain is attributed to the use of metformin.⁴⁸⁻⁵¹ Metformin crosses the placenta, followed by a higher concentration of it in the umbilical cord, compared to maternal levels.^{52,53} Smaller neonates with an acceleration of postnatal growth, resulting in higher BMI in childhood were found in metformin exposure. Based on randomized, double-blind, controlled trials comparing metformin with other therapies for ovulation induction in women with polycystic ovary syndrome, resulting in no benefit in preventing spontaneous abortion or GDM, neither evidence-based need to continue metformin in such patients.³⁶ Women with GDM who needs medical therapy may not be able to use insulin due to difficulties such as cost, language barriers, comprehension, and cultural influences. Oral anti-diabetic agents such as metformin may be used as an alternative after the associated risk of using OAAs are discussed. Women with hypertension, preeclampsia, or at risk for intrauterine growth restriction should not use metformin due to the potential for growth restriction or acidosis in the setting of placental insufficiency.^{54,55}

Insulin versus OAs

Insulin was once considered the only safe therapy for GDM patients, as recommended by the American Congress of Obstetricians and Gynecologists, the American Diabetes Association, and the Federal Drug Administration (FDA).⁵⁶ Since then, several antidiabetic agents have been compared to it in order to establish their safety and efficacy to treat GDM. Generalizing insulin, which itself has several types is considered ignorance.

Insulin usage is associated with risks such as hypertensive disorders during pregnancy;⁵⁷⁻⁶⁰ cesarean sectioning birth;⁶¹⁻⁶⁵ development of T2DM⁶⁶ maternal hypoglycemia⁶⁷ weight gain in pregnancy⁶⁸ induction during labour^{58,60} and postpartum haemorrhage⁶⁸, compared to women with GDM using OAs. To summarize:

- 1). Insulin treatment is associated with the increased risk for hypertensive disorders during pregnancy, although there was no clear evidence of the risk of preeclampsia between women using insulin and women who use OAs.
- 2). There was no clear evidence attributed to the risk of birth by cesarean section between women treated with insulin compared to women who are treated with OAs.
- 3). There were no significant differences between groups, although the risk of bias is present due to the open-label nature of the studies.
- 4). There were no significant differences in the risk of maternal hypoglycemia between women who had been treated with insulin and those who had been treated with OAs.
- 5). Insulin was associated with an increase in gestational weight gain compared with oral antidiabetic agents although none of the studies detailed whether the gestational weight gain was within, above, or below acceptable standards.
- 6). Insulin may possibly increase the risk of induction of labor compared with OAs although the evidence was not clear.
- 7). There was no significant difference in the risk of postpartum hemorrhage between women who had been treated

with insulin and those who had been treated with OAs.

The risks associated with insulin usage during pregnancy for neonates/infants were perinatal (fetal and neonatal death) and later infant mortality.^{59,66-70} Large-for-gestational age (LGA);^{13,58,59,64,66,71} death or serious morbidity composite;^{68,72} neurosensory disability in later childhood;⁵⁷ and neonatal hypoglycemia. To summarize:

- 1). There was no clear evidence for the risk of perinatal death between infants whose mothers had been treated with insulin and those treated with OAs.
- 2). There was no clear evidence between infants whose mothers had been treated with insulin and those treated with OAs for the risk of being born LGA.
- 3). Two studies that compared insulin with metformin reported a composite outcome of serious infant morbidity. There was no evidence between infants whose mothers had been treated with insulin and those who had been treated with OAs (metformin) for the risk of serious infant morbidity.
- 4). At 18 months of age, there was no evidence of the risk of any mild developmental delay between infants whose mothers had been treated with insulin and those who had been treated with OAs.
- 5). Overall, there was no difference in the incidence of neonatal hypoglycemia between infants whose mothers had been treated with insulin and those treated with OAs.

The use of OAs is being considered lately for multiple reasons, mainly the ease of administration, low cost of therapy, and adverse events such as hypoglycemia and weight gain are unlikely to occur. The use of metformin is further conducted, mainly compared to insulin^{4,14} and a few with glyburide.¹⁵⁻¹⁷ Additional therapy with insulin is needed by a considerable number of patients due to their inability to achieve glycemic targets, especially in patients receiving OAs such as metformin and glyburide.^{4,15,23,72,73} Both of these drugs reported efficacy comparable to insulin.^{8,10} Efficacy and safety profile of

these OAs is also equivalent in several studies.^{15,16} However, all the studies were concluded within the short-term observation, therefore more research is needed to conclude the effect in a long-term setting.

