

Gestational diabetes mellitus

Eman M. Alfadhli, MD, FRCP

ABSTRACT

يعد سكري الحمل من المضاعفات الطبية الأكثر شيوعاً في الحمل، وقد يؤدي إلى نتائج سلبية للأمهات والمواليد. ويقلل الحفاظ على مستوى السكر في الدم من المضاعفات التي يمكن أن تتعرض لها الأم والطفل. إن هناك عدد محدود من الطرق والمعايير الصحية اللازمة لفحص وتشخيص هذه الحالة عالمياً. لذلك يهدف هذا المقال إلى دراسة ماجد به البحث في مجال تشخيص ومعالجة سكري الحمل. يتكون العلاج الأولي لسكري الحمل من التغذية الطبية وممارسة الرياضة. وفي حال فشل هذه الإجراءات في التحكم في نسبة السكر في الدم فإنه ينبغي الشروع بعلاج الأنسولين. يعد نظير الأنسولين أكثر فسيولوجية من الأنسولين الإنساني، كما أنه يقلل من خطر الإصابة بهبوط السكر وتحسين مستوى السكر في الدم بشكل أفضل. ويُصرح استخدام أنسولين ليسبرو (lispro)، وأسبارت (aspart)، وديتيرمير (determir) للنساء الحوامل وذلك من قبل منظمة الغذاء والدواء الأمريكية. في حين لم تتم الموافقة على استخدام أنسولين غلارغرين (glargine) في معالجة سكري الحمل بعد، ولكن لم تظهر الدراسات الحالية أي موانع من استخدامه. كذلك لم يُصرح باستخدام الحبوب الخافضة للسكر لمعالجة سكري الحمل، ولكن الدراسات أظهرت أن استخدام حبوب غليبيريد (glyburide) وميتفورمين (metformin) آمن أثناء الحمل بالإضافة إلى قدرتها على تحسين مستوى السكر في الدم لدى النساء الحوامل.

Gestational diabetes mellitus (GDM) is the most common medical complication of pregnancy. It is associated with maternal and neonatal adverse outcomes. Maintaining adequate blood glucose levels in GDM reduces morbidity for both mother and baby. There is a lack of uniform strategies for screening and diagnosing GDM globally. This review covers the latest update in the diagnosis and management of GDM. The initial treatment of GDM consists of diet and exercise. If these measures fail to achieve glycemic goals, insulin should be initiated. Insulin analogs are more physiological than human insulin, and are associated with less risk of hypoglycemia, and may provide better glycemic control. Insulin lispro, aspart, and determir are approved to be used in pregnancy. Insulin glargine is not approved in pregnancy, but the existing studies did not show any contraindications. The use of oral hypoglycemic agents; glyburide and metformin seems to be safe and effective in pregnancy.

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From the Department of Internal Medicine, Endocrine Section, Taibah University Medical College, Al-Madinah Al-Munawwarah, Kingdom of Saudi Arabia.

Address correspondence and reprint request to: Dr. Eman M. Alfadhli, Department of Internal Medicine, Endocrine Section, Taibah University Medical College, Aljameat Road, PO Box 344, Al-Madinah Al-Munawwarah, Kingdom of Saudi Arabia. Fax. +966 (14) 8443195. E-mail: Alfadhli2005@yahoo.com

Pregnancy is associated with insulin resistance (IR) and hyperinsulinemia that may predispose some women to develop diabetes. Gestational diabetes has been defined as any degree of glucose intolerance with an onset, or first recognition during pregnancy.¹ This definition does not exclude the possibility that unrecognized glucose intolerance may have antedated the pregnancy, and so, the term hyperglycemia in pregnancy emerges to be more appropriate as suggested lately by the Endocrine Society.² The International Association of Diabetes and Pregnancy Study Groups (IADPSG) classify hyperglycemia first detected during pregnancy as either 'overt diabetes' or 'gestational diabetes mellitus (GDM)'.³ In 2013, the World Health Organization (WHO) recommended that hyperglycemia first detected during pregnancy be classified as either 'diabetes mellitus (DM) in pregnancy' or 'GDM'.⁴

