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Gestational Diabetes Mellitus: Diagnostic Approaches and Maternal-Offspring Complications

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Gestational diabetes mellitus (GDM) is the most common complication during pregnancy and is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. GDM is associated with adverse pregnancy outcomes and long-term offspring and maternal complications. For GDM screening and diagnosis, a two-step approach (1-hour 50 g glucose challenge test followed by 3-hour 100 g oral glucose tolerance test) has been widely used. After the Hyperglycemia and Adverse Pregnancy Outcome study implemented a 75 g oral glucose tolerance test in all pregnant women, a one-step approach was recommended as an option for the diagnosis of GDM after 2010. The one-step approach has more than doubled the incidence of GDM, but its clinical benefit in reducing adverse pregnancy outcomes remains controversial. Long-term complications of mothers with GDM include type 2 diabetes mellitus and cardiovascular disease, and complications of their offspring include childhood obesity and glucose intolerance. The diagnostic criteria of GDM should properly classify women at risk for adverse pregnancy outcomes and long-term complications. The present review summarizes the strengths and weaknesses of the one-step and two-step approaches for the diagnosis of GDM based on recent randomized controlled trials and observational studies. We also describe the long-term maternal and offspring complications of GDM.

Keywords: Diabetes, gestational; Glucose tolerance test; Incidence; Pregnancy outcome

INTRODUCTION

Pregnancy imposes a metabolic burden on women that accompanies weight gain and insulin resistance. In parallel with the global epidemic of obesity and its related metabolic disorders, gestational diabetes mellitus (GDM) is the most common complication during pregnancy [1,2]. GDM has been defined as glucose intolerance of variable severity with onset or first recognition during pregnancy [3]. GDM is associated with adverse pregnancy outcomes, including premature delivery, primary cesarean delivery and preeclampsia [4,5]. Prenatal exposure to maternal hyperglycemia leads to hyperinsulinemia in the fetus, which in turn increases the risk of macrosomia, neonatal hypoglycemia, hyperbilirubinemia, etc. Two randomized clinical trials (RCTs) in women with GDM demonstrated the improvement of these pregnancy outcomes in women identified with and treated for GDM compared with women left untreated [6,7]. In addition, offspring born from mothers with GDM were more obese and conveyed more cardiovascular risks to their child continuing to early adulthood [8]. Women who had GDM during pregnancy may develop metabolic perturbations after delivery, which include type 2 diabetes mellitus and cardiovascular disease (CVD) [9-11]. Given the enormous impact of GDM, it is crucial to establish appropriate diagnostic criteria for GDM to prevent complications through proper management.

In clinical practice, the aim of screening and diagnosis of GDM is to identify women at risk for an adverse pregnancy outcome. The first diagnostic criteria for GDM were set in 1964 by O'Sullivan and Mahan [12] using a 100 g, 3-hour oral

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glucose tolerance test (OGTT) to determine diagnostic criteria for GDM according to the maternal diabetes risk. This diagnostic approach for GDM suggested by O'Sullivan et al. has been used to date after Carpenter and Coustan [13] made some modifications to diagnostic cutoff values. In 2010, the International Association of Diabetes and Pregnancy Study Group (IADPSG) presented a new diagnostic approach and diagnostic criteria for GDM based on the results of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [14]. However, the diagnosis of GDM by the IADPSG criteria has more than doubled the incidence of GDM and debate continues over which diagnostic methods are clinically efficient. Another debate regarding GDM is whether GDM affects perinatal and/or long-term adverse outcomes independently of obesity or age because GDM occurs more frequently in obese or older women.

We will address two issues in this article: (1) which diagnostic approach for GDM is more feasible in terms of clinical practice in Korea and (2) long-term outcomes in GDM mothers and their offspring.

ONE-STEP VS. TWO-STEP APPROACH

Screening and diagnostic approaches for GDM
Diagnosing GDM in asymptomatic pregnant women involves either a one-step (a diagnostic test performed for all pregnant women) or two-step (screening test followed by a diagnostic test) approach (Table 1). Currently, the Korean Diabetes Asso-

ciation recommends both one-step and two-step approaches equally for the diagnosis of GDM.

