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Gestational Diabetes Mellitus Update and Review of Literature

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Abstract

Gestational diabetes mellitus has been associated with various maternal and perinatal adverse outcomes. Screening and subsequent treatment are associated with short term benefit. With the recent recommended diagnostic criteria by the International Association of Diabetes and Pregnancy Study Groups and increasing rate of obesity, the prevalence will continue to rise. It remains uncertain whether this new diagnostic criteria is cost effective or beneficial. Interventions include lifestyle modification, oral hypoglycaemic agents and insulin. The encouraging result and safety profile with oral hypoglycaemic agents may provide a safe alterative to insulin in patients who fail lifestyle modification.

Introduction

Gestational diabetes mellitus (GDM) is defined by glucose intolerance of variable severity with onset of first recognition during pregnancy [1]. Hyperglycaemia during pregnancy is found to be associated with various maternal and perinatal adverse outcomes [2,3]. Their offsprings will have a life-long increase risk of glucose intolerance, obesity and metabolic syndrome whereas the mothers will have a higher risk of metabolic syndrome and diabetes in the future [4]. The detection of GDM during pregnancy provides an opportunity to identify women at risk of short term and long term complications. We now have evidence that early diagnosis and intervention can reduce the adverse perinatal outcomes [5-7]. Throughout all these years, there is still no consensus on the optimal diagnostic cut-off until the recent recommendation by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) [8]. The purpose of this review is to provide a recent update and discuss the current controversies on GDM. The implications of the recent international consensus statement on new diagnostic criteria for GDM are discussed.

Historic Evolution

The history of GDM dated back to 1964 when O'Sullivan proposed specific criteria to interpret the glucose tolerance level in pregnancy to identify women at a higher risk for developing diabetes after delivery [9]. The criteria was later modified by the National Diabetes Data Group (NDDG) in 1979 [10] and Carpenter and Coustan [11] in view of the change from using venous whole blood samples to plasma or serum samples and the technique in analyzing blood glucose levels. The Carpenter and Coustan criteria were lower than the NDDG criteria and therefore resulted in a higher prevalence of GDM.

In 2000, the American Diabetes Association (ADA) recommended the use of the Carpenter and Coustan criteria for diagnosis of GDM. Despite this recommendation, various authorities had their own diagnostic threshold which resulted in a lot of confusions to the physicians and their patients. In 2008, the result of "Hyperglycemia and Adverse Pregnancy Outcomes (HAPO)" study was published [2]. This major observational study provided us valuable information regarding the risks of adverse outcomes associated with various degrees of maternal glucose intolerance. Based on the result of this study, the IADPSG proposed a new diagnostic criteria in 2010 [8]. However, controversies and debates continued.

Epidemiology

The quoted prevalence of GDM ranged from 1 to 14% [4]. It depended on which population was being studied and which screening strategies and diagnostic criteria were used [12]. The prevalence in the United Kingdom, United States and among European countries was estimated to be 5%, 3-7% and 2-6% respectively [13-15]. The prevalence would be increased to 2.4-times higher if the modified IADPSG criteria were used compared with the World Health Organization (WHO) criteria [16]. Higher prevalence of GDM was noted in African, Asian, Indian and Hispanic women [17-19]. Other reported risk factors were advanced maternal age, high parity, obesity, polycystic ovarian syndrome (PCOS), multiple pregnancy, family history of diabetes, obstetric history of congenital malformation, stillbirth, macrosomia and previous GDM.

Once a disease of older people, type 2 diabetes was increasingly affecting women during their fertile years [20], many population studies indicated that the increasing incidence of GDM parallels that of its type 2 group [21,22]. Together with the new diagnostic criteria which included more patients with lesser extent of hyperglycaemia and increasing rate of obesity, the prevalence would continue to rise [8,23].

Screening

Screening for GDM was recommended because of its asymptomatic nature and a proportion of patients had no classic risk factors. Numerous national guidelines existed and recommended how we should screen for the disease. For the timing of screening, apart from allowing detection of overt diabetes and earlier intervention, there was no sufficient data for other benefits to screen before 24 weeks of gestation. Screening before this period might miss GDM due to its pathophysiology of rising insulin resistance from the second trimester. The widely adopted timing was between 24-28 weeks, which timely intervention could potentially avoid the fetus being affected by maternal hyperglycaemia.