The prevalence of GDM varies from 1-20%, and is rising worldwide, parallel to the increment in the prevalence of obesity and type 2 diabetes mellitus (T2DM).⁵ The amount of GDM varies in direct proportion to the prevalence of T2DM in a given population, or ethnic group. The prevalence rates for GDM are higher for African, Hispanic, Indian, and Asian women than for Caucasian women.^{5,6} Recently, the prevalence of GDM has increased by 2-3 folds, ranging from 8.9-53.4%.⁷⁻¹⁶ This is mainly due to the adoption of the new criteria proposed by the IADPSG on screening, and diagnosis of GDM.³ The IADPSG recommends universal screening for GDM, and requires

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one single glucose value above the cut-off value (instead of 2) during the oral glucose tolerance test (OGTT) for diagnosis.³ This dramatic rise in the GDM prevalence will have a major impact on health care systems. Also, the consequences of labeling a large number of women with GDM are not known. The GDM is associated with adverse maternal and neonatal sequelae.^{17,18} In a Hyperglycemia and Adverse Pregnancy Outcomes Study (HAPO),¹⁷ a large-scale (25,000 pregnant women) multinational epidemiologic study found significant associations between adverse pregnancy outcomes, and higher levels of maternal glucose with no defined levels, after which the risk increases. Furthermore, the Australian Carbohydrate Intolerance Study (ACHOIS) in pregnant women,¹⁹ and the US multicenter randomized trial of treatment for mild gestational diabetes studies²⁰ indicated that maternal hyperglycemia that does not meet diagnostic criteria for overt diabetes still has a correlation with perinatal disorders and problems. This association suggests a need to re-evaluate the standard criteria for diagnosing, and treating hyperglycemia in pregnancy, and welcome the new criteria. The goal of this review is to discuss the latest update in the diagnosis and management of GDM.

Pathophysiology. During normal pregnancy, a progressive IR develops beginning around mid-pregnancy, and progresses during the third trimester.²¹ Hormones and adipokines secreted from the placenta, including tumor necrosis factor (TNF)- α , human placental lactogen, and human placental growth hormone are possible causes of IR in pregnancy. In addition, increased estrogen, progesterone, and cortisol during pregnancy contribute to a disruption of the glucose insulin balance.²² To compensate for the peripheral IR during pregnancy, insulin secretion increases from a woman's pancreas. The development of GDM occurs when a woman's pancreas does not secrete enough insulin to keep up with the metabolic stress of the IR. In addition, increased maternal adipose deposition, decreased exercise, and increased caloric intake contribute to this state of relative glucose intolerance.

Course of insulin sensitivity during pregnancy. In early pregnancy, insulin secretion increases, while insulin sensitivity is unchanged, decreased, or may even increase. At mid pregnancy, insulin sensitivity starts to decline progressively, and became worse during the rest of the pregnancy, being worst in the late third trimester. It rebounds with the delivery of the placenta. Therefore, GDM usually develops in the late second trimester and disappears, instantly, post delivery.²¹

Risk factors for GDM. Several risk factors are associated with the development of GDM. The most common risk factors are; obesity, older maternal age, past history of GDM, strong family history of diabetes, member of an ethnic group with a high prevalence of T2DM, polycystic ovary syndrome, and persistent glucosuria. A history of delivering big baby (birth weight ≥ 4000 g), history of recurrent abortions, and history of unexplained stillbirths, and history of essential hypertension, or pregnancy-related hypertension are other risk factors for GDM.²³

Risks of GDM. Women with GDM have an increased incidence of hypertensive disorders during pregnancy, including gestational hypertension, pre-eclampsia, and eclampsia.¹⁷ There is an increase risk of polyhydramnios that may increase the risk of preterm labor. Excessive fetal growth remains an important perinatal concern in GDM. Consequences of excessive fetal growth include birth trauma, maternal morbidity from cesarean deliveries, shoulder dystocia, and neonatal hypoglycemia.¹⁷ Other neonatal morbidities that potentially occur more frequently in infants of women with GDM include hyperbilirubinemia, hypocalcemia, erythema, and respiratory distress syndrome.¹⁷ Long-term complications of GDM include diabetes and cardiovascular disease in the mothers,²⁴ and obesity and diabetes in the offspring.²⁵ Congenital anomalies do not occur at an increased rate in patients with gestational diabetes, as GDM usually occurs at the late second trimester when embryogenesis is completed.