In 1973, O'Sullivan et al. [15] introduced a 50 g, 1-hour glucose challenge test (GCT) for the screening test, and it was used to determine whether a 100 g, 3-hour OGTT was to be performed to diagnose GDM. In their analysis, they found that the screening threshold of ≥130 mg/dL for the GCT had a sensitivity of 79% and specificity of 87% for the detection of women with GDM. The GCT has several advantages, including that it can be performed regardless of the time of last meal or the time of day, and 70% to 80% of pregnant women would not require further fasting confirmatory tests (i.e., the 100 g, 3-hour OGTT). A systematic review from the U.S. Preventive Services Task Force in 2013 demonstrated that the GCT is acceptable as a screening test [16]. The sensitivity and specificity of the GCT cutoff of 130 mg/dL were 99% and 77%, respectively, when the Carpenter-Coustan cutoffs for the 100 g, 3-hour OGTT were used as the gold standard.

In 1979, the National Diabetes Data Group (NDDG) adopted the GDM diagnostic criteria of O'Sullivan by adding 15% to each value because venous plasma glucose was measured instead of whole blood glucose [17]. The Carpenter-Coustan criteria, which we currently use as a 'two-step approach,' modified the glucose cutoffs for the diagnosis of GDM with the evolution of measurement methods employing enzymatic methods with hexokinase [13]. From the early 1980s to date, the two-step approach has become widely used in the United States and in other countries [18]. In Korea, a two-step approach has be-

Table 1. Diagnosis of gestational diabetes mellitus

Screening methods		Glucose concentration, mg/dL			
		Fasting	1-hour	2-hour	3-hour
One-step	All women undergo a 75 g OGTT after fasting for ≥8 hours.				
	GDM is diagnosed when ≥1 value exceeds the criteria.				
	IADPSG (plasma)[a]	92	180	153	NA
Two-step	Initial screening: a 50 g GCT is done without fasting.				
	Women with a positive GCT whose 1-hour glucose ≥130 to 140 mg/dL undergo a 100 g OGTT after fasting for ≥8 hours.				
	GDM is diagnosed when ≥2 values exceed the criteria.				
	O' Sullivan (whole blood)	90	165	145	125
	NDDG (plasma)	105	190	165	145
	Carpenter and Coustan (plasma)[a]	95	180	155	140

OGTT, oral glucose tolerance test; GDM, gestational diabetes mellitus; IADPSG, International Association of Diabetes and Pregnancy Study Group; GCT, glucose challenge test; NDDG, National Diabetes Data Group.
[a]Currently recommended criteria from the Korean Diabetes Association for the diagnosis of gestational diabetes mellitus.

come popular in clinical practice since the mid-1990s [19].

The HAPO study was a multinational, observational study to establish universal GDM diagnostic criteria using a 75 g, 2-hour OGTT [5]. This study demonstrated strong and continuous associations of maternal glucose levels with primary outcomes, such as birthweight, cord blood C-peptide levels, primary cesarean delivery, and neonatal hypoglycemia. In addition, secondary adverse outcomes, including preeclampsia, birth injury, prematurity, and neonatal fat amounts, were similarly associated with maternal glucose levels. However, there were no obvious thresholds for diagnosing GDM. Thus, the IADPSG proposed the OGTT cutoffs, which are average glucose values at an adjusted odds ratio of 1.75 of adverse perinatal outcomes (birthweight >90th percentile, cord C-peptide level >90th percentile, and neonatal percent body fat >90th percentile) [14]. These OGTT cutoffs recommended by the IADPSG are somewhat similar to the Carpenter-Coustan criteria. The IADPSG recommends a one-step approach to diagnose GDM when one or more glucose values exceed the criteria. When the IADPSG criteria were applied in the HAPO study, 64% of women with GDM were diagnosed with one abnormal value, and only 36% of women with GDM were diagnosed with two or more abnormal values [20]. These findings explained the doubling of the incidence of GDM with a one-step approach for GDM.