Screening of GDM could be performed to the whole obstetric population (universal screening) or targeted at the high risk groups (risk factor screening). In the summary and recommendations of the Fourth International Workshop Conference in 1997 [24], risk factor screening was recommended and the statement was reaffirmed at the Fifth International Workshop Conference in 2005 [25]. At that time, ADA recommended all obstetric patients to be classified into low, average and high risk [24,25]. Patients who fulfilled all of the following criteria would be low risk and required no GDM screening: less than

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	Carpenter and Coustan/ ADA (2004)*		ACOG (2011)*	WHO/NICE (2008)+	RANZCOG (2011)+	IASPSG/ ADA (2012)+
	75g OGTT	100g OGTT	100g OGTT	75g OGTT	75g OGTT	75g OGTT
Fasting	5.3mmol/l	5.3mmol/l	5.3mmol/l	7 mmol/l	5.5 mmol/l	5.1mmol/l
1-h	10 mmol/l	10 mmol/l	10 mmol/l			10.mmol/l
2-h	8.6mmol/l	8.6mmol/l	8.6mmol/l	7.8mmol/l	8.0/9.0mmol/l #	8.5mmol/l
3-h		7.8mmol/l	7.8mmol/l			

*Diagnosis made if two or more glucose value met or exceeded.
+Diagnosis made if one or more glucose value met or exceeded.
#8.0 mmol/l by Australian criteria, 9.0 mmol/l by NZ criteria.

Table 1: Diagnostic criteria by various authorities

25 years old, ethnic group with a low prevalence of GDM, no known diabetes in first-degree relatives, normal pre-pregnancy weight, no history of abnormal glucose metabolism and no history of poor obstetric outcome. Patient with severe obesity, strong family history of type 2 diabetes, previous history of GDM, impaired glucose metabolism, or glucosuria would be high risk and testing would be performed as soon as possible in this group. The remaining patients were average risk and should receive GDM testing at 24–28 weeks. High risk patients who were not diagnosed earlier would have a second test at the same time. In 2008, National Institute for Health and Clinical Excellence (NICE) guideline recommended all women should be assessed for risk factors at the first antenatal visit [26]. Women with body mass index (BMI) > 30 kg/m^2, previous macrosomic baby weighing 4.5 kg or above, previous GDM, family history of first-degree relatives with diabetes or family origin with a high prevalence of diabetes should be offered a diagnostic test using 75g, 2-hour oral glucose tolerance test (OGTT) at 24-28 weeks. Women with history of GDM should receive OGTT at 16–18 weeks and a further OGTT at 28 weeks if the results were normal.

However, selective screening by risk factors might miss at least 30% of the women with GDM leaving them at risk of developing adverse outcome, making this approach unattractive [27]. Recent randomized trial had shown the benefit of treatment of GDM and a possible reduction of healthcare cost with universal screening. Therefore, in 2011, American College of Obstetricians and Gynecologist (ACOG) [23], ADA [28] and Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) [29] recommended universal screening because of the beneficial effect from screening, diagnosis and subsequent treatment.

After identifying the screening population, the next question would be how we should screen them. There were two strategies to screen the target population. The "one-step" approach referred to diagnosing GDM with diagnostic OGTT without prior plasma or serum glucose screening. The "two-step" approach was to perform a diagnostic OGTT only if the first screening test was positive. Random glucose, glycated protein, fasting capillary glucose, fasting glucose, 50g 1-hour glucose challenge test (GCT) had all been proposed as the screening tool before a diagnostic OGTT in "two-step" approach [30-35]. These screening tests had various sensitivities. For example, using a threshold of 7.8 mmol/l in 50g GCT, pooled estimate of sensitivity ranged between 0.74 (95% CI 0.62–0.87) and 0.83 (95% CI 0.75–0.91) [35]. Lowering the threshold to 7.2 mmol/l could increase the sensitivity of the test to 0.9 [4]. This false negative result might lead to false reassurance to the patients and physicians. In contrary, the "one-step" approach could eliminate the problem of a false negative test and the potential drop-off after a positive screening test [34]. It also decreased administrative workload, avoided delay in commencement of treatment, and might be more cost effective in the high risk population as it saved the need for subsequent confirmatory testing [4, 24]. The main drawback with this approach would be its cost [36, 37] and the need for patients to undergo overnight fasting. In 2011, ADA recommended "one-step" test using 75g, 2-hour OGTT at 24–28 weeks of gestation [28]. ACOG recommended a "two-step" test which all pregnant women should be screened by patient history, clinical risk factors, or a 50g GCT (23). RANCZOG accepted either approach [29].