Other agents

The risk of neonatal hypoglycemia is best achieved by acarbose, followed by metformin (added with insulin when it is required), insulin, and glyburide.² Several other OAs are being studied to be used in GDM, such as non-sulfonylurea secretagogues (nateglinide, repaglinide), thiazolidinediones (pioglitazone, rosiglitazone), α -glucosidase inhibitors (acarbose, miglitol) and dipeptidyl peptidase IV inhibitors (sitagliptin and others), however, the usage data during pregnancy is still limited. Therefore, the use of OAs should refer to guidelines for management in non-pregnant adults, while emphasizing both maternal and fetal safety.⁴⁵

Glucose monitoring

American Diabetes Association (ADA) recommends fasting and postprandial monitoring of glucose in order to maintain and meet the glucose target of pregnant women. Patients using insulin pumps and basal-bolus therapy are recommended to do pre-prandial testing of glucose, mainly due to the rapid-acting of insulin dose adjustment before their meal. Better glycemic control and lowered preeclampsia risks are seen in patients who regularly monitor their postprandial glucose.⁷⁴⁻⁷⁶ The current ADA recommendation for glucose monitoring for pregnant women with T1 and T2 DM is as follows³⁶:

- 1). Fasting Glucose : 70-95 mg/dL
- 2). 1h Postprandial glucose : 110-140 mg/dL
- 3). 2h Postprandial glucose : 100-120 mg/Dl

The fifth International Workshop-Conference on Gestational Diabetes Mellitus currently recommends targets for glucose control as follows:

- 1) Fasting Glucose : 95 mg/dL
- 2) 1h Postprandial glucose : 140 mg/dL
- 3) 2 h Postprandial glucose : <120 mg/dL

During pregnancy, A1C targets are individualized for each patient, with a target of <6% to <7% to avoid maternal hypoglycemia. A1C targets for the second and third semester is set at <6%, which is the optimal goal to achieve without patients suffering from severe hypoglycemia. Red blood cell kinetics are altered during pregnancy, which requires more frequent monitoring than in non-pregnant patients (e.g., monthly monitoring).³⁶

Postpartum follow-up

GDM patients are usually undiagnosed for their prediabetes, T2DM, maturity-onset diabetes of the young, and developing T1DM. These conditions require GDM patients to test for 4-12 wk postpartum with a fasting 75 g Oral Glucose Tolerance Tests (OGTT) to detect the tendency of persistent diabetes or prediabetes, with the parameters (similar to nonpregnant threshold) as follows⁷⁷:

- 1) Fasting : 92 mg/dL
- 2) 1 h : 180 mg/dL
- 3) 2 h : 153 mg/dL

If there are uncertainties during the diagnosis of hyperglycemia, a minimum of two abnormal test values are required to ascertain the condition. If fasting plasma glucose (≥ 126 mg/dL) and 2-h plasma glucose (≥ 200 mg) are abnormal during a single screening test, diabetes can then be diagnosed. The OGTT test should be repeated if only one parameter is abnormal during the initial test.⁷⁸ The OGTT is preferred over A1C especially 4-12 wk after childbirth mainly due to red blood cell turnover during pregnancy, blood loss during delivery, or preceding 3-month glucose profile. These factors could persistently impact the amount of A1C in the serum, hence the lowered

sensitivity of the A1C test and the recommendation of using OGTT is made. Women of reproductive age may develop T2DM during their next pregnancy, in which preconception evaluation is required to assess the risks. Gestational diabetes mellitus increases maternal risk by 50-60%, hence, needs to be tested every 1-3 yr if the 4-12 wk postpartum 75 g OGTT is normal. On going evaluation for blood glucose may be performed with any recommended methods, such as annual A1C, annual FPG, or triennial 75g OGTT with nonpregnant thresholds.³⁶

CONCLUSION

Gestational diabetes mellitus is defined as any degree of glucose intolerance that was first recognized during pregnancy. It is characterized by the increasing risks of large-for-gestational-age birth weight, neonatal and pregnancy complications, and the increasing risk of long-term maternal T2DM and offspring abnormal glucose metabolism in childhood. Therefore, pregnant women should be tested for GDM treatment. Currently, management of GDM are lifestyle management, medical nutrition therapy, pharmacologic therapy, and telehealth visits. Lifestyle behavior can change an essential component and may suffice for the treatment. Medical nutrition therapy is an individualized nutrition plan developed between the pregnant woman and an RD/RDN familiar with the management of GDM. Telehealth visits for pregnant women with GDM improve outcomes compared with the standard in person care. Lifestyle modification is the initial management of GDM, but in the special case of disorder glucose levels, a treatment using a pharmacological agent needs to be considered. Pharmacological agents used in diabetes management such as insulin and select OAs can be used safely during pregnancy, it will decrease maternal blood glucose and ultimately lowering perinatal adverse outcomes, according to several studies. Insulin

should be added as a first-line agent if it is necessary to achieve glycemic targets in patients with GDM. Oral agents such as metformin and glyburide should not be used as the first-line agent for treatment, since they may cross the placenta to the fetus. Insulin is selected as the first-line agent treatment for women in GDM mainly due to its safety and the inability to cross the placenta. However, OAs are being considered recently, and to some extent, preferred over insulin due to some reasons including ease of use, low cost of therapy, and minimum adverse events such as hypoglycemia and weight gain. Both are equal in terms of efficacy and safety comparable as a treatment for GDM, although in the case of OAs usage, some patients may need insulin as a supplemental therapy to achieve their glycemic targets. Other oral and non-insulin injectable forms are lacking long-term safety data.

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