Randomized clinical trials

Recently, two RCTs comparing the one-step and two-step approaches in terms of perinatal pregnancy outcomes were published (Fig. 1) [21,22]. Hillier et al. [21] investigated whether the one-step or two-step approach for the diagnosis of GDM and its treatment improved perinatal pregnancy outcomes in the setting of standard clinical care. More than 20,000 pregnancies from Kaiser Permanente (Northwest and Hawaii) were included in this study, which consisted of 55% White individuals and 15% Asian individuals. With the one-step approach, more diagnoses of GDM were made (one-step vs. two-step, 16.5% vs. 8.5%), but there were no differences in perinatal outcomes, including large for gestational age (LGA) births (8.9% vs. 9.2%), perinatal composite outcomes (stillbirth, neonatal death, shoulder dystocia, bone fracture, and any arm/hand nerve palsy) (3.1% vs. 3.0%), and primary cesarean section (24.0% vs. 24.6%). A similar proportion that were diagnosed with GDM using the two approaches required medication to manage glucose levels during pregnancy (42.6% [n=783] for
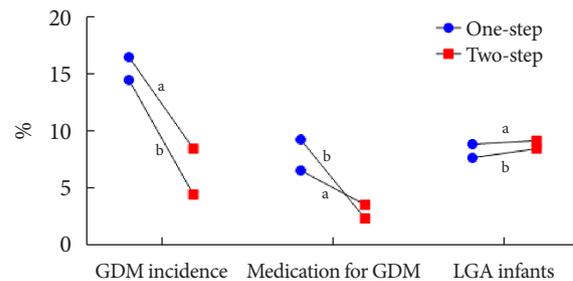

Fig. 1. Summary of two randomized controlled trials comparing the one-step and two-step approaches for the diagnosis of gestational diabetes mellitus (GDM). A one-step approach classifies more women as having GDM and requires more women to be treated for their glucose during pregnancy. The incidence of adverse pregnancy outcomes, including large for gestational age (LGA) births, did not differ between the one-step and two-step approaches. [a][21], [b][22].

one-step and 45.5% [n=431] for two-step), meaning that more women who underwent the one-step approach received treatment to manage glucose during pregnancy.

There is some clinical controversy regarding whether a one-step approach leads to overtreatment of GDM versus whether a two-step approach is missing pregnant women who require treatment. The major difference in the diagnostic criteria between the two approaches is one versus two or more abnormal values in the above the criteria. In addition, for a total of 39% of GDM diagnosed with the one-step approach, the diagnosis was based on the isolated fasting plasma glucose level alone, and half these women had a fasting plasma glucose between 92 and 94 mg/dL. These women who may not have been diagnosed with GDM by the two-step approach, as the cutoff of fasting plasma glucose is more stringent in the one-step approach (one-step vs. two-step, ≥92 mg/dL vs. ≥95 mg/dL), which ultimately classifies a milder form of hyperglycemia as GDM.

Davis et al. [22] also reported a RCT in 2021 that was a single-center, randomized trial comparing the one- and two-step strategies for GDM screening and treatment. This study enrolled 1,016 pregnant women, and a 50 g GCT was performed in all participants. If the GCT value was less than 200 mg/dL, participants were randomized to either the IADPSG (75 g OGTT, n=461) or Carpenter-Coustan group (100 g OGTT, n=460). GDM was diagnosed based on the results of a 75 g OGTT in the IADPSG group (regardless of GCT values), and in the Carpenter-Coustan group, GDM was diagnosed based on the results of a 100 g OGTT when the GCT value exceeded

Table 2. Strengths and weaknesses of the two screening methods for gestational diabetes mellitus

	One-step	Two-step
Fact	More women are diagnosed GDM (2- to 3-fold compared to the two-step approach).	Less women are diagnosed with GDM.
Strength	Using a 75 g OGTT as in the nonpregnant state GDM screening test can be done at a single visit. Based on a large-scale, multinational study assessing adverse pregnancy outcomes (HAPO study) May prevent long-term maternal and offspring complications by including milder forms of GDM (but no differences were found for adverse pregnancy outcomes from the two RCTs).	Easier screening (a 50 g GCT), which does not require fasting Less socioeconomic burden
Weakness	All pregnant women need fasting ≥8 hours and undergo a 2-hour OGTT. More women may suffer from mental stress having been diagnosed and treated for GDM. Higher socioeconomic burden	~20% of women should return for a 3-hour OGTT with fasting ≥8 hours.

GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; HAPO, the Hyperglycemia and Adverse Pregnancy Outcome; RTC, randomized controlled trial; GCT, glucose challenge test.

130 mg/dL. Their results were consistent with the report by Hillier et al. [21]. The IADPSG group had a significantly higher incidence of GDM than the Carpenter-Coustan group (one-step vs. two-step, 14.4% vs. 4.5%) and a higher number of women with GDM requiring medication (9.3% vs. 2.4%). However, there was no significant difference in the primary outcome of LGA neonates (7.7% vs. 8.5%), and no differences in other maternal or neonatal adverse pregnancy outcomes, with the exception of a higher risk of neonatal hypoglycemia in the IADPSG group.

Taken together, these RCTs suggest a significant increase in both GDM incidence and health care utilization when using the one-step approach suggested by the IADPSG, with no commensurate improvement in adverse pregnancy outcomes compared to the two-step approach (Table 2).

Observational studies implementing the IADPSG criteria
Kim et al. [23] performed a prospective observational study to investigate the pregnancy outcome in Korean women with GDM diagnosed exclusively by the IADPSG criteria. They found that the incidence of GDM increased nearly three-fold when the IADPSG criteria were applied instead of the Carpenter-Coustan criteria (one-step vs. two-step, 6.2% vs. 2.1%). The women with GDM diagnosed exclusively by the IADPSG criteria but not treated had a higher risk of preeclampsia, LGA neonates and neonatal hypoglycemia than women without GDM. A recent systematic review including eight cohort studies demonstrated that women with GDM diagnosed by the

IADPSG criteria but not by the Carpenter-Coustan criteria or Canadian Diabetes Association criteria had a higher risk for adverse pregnancy outcomes, including preeclampsia, cesarean delivery and LGA birth, than women without GDM [24]. Therefore, milder forms of GDM diagnosed by the IADPSG criteria but not by the Carpenter-Coustan criteria are associated with adverse pregnancy outcomes compared with non-GDM births.

A number of observational studies assessed the adverse pregnancy outcomes of the two screening methods by comparing women who were screened for GDM using the Carpenter-Coustan criteria in the period before the IADPSG criteria were introduced, with women screened with the IADPSG criteria afterward. Duran et al. [25] reported that when the IADPSG criteria were applied in Spanish pregnant women, the GDM incidence increased 3.5 times, but adverse pregnancy outcomes, including gestational hypertension, prematurity, cesarean delivery, LGA birth, and admission to the neonatal intensive care unit, were improved. Another observational study found that application of the IADPSG criteria increased the incidence of GDM and medication, whereas there was no association with pregnancy outcomes, including cesarean delivery, LGA birth and macrosomia [26]. Further studies are needed that compare the long-term maternal and offspring complication rates after implementing the two methods and evaluate the cost-effectiveness of treating more pregnant women who have a relatively milder degree of hyperglycemia.

OFFSPRING COMPLICATIONS OF GDM

Fetal hyperinsulinemia and excessive fetal growth

Hyperglycemia occurring in the middle and late stages of pregnancy increases the concentration of amino acids and fatty acids in the maternal blood and delivers excessive nutrients to the fetus through the placenta [27]. An excessive nutrient supply stimulates fetal pancreatic β-cells to increase insulin secretion. Fetal hyperinsulinemia induces excessive growth of insulin-sensitive tissues, such as the liver, adipose tissue, and heart. Using ultrasound, fetal abdominal overgrowth can be detected as early as 24 to 28 weeks of gestation [28,29]. This ultimately increases the risk of LGA birth in women with GDM.