Diagnosis

The test employed and the threshold used for diagnosis was extremely crucial to facilitate patient care, to avoid confusion and to gain consensus in future research. The commonly utilized tests were the 75g 2-hour OGTT (NICE, ADA, RANZCOG) [26, 28, 29] and the 100g 3-hour OGTT (ACOG) [23] (Table 1). However, various authorities had their own diagnostic threshold which resulted in a significant dilemma [12]. The WHO extrapolated the diagnostic cut-off from non pregnant population while the ADA used the same diagnostic threshold for both 100g and 75g OGTT [4]. The diagnostic cut-off should be deduced from where there would be an increase in maternal or perinatal complications, and where effective treatment could be offered to decrease such complications. The aim of HAPO was to clarify any risks of adverse outcomes associated with a lesser degree of hyperglycaemia and aid the development of an internationally agreed diagnostic criterion [2]. 25,505 pregnant women were included from 15 centers in nine countries and tested by a 75g 2-hour OGTT within 24 to 32 weeks. A continuous association was noted between glucose values and the likelihood of large for gestational age, primary caesarean delivery, fetal insulin levels and neonatal adiposity. An odds ratio of 1.75 times the mean for the outcomes of increased neonatal body fat, large for gestational age and cord serum C-peptide greater than the 90^{th} centile was arbitrarily chosen for the proposed new diagnostic criteria by the IADPSG [8]. Using a 75 g 2-hour OGTT, any of the fasting glucose ≥ 5.1mmol/l, 1 hour plasma glucose ≥ 10 mmol/l or 2 hour plasma glucose ≥ 8.5 mmol/l would be diagnostic of GDM. However, it was estimated that 18% of women would be diagnosed under the new criteria. Roughly 1 in 5 women would be labeled as GDM which may lead to medicalization of pregnancy. This would pose a significant financial burden to the health care system. More importantly, there was no proven advantage to treat under the new recommendation.

To change or not to change?

Despite the generous effort by the IADPSG trying to unite the confusing approaches to GDM, different groups still have a lot of reservations regarding the implementation of the new criteria [18,23,38,39]. Since the IADPSG was derived from HAPO which only included a specific population, its application to the general population would need to be further evaluated [40]. Obesity was another factor leading to adverse perinatal outcomes. Higher maternal BMI was independently associated with an increasing frequency of birth weight >90th percentile, percentage body fat >90th percentile, primary caesarean delivery, and cord C peptide >90th percentile [41]. The risk was further exacerbated when both factors were present [42]. Thus, addressing the problem of obesity was also needed to decrease such

complications. The cost involved in the new screening strategy should not be underestimated. Cost effectiveness analysis should be set up in each locality [43]. The IADPSG approach to GDM would only be cost effective compared to current screening if this would provide an opportunity for treatment and prevention of future overt diabetes [44]. Therefore, it would be vital to develop strategies to reduce the long term risks to enhance the potential benefit of screening and treatment. Evidence on treatment for hyperglycaemia under the new criteria was lacking. Before such information was available for short term and long term benefit, it may not be worthwhile changing the current clinical practice. Since the relative diagnostic accuracies of fasting, 1-h, and 2-h glucose levels were different in different centers, some authors proposed the screening strategy could be modified according to the respective diagnostic values in different centers to improve its cost effectiveness [33, 45].

Treatment

The detection of GDM during pregnancy provided an opportunity to identify women at risk of short term and long term complications. Some argued that pregnancy related hyperglycaemia might be completely physiological to provide nutrient to the fetus and whether there was a need to diagnose and