Screening and diagnosis of GDM. There is a lack of uniform strategies for screening and diagnosing GDM globally (Table 1). The first diagnostic criteria for gestational diabetes were provided by O'Sullivan and Mahan in the 1960's based on a 3-hour 100 g OGTT.²⁶ These criteria have been derived to identify women at high risk of developing diabetes after pregnancy. Many medical organizations around the world followed the original work of O'Sullivan and Mahan,²⁶ and modified by either Carpenter and Coustan,²⁷ or the National Diabetes Data Group (NDDG),¹ although frequently selecting different thresholds for GDM diagnosis.

In March 2010, a consensus panel from the IADPSG; an international consensus group with representatives from multiple obstetrical and diabetes organizations including the American Diabetes Association (ADA), published new recommendations for the screening and diagnosis of GDM.³ The IADPSG recommend universal screening for gestational diabetes. At the first antenatal visit, IADPSG recommends screening pregnant women for GDM using standard criteria to diagnose diabetes in non pregnant state to identify women with overt diabetes "pre-existing diabetes". A

diagnosis of overt diabetes can be established in women who meet any of the following criteria: fasting plasma glucose level (FPG) ≥ 7.0 mmol/l (126 mg/dl), a casual plasma glucose of 11.1 mmol/l (≥ 200 mg/dl), or HbA1c ≥ 6.5 . In the absence of unequivocal hyperglycemia, the diagnosis must be confirmed on a subsequent day. Confirmation of the diagnosis precludes the need for OGTT. If FPG is >5.0 mmol/l (90 mg/dl) but <7.0 mmol/l (126 mg/dl) at any gestational age, a diagnosis of GDM can be made. If early screening is negative, the IADPSG recommends universal screening to be performed at 24-28 weeks of gestation with a 2-hour (h), 75-g OGTT "one-step approach". Gestational diabetes is diagnosed, if one or more values equal, or exceeds thresholds; FPG (5.1 mmol/l [92 mg/dl]), one h plasma glucose (10 mmol/l [180 mg/dl]), and 2-h plasma glucose (8.5 mmol/l [153 mg/dl]). These cut-off values were chosen arbitrary by the IADPSG based on the HAPO study¹⁷ to express an odds ratio for adverse outcomes of at least 1.75 compared with women with mean glucose levels in the HAPO study.¹⁷ The OGTT should be performed after fasting overnight for 8-14 hours, and not reducing the usual carbohydrate intake for the preceding several days.³

In January 2011, the Standards of Care of ADA endorsed the IADPSG recommendations.⁶ In addition, the Endocrine Society recently endorsed the IADPSG recommendations.² The WHO updated their recommendations in 2013, and recommended glucose cut-off values for GDM corresponding to those proposed by IADPSG.⁴ The difference from the IADPSG guidelines is that the new WHO guidelines set a range of plasma glucose levels to distinguish diabetes in pregnancy and GDM (Table 1).⁴ The past diagnostic criteria recommended by the WHO in 1999²⁸ for hyperglycemia in pregnancy were those used in non-pregnant individuals (Table 1). An issue that has been problematic with these criteria relates to the

FPG criterion, as the diagnostic level of ≥ 7.0 mmol/l is universally considered to be too high. Other organizations around the world are re-addressing their criteria for screening and diagnosis of GDM since the emergence of IADPSG recommendations. On the other side, the American Association of Obstetricians and Gynecologists (ACOG),²⁹ and the National Institute of Health (NIH)³⁰ have not endorsed the IADPSG recommendations, and still recommend the traditional "2-step approach", in which an initial screening between 24-28 weeks by 50 g oral glucose challenge test (GCT), and measuring the plasma glucose concentration after one hour. Afterward, a diagnostic 3-hour 100-g OGTT is recommended for those women who exceeded the glucose threshold of ≥ 7.2 , or ≥ 7.8 mmol/L (130 or 140 mg/dL) in GCT.^{29,30} In the 2014 Standards of Care,³¹ the ADA readdressed the NIH recommendation along with the IADPSG guidelines as there is insufficient data to strongly demonstrate the superiority of one strategy over the other.