A larger fetus born to women with GDM is a major factor contributing to adverse perinatal outcomes. Given that fetal size is positively associated with maternal body mass index (BMI), it is expected that Korean women with GDM who have a relatively lower BMI might have a lower risk of delivering larger babies than Caucasians. A single center study from Korea reported that the incidence of macrosomia decreased in mothers with GDM from 4.5% before 2010 to 2.8% after 2010 [30]. However, one interethnic study reported that the incidence of macrosomia in East Asians and Caucasians was not different (3 to 4% in both populations) [31]. Future studies are needed to determine whether the incidence of macrosomia and perinatal complications of Korean mothers with GDM are distinguishable from those of other ethnicities, which may affect the strictness of diagnostic criteria and/or glycemic control during pregnancy in Korean women with GDM.

Given the importance of monitoring fetal size, the American College of Obstetricians and Gynecologists (ACOG) recommends performing ultrasonographic surveillance in mothers with pregnancies complicated by GDM [32,33]. The diagnostic threshold and treatment target may need to be individualized by fetal condition (e.g., women with small for gestational age fetuses due to placental insufficiency may require loose glycemic control). No guidelines are currently available for specific indications for glycemic control according to fetal ultrasonographic findings due to the lack of well-designed studies that should be further investigated.

Metabolic perturbations in offspring of mothers with GDM in their childhood and early adulthood

Neonates born to mothers with GDM have higher body weights at birth than those born to normoglycemic mothers.

The following questions are asked: (1) Would the offspring of mothers with GDM have metabolic perturbations later in their childhood/adulthood? (2) Does tight glycemic control during pregnancy protect offspring from developing metabolic perturbations?

The HAPO follow-up study examined associations of maternal glucose levels of the 75 g OGTT during pregnancy with childhood adiposity and glucose metabolism. Among 15,812 subjects from 10 centers that participated in the follow-up study, 4,834 children were assessed for their metabolic phenotypes in early childhood. In 10- to 14-year-old offspring, maternal hyperglycemia was linearly and positively correlated with increased total fat percent (measured by air displacement plethysmography), sum of skinfolds, and the incidence of obesity after adjusting for maternal BMI during pregnancy [8]. Consistent with obesity parameters, offspring glucose levels from the 75 g OGTT and glycosylated hemoglobin were linearly associated with maternal glucose levels during pregnancy independent of maternal and child BMI [34,35]. Maternal glucose levels were inversely associated with insulin sensitivity (Matsuda index) and β-cell function (disposition index and insulinogenic index), which resulted in a higher prevalence of impaired glucose tolerance in offspring from GDM mothers than in offspring from non-GDM mothers (10.6% of offspring born to mothers with GDM vs. 5.0% of offspring born to normoglycemic mothers).

In Korean children aged 5 years, BMI was comparable between offspring born to mothers with GDM or to normoglycemic mothers (16.0 kg/m^2 from mothers with GDM vs. 16.1 kg/m^2 from normoglycemic mothers) [36]. Body composition analysis by dual-energy X-ray absorptiometry revealed that total, truncal, and leg fat masses were higher and total lean mass was lower in offspring born to mothers with GDM. Regional fat mass was positively correlated with maternal glucose levels during pregnancy. However, the association between glucose intolerance in childhood and maternal glucose levels was not evident at this age. A subgroup of the HAPO study from Hong Kong showed a significant but modest increase in BMI at age 7 years (15.3 kg/m^2 from mothers with GDM vs. 15.0 kg/m^2 from normoglycemic mothers) [37]. To summarize, BMI differences in East Asian children born to mothers with either GDM or normoglycemia were less evident than those in children of other ethnicities. Therefore, body composition analysis and/or skinfold thickness measurement may be preferable in Asian offspring born to mothers with GDM to assess their adi-

posity and cardiometabolic risk. Perturbations in glucose tolerance in Asian children born to mothers with GDM should be further investigated.

The molecular basis of offspring adiposity and glucose intolerance is expected to be multifactorial—genetic and epigenetic inheritance, exposure to intrauterine hyperglycemia, rapid adiposity gain after birth, etc. Epigenetic alteration owing to intrauterine hyperglycemia has been assessed by comparing pairwise DNA methylation differences between siblings whose maternal GDM status was discordant [38]. Twelve differentially methylated regions were discovered that included regions in HNF4A and RREB1 that are associated with monogenic diabetes and obesity, respectively. Recent multiomic cord blood analyses from GDM deliveries present possible molecular candidates contributing to the transgenerational cycle of obesity and diabetes [39-41], but further investigation and validation are needed.

MATERNAL COMPLICATIONS OF GDM

Screening for postpartum type 2 diabetes mellitus

Women with a previous history of GDM are 10 times more likely to develop postpartum type 2 diabetes mellitus [42-44]. More than 50% of women with a previous history of GDM develop type 2 diabetes mellitus within 10 years after delivery [45,46]. The American Diabetes Association recommends that women with a previous history of GDM be screened for postpartum glucose intolerance by OGTT at 6 to 12 weeks postpartum and to have lifelong evaluations for diabetes at least every 3 years [47]. In a Korean study, the 2-hour glucose from the initial postpartum OGTT was an independent predictor of future development of diabetes, but fasting glucose was not [48]. This emphasizes the need to perform OGTTs in women with GDM after delivery, which should not be restricted to fasting blood tests.

Concurrent measurement of insulin levels during the OGTT to assess β-cell function may be helpful because women who progressed to type 2 diabetes mellitus in later life had lower β-cell function (1-hour insulinogenic index and disposition index) during pregnancy [45,49]. However, the cutoffs for impaired β-cell function are lacking and need to be individualized by each institution considering the difficulty of standardizing insulin concentrations.

Multiethnic studies assessing postpartum diabetes reported a higher risk of developing diabetes or impaired glucose tolerance in Asians than in Caucasians (Ignell et al. [50] 5-fold increased risk of diabetes at 1 to 2 years postpartum; Kousta et al. [51] 44% vs. 28% with impaired glucose tolerance at 20 months postpartum). In these studies, Asian women with a previous history of GDM who resided in Western countries had similar BMIs to Caucasians but had a higher risk of postpartum glucose intolerance. The ethnic-specific risk in women who reside in their native regions remains elusive, but Asian women possess a higher risk when exposed to a Western environment or diet.

Risk factors for postpartum type 2 diabetes mellitus

The risk factors for the progression to type 2 diabetes mellitus include maternal age, family history of diabetes, glycemic indices during pregnancy, and genetic predisposition, which are not modifiable after delivery [10,46]. Genetic variants, including CDKN2A/2B, HHEX, and CDKAL1, are associated with impaired β-cell function and an increased risk for postpartum type 2 diabetes mellitus [45,52].

In addition to these nonmodifiable risk factors, clinicians should be aware of improving modifiable risk factors, including lactation, exercise, healthy diet, postpartum weight loss, and improving body composition [46,53-56], all of which correlate with improvement in insulin sensitivity. A Korean study showed that women who lost weight after delivery had improvements in insulin sensitivity and less frequently progressed to type 2 diabetes mellitus, while women who gained weight showed the opposite during 4 years of follow-up [54]. We recently investigated whether higher muscle mass defined by appendicular skeletal muscle mass/BMI was associated with lower insulin resistance and a reduced risk of prediabetes and type 2 diabetes mellitus after delivery in Korean women with a previous history of GDM. We have further discussed the other modifiable risk factors (obesity, diet, exercise, etc.) for progression to postpartum diabetes in another review paper [46].

Cardiovascular disease and metabolic perturbation

Not surprisingly, GDM is associated with postpartum metabolic perturbation and an increased risk of CVD [57-59]. Recently, the American Heart Association released a scientific statement describing a 2-fold higher risk of developing CVD in women with GDM [11,60,61]. This increased risk was independent of the subsequent development of postpartum type 2 diabetes mellitus.

Women who develop GDM already have higher BMIs and

worse metabolic profiles before pregnancy, which includes higher total cholesterol, triglycerides, and homeostatic model assessment for insulin resistance and lower high-density lipoprotein cholesterol [62,63]. Immediately after delivery, women with a previous history of GDM are more obese and have a higher prevalence of metabolic syndrome [64,65]. Over time after delivery, the annual increases in BMI, blood pressure, and total cholesterol did not differ between women with and without GDM. Therefore, women with a previous history of GDM persistently have worse cardiometabolic risk factors than women without GDM over time [64]. As a result, women with a previous history of GDM have increased coronary artery calcium scores and carotid intima media thickness, which are surrogates for atherosclerosis and future CVD, after delivery [66,67]. More surprisingly, women who sustained normoglycemia after a delivery complicated by GDM could not eliminate their future cardiovascular risk, as evidenced by a >2-fold prevalence of positive coronary artery calcium scores (26.3% vs. 12.9%) [67].