Management of GDM. The cornerstone of GDM management is glycemic control. The initial treatment for GDM is lifestyle interventions, which include medical nutrition therapy and daily exercise. Patients are required to check their glucose level frequently at home to assure that the glycemic targets are achieved. If the glycemic goals are not accomplished with these measurements, medical therapy should be initiated.

Blood glucose monitoring. Women are instructed to carry out self monitoring of blood glucose (SMBG) 4 times a day, fasting glucose (upon awakening), and one or 2 hour post-meals (after the first bite of a meal). In GDM, monitoring of blood glucose after meals is preferred over pre-meal testing as the risk of macrosomia increases with increased maternal glucose levels post-meals.³³ This was illustrated in a randomized clinical trial,³⁴ which compared preprandial glucose monitoring to one hour post-prandial (PP) testing, and

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)	-
	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)	-
WHO, 2013 ⁴	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

found macrosomia, cesarean deliveries, and neonatal hypoglycemia were significantly less frequent in women who monitor their glucose post-meals. However, it is not known whether a one hour, or 2-hour PP testing is the ideal goal for the prevention of fetal risks. Therefore, patients can monitor their glucose levels at one or 2 hours post-meal, whatever is convenient, or at the estimated peak blood glucose is most likely to occur post prandial, for example, choosing the time at which glucose was elevated during OGTT.²

The glycosylated hemoglobin (HbA1C) values tend to be less in pregnant women than in non-pregnant, and this is because the average blood glucose concentration tends to be lower in pregnant women. In addition, the rise in red cell mass and the rise in red blood cell turnover during pregnancy contributes to a lower HbA1C. For this reason, frequent monitoring of HbA1C to assess glycemic control during pregnancy in women with GDM may not be useful in those with low HbA1C levels at initial visit. However, its measurement may be helpful in those with overt diabetes with an HbA1C >6.5%.³⁵

Glycemic targets. The target glycemic goals for women with GDM is to keep the fasting glucose ≤ 5.3 mmol/l (90-95 mg/dl), and either one-hour post-meal ≤ 7.8 mmol/l (140 mg/dl), or 2-h post-meal ≤ 6.7 mmol/l (120 mg/dl).^{2,36} These values are more stringent for pregnant women than they are for non-pregnant patients with diabetes.

Medical nutritional therapy. Medical nutritional therapy is the keystone of treating GDM as it maintains desired glycemic goals in 80-90% of GDM women.³⁷ The optimal dietary prescription would be a diet that provides adequate nutrition to support fetal and maternal well-being, while maintaining normoglycemia with absence of ketones, and achieving appropriate weight gain in pregnancy.³⁸ Caloric allowance could be calculated based on ideal body weight: 30 kcal/kg for women with a BMI of 22-25; 24 kcal/kg for women with a BMI of 26-29; and 12-15 kcal/kg for women with a BMI above 30.³⁷ The carbohydrate intake should be reduced to 35-45% of the total calories, and distributed over 3 meals, and 2-4 snacks including bedtime snack, this assists in reducing PP glucose peak, but ensures adequate nutrition to the mother and the fetus.² Excessive weight gain should be discouraged as it increases further the risk of delivering a large-for-gestational-age infant, adverse pregnancy outcome, and childhood obesity.³⁹ The recommended weight gain during singleton pregnancy is dependent on pre-pregnancy BMI: 12.5-18 kg of weight gain for underweight women (BMI <18.5 kg/m²); 11.5-16 kg for normal weight (BMI 18.5-24.9 kg/m²); 7-11.5 kg

for overweight (BMI 25-29.9 kg/m²), and 5-9 kg for obese (BMI ≥ 30.0 kg/m²).⁴⁰

Exercise. Exercise has been shown to improve glycemic control in GDM. Daily moderate exercise for 30 minutes or more is recommended for a woman with GDM, if she has no medical or obstetrics contraindications. Advising GDM patients to walk briskly, or do arm exercises while seated in a chair for at least 10 minutes after each meal facilitates in reducing glucose rise post-meal, and help in achieving glycemic goal.^{2,36}

Pharmacological interventions. Insulin therapy. If the medical nutrition therapy and exercise fail to achieve glycemic goals for a woman with GDM, insulin therapy should be initiated. The type and timing of insulin should be chosen based on the specific blood glucose elevation. If the fasting glucose is greater than 90-95 mg/dl (whole blood capillary) then basal insulin, long-acting insulin analog, or neutral protamine Hagedorn (NPH); 4 units for example, should be started before bedtime. If fasting glucose level is too high, then basal insulin dose can be calculated according to the patient's weight, 0.2 units/kg/day. In cases where glucose level is elevated following a meal, rapid-acting insulin, or regular insulin should be prescribed before that specific meal, beginning with 2-4 units, or a dose of one unit per 10-15 g of carbohydrates. If both fasting and PP glucose levels are elevated, a 4-injections-per-day regimen "basal and meal time insulin regimen" should be prescribed.³⁷ Basal and meal time insulin regimen is preferred over twice dose regimen because it is more likely achieves, maintains target blood glucose, and allows more flexibility.² One could start by 2-4 units of rapid-acting insulin, or regular insulin before each meal, and 2-4 units of basal insulin before bed time. Another approach to determine the insulin doses is based on a woman's body weight and gestational week. In the first trimester, the total daily insulin requirement is 0.7 units/kg/day, in the second trimester it is 0.8 units/kg/day, and in the third trimester it is 0.9-1.0 units/kg/day.³⁷ In a morbidly obese woman, the initial doses of insulin may need to be increased to 1.5-2.0 units/kg to overcome the combined IR of pregnancy and obesity.³⁷ Subsequently, the calculated total daily dose of insulin should be divided into 2 halves; one half given as basal insulin at bed time, and the other half divided between 3 meals, and given as rapid-acting, or regular insulin before meals (Figure 1). As insulin requirement may increase with the progression of pregnancy, it is crucial to follow patients' SMBG regularly, and optimize their insulin doses.

In the past, regular insulin and NPH were commonly used to treat GDM. However, currently

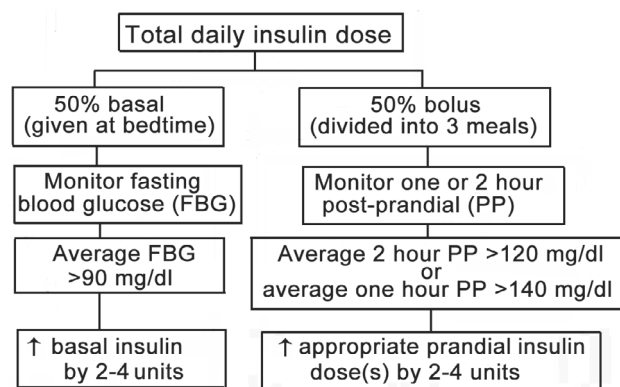


Figure 1 - Initiation and optimization of insulin therapy in hyperglycemia during pregnancy.

rapid-acting insulin analogs are preferred over regular insulin in pregnancy as they are associated with less risk of hypoglycemia, and may also provide better PP blood glucose control.^{41,42} Both lispro and aspart insulin are approved to be used in pregnancy.² There is no data regarding the safety of glulisine in pregnancy. The long-acting insulin analogs do not have a pronounced peak effect as NPH, and therefore, cause less nocturnal hypoglycemia. Insulin detemir has not shown to have adverse maternal or neonatal effects, and has been approved by the Food and Drug Administration (FDA) to be used in pregnancy.⁴³ The use of insulin glargine in pregnancy is not approved yet, but the existing studies did not show any contraindications, and the outcome with glargine treatment was not different from, or superior to, NPH insulin.^{44,45}

Non-insulin antihyperglycemic agent therapy. While insulin is considered the gold standard for management of GDM, it is expensive, invasive, involves daily injections, and patient compliance is often suboptimal. On the other hand, oral hypoglycemic agents are less expensive, less invasive, and more acceptable, and could enhance patient compliance, and might achieve similar perinatal outcome as insulin.