To date, there are no well-designed prevention trials for CVD in women with a previous history of GDM. It is expected that intensive lifestyle modification (e.g., healthy diet and exercise) would reduce the future development of CVD by improving cardiometabolic risk factors. Postpartum weight loss in Korean women with a previous history of GDM significantly improved blood pressure, lipid profile, % body fat, insulin sensitivity (Matsuda index) and β-cell function (disposition index) [54]. Lactation improves maternal cardiometabolic risk, which is further discussed below. Clinicians should also ask for a woman's obstetric history to assess their CVD risk, as a history of preeclampsia, preterm birth, placental abruption, etc. are independent risk factors, along with GDM, for the development of postpartum CVD [60].

Benefits of lactation

Lactation increases energy consumption (up to 500 kcal/day) due to breastmilk production and reduces the risk of maternal postpartum diabetes in a dose (duration)-dependent manner [68,69]. This beneficial effect of lactation in preventing postpartum diabetes lasts up to 30 years after delivery [70,71].

Metabolic outcomes related to pregnancy and/or GDM have been comprehensively examined in the Coronary Artery Risk Development in Young Adults (CARDIA) study, which examined the development and determinants of clinical and subclinical CVD [72]. This study began in 1985 and 1986 with

2,787 women aged 18 to 30 years and follow-up is ongoing for >30 years. From the CARDIA study, a longer duration of lactation improved postpartum glucose tolerance and other metabolic perturbations, including metabolic syndrome [73], nonalcoholic fatty liver disease [74], and the amount of visceral and pericardial fat [75]. In other studies, a longer duration of lactation was associated with a lower risk of maternal hypertension [76] and CVD-related hospitalization or mortality [77]. Therefore, lactation has persistent favorable effects on the cardiometabolic health of women. Recent metabolomic analysis has discovered that lactation decreases circulating glycerolipids (triglycerides and diacylglycerol species) and increases phospholipids and sphingolipids, possibly as a result of suppressing endogenous lipogenesis and upregulating catabolism of lipids to produce breastmilk [78].

Strong epidemiologic evidence supports the beneficial effect of lactation on preventing metabolic disorders and CVD. However, its underlying mechanism is less well understood. Prolactin, a hormone secreted from the pituitary during pregnancy and lactation, regulates β-cell adaptation against increased insulin resistance during pregnancy [79]. In animal studies, β-cell proliferation occurs during pregnancy via prolactin receptor-STAT5-serotonin-HTR2B activation [80]. During lactation, β-cell mass expansion and insulin secretion are potentiated with increased circulating prolactin [56]. Human studies support the beneficial role of prolactin in β-cells, as serum prolactin in pregnancy was positively associated with postpartum β-cell function. Also, women who progressed to type 2 diabetes mellitus had lower prolactin during pregnancy than those who maintained normoglycemia after delivery [81]. These factors resulted in improved β-cell function at 4 years postpartum in Korean women with GDM who previously lactated compared to those who did not lactate (40% increase in disposition index) [56]. Furthermore, higher prolactin levels and prior lactation are linked to improved insulin sensitivity in women of reproductive age and in the general population [82-84]. Considering the health benefits of lactation for both infants and mothers, clinicians should strongly promote mothers to lactate as long as possible or consider using breastmilk pumps in working mothers.