Since GDM is characterized by IR and relatively decreased insulin secretion, a treatment with non-insulin antihyperglycemic agents could be of a potential interest. The main concerns of using non-insulin antihyperglycemic agents in pregnancy are congenital anomalies and fetal hypoglycemia. Most available data on non-insulin antihyperglycemic agents' safety in pregnancy focuses on glyburide and metformin. In Europe and South Africa, glyburide and metformin have been used in pregnancy for years without reported adverse side effects to the fetus. Most oral antihyperglycemic agents cross the placenta and stimulate fetal hyperinsulinism, except glyburide.⁴⁶

Glyburide (glibenclamide). Clinical experience with glyburide treatment of GDM is increasing. When compared with insulin, glyburide had a similar success rate in achieving targeted glucose levels, favorable pregnancy outcomes, and significantly fewer hypoglycemic episodes than insulin.⁴⁷ However, several of these patients treated with glyburide continue to require insulin, in order to maintain optimal glycemic control. The rate of glyburide failure in GDM is 20%. Failure is predicted if fasting glucose levels is greater than 115 mg/dL, higher glucose levels in the OGTT, in obese patients and if the diagnosis is made before 25 weeks' gestation.^{48,49} Suggested glyburide dosing in pregnancy is to start with 2.5 mg in the morning. If glycemic control is not achieved, increase glyburide to 5 mg in the morning, then add 5 mg in the evening when advisable. If the targeted level of glycemic control is still not achieved, 5 mg should be added to the morning, and then to the evening doses for a total of 20 mg.⁵⁰ Long-acting insulin can be added if glyburide dosing is not adequate.

Metformin. Metformin is the other oral hypoglycemic agent that is being considered as a substitute to insulin in treating patients with GDM. Metformin may be a more logical alternative to insulin for women with GDM, as it is not associated with risks of maternal hypoglycemia and weight gain. Metformin is classified as a category B drug, which implies that there is no evidence of animal, or fetal toxicity or teratogenicity. Although, metformin has been shown to pass freely across the placenta,⁵¹ there are no reported adverse side effects to the fetus when it is used to treat women with infertility caused by polycystic ovary syndrome (PCOS).^{52,53} In this situation, PCOS women might be exposed to metformin during part, or the entire period of embryogenesis.

The study of metformin in pregnancy revealed that the use of metformin in women with GDM was not associated with increased risk of congenital anomalies, or maternal and neonatal complications compared to insulin, except for higher rates of preterm labor.⁵⁴ Metformin was associated with lower rates of neonatal hypoglycemia than insulin. Moreover, women who used metformin were more likely to say they would use metformin in a subsequent pregnancy than were women on insulin.⁵⁴ The failure rate of metformin in GDM appeared to be higher than glyburide.^{48,54} In the aforementioned study, 46% of the women on metformin needed to be on supplemental insulin.⁵⁴ Metformin is prescribed at a starting dose of 500 mg, and can be increased gradually up to 2500 mg, as tolerated, and depending on maternal glucose level. If diabetes control is not achieved, insulin should be started.⁵⁴

While the use of oral hypoglycemic agents is not approved by the US FDA, many practices have successfully used glyburide,⁵⁵ or metformin⁵⁶ to manage GDM. Recently, the Endocrine Society Clinical Practice Guidelines in Diabetes and Pregnancy suggests that glyburide is a suitable alternative to insulin therapy for glycemic control in women with GDM, who fail to achieve sufficient glycemic control with medical nutrition therapy and exercise. It also suggests metformin therapy to be used in women with GDM, only for those who do not have satisfactory glycemic control despite medical nutrition therapy, and who refuses or cannot use insulin or glyburide, and are not in the first trimester.² The latest practice bulletin by the ACOG on the management of GDM has indicated that insulin and oral medications are equivalent in efficacy, as pharmacologic treatment of gestational diabetes and either can be an appropriate first-line therapy.²⁹ Before instituting glyburide or metformin to treat pregnant woman with GDM, the physician should discuss fully with her, the possible advantages and disadvantages of glyburide, or metformin compared to insulin therapy, and their lack of FDA approval for this indication.²

There is no controlled data on the use of other non-insulin antihyperglycemic agents during pregnancy, and they should not be used.