CONCLUSIONS

GDM is associated with adverse pregnancy outcomes and long-term offspring and maternal complications. From a series
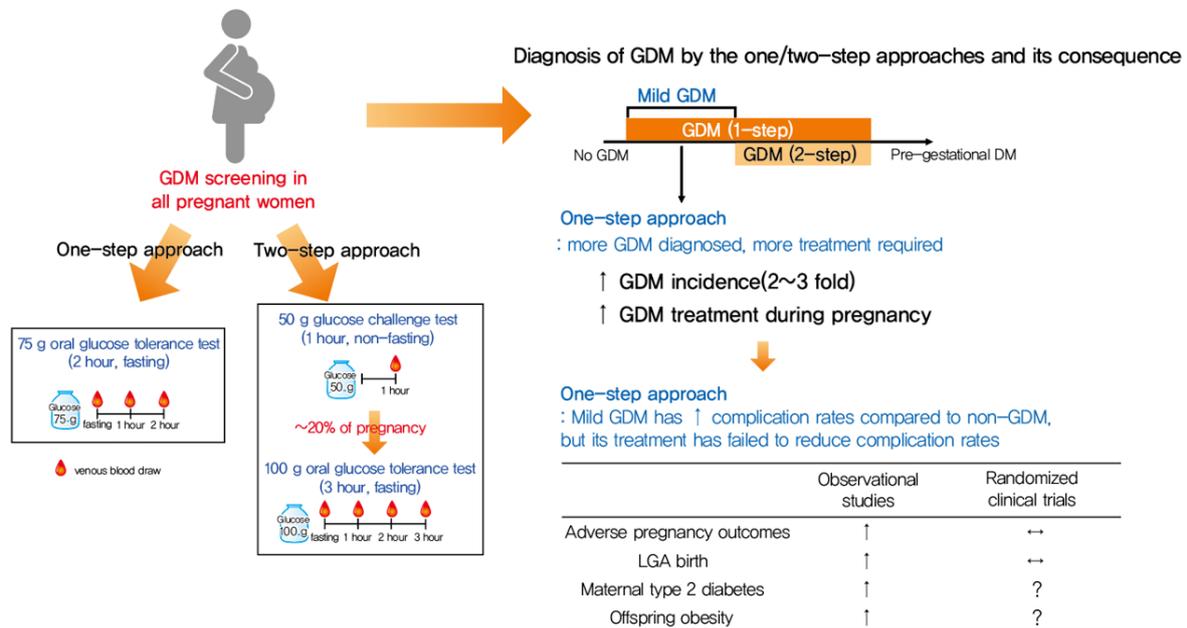
Fig. 2. Schematic summary of the two diagnostic approaches of gestational diabetes mellitus (GDM). DM, diabetes mellitus; LGA, large for gestational age.

of studies, the one-step approach caused two to three times more women to be diagnosed with GDM than the two-step approach. In recent RCTs, adverse pregnancy outcome rates were generally similar between the two methods, although more women were diagnosed with GDM by the one-step approach. Exploratory analyses of the HAPO follow-up study demonstrated a significant increasing trend of worse maternal (glycemic profile) and offspring (adiposity) outcomes from non-GDM to GDM exclusively by the IADPSG criteria to GDM by the Carpenter-Coustan criteria [85]. We have discussed the merits and demerits of the one-step and two-step approaches in this review but controversy remains (Table 2, Fig. 2).

Pros to the one-step approach: There is copious high-level evidence that identification and treatment of milder forms of GDM are of benefit to the individual mother and child [86]. Cons to the one-step approach: There is insufficient evidence to justify the increase in health care costs of broadening the diagnosis by implementing a one-step approach [87].

The Korean Diabetes Association equally recommends the one-step and two-step approaches for the diagnosis of GDM. Taking the controversies into account, choosing the diagnostic approach for GDM should be based upon locally validated evidence, cost-effectiveness, and feasibility in clinical practice. For example, if a lower prevalence of GDM has been estimated or

is expected at a certain clinic, ruling out non-GDM pregnancies by a non-fasting 50 g GCT (two-step approach) may be cost-effective than performing a fasting 75 g OGTT (one-step approach) in all pregnant women. Currently, only pregnant women are using a 3-hour 100 g OGTT (two-step approach) for diagnosis. The OGTT conducted by pregnant women will have to be changed to 75 g OGTT in the future.

Adverse pregnancy outcome rates according to the two diagnostic approaches have been assessed in RCTs, but long-term maternal and offspring complications have not been assessed in RCTs or interventional trials. Future studies are needed to determine whether treating milder forms of GDM can prevent long-term maternal and offspring complications described in this review.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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