Intrapartum care. There is no universal recommendation on the ideal time for delivering mothers with GDM, and it is not known whether induction of labor, or expectant labor is more efficacious. However, there are no indications to pursue delivery before 40 weeks of gestation in patients with good glycemic control, and with no other complications. On the other hand, some studies suggested induction of labor at 38-39 weeks in the case of insulin-treated GDM patients, or when the ultrasound exam shows signs of fetal macrosomia.⁵⁷

During labor and delivery, the goal is to maintain normoglycemia, that is, blood glucose level between 4-7 mmol/L (72-126 mg/dL)² in order to prevent neonatal hypoglycemia.⁵⁸ Generally, patients with diet-controlled diabetes will not require intrapartum insulin, and may simply need glucose level monitoring on admission, and then every 4-6 hours. Patients with insulin-requiring GDM need capillary glucose monitoring every one to 2 hours. There is no clear recommendation for an optimal approach for glucose/insulin management during labor. A suggested approach is to administer dextrose 5% normal saline (NS) at a rate of 125 cc/ hour, and change it to NS, or Ringer Lactate when glucose level exceeds 5.6 mmol/L (100 mg/dl). Insulin infusion should be initiated when glucose level exceeds 7.8 mmol/L (140 mg/dl), and the dose should be titrated according to the

capillary glucose level to keep the glucose level in the target range.⁵⁹

Postpartum care. Fasting glucose level should be monitored 24-72 hours after delivery to ascertain that the mother is no longer hyperglycemic according to the criteria for non-pregnant individuals. In general, no further insulin is required postpartum for women with GDM, and they should be able to resume a normal diet, as 95% of them will return to a completely normal glucose status. If fasting glucose concentrations suggests overt diabetes (fasting ≥ 7 mmol/L [126 mg/dl]), or random glucose ≥ 11.1 mmol/L (200 mg/dL), treatment is warranted; which includes diet, exercise, reducing weight, and medication if needed. For those who have fasting glucose levels below 7 mmol/L (126 mg/dl), they should perform OGTT within 6-12 weeks after delivery to help detect the women who remain diabetic, and require further treatment. For this screening, the 75 g 2-hour OGTT is recommended, using the non-pregnant criteria.

If the OGTT is negative, there should be repeat screening for diabetes every 3 years as 5-50% of women develop T2DM within 5 years after GDM. Risk factors for developing future diabetes are obesity, diagnosis of GDM in early gestational age, insulin therapy during the index pregnancy, neonatal hypoglycemia, and repeated history of GDM.⁶⁰ Lifelong healthy eating and regular physical activity should be encouraged post delivery to all women with GDM. Breastfeeding should be also encouraged as it may reduce maternal and neonatal risk for the later development of T2DM.⁶¹⁻⁶³ Drug therapy, like metformin or glyburide, might be considered for those with overt diabetes. The use of metformin and glyburide by breastfeeding mothers, when necessary, appears to be safe. The concentration of metformin in breast milk is generally low.^{64,65} The available data suggest that the levels of glyburide in milk are negligible, and hypoglycemia was not observed in nursing infants of women using glyburide.⁶⁵ Recent Endocrine Society Clinical Practice Guideline on Diabetes and Pregnancy suggest women with overt diabetes who used metformin, or glyburide therapy during pregnancy can continue to use these medications, if necessary, during breastfeeding.²

In conclusion, the prevalence of GDM is raising worldwide parallel to the increment in the prevalence of obesity and T2DM. Gestational diabetes mellitus is associated with maternal and neonatal adverse outcomes. Maintaining adequate blood glucose levels in GDM reduces morbidity for both mother and baby. There is still a lack of uniform strategies for screening and diagnosing GDM worldwide. Therefore, there is a need to standardize the screening and the diagnostic criteria for GDM globally.

Treatment of GDM consists of diet and exercise. Insulin should be initiated if the initial measures fail to achieve glycemic goals. Insulin analogs are associated with less risk of hypoglycemia, and may provide better glycemic control than human insulin. The use of oral hypoglycemic agents in pregnancy might soon shift the paradigm in the treatment of GDM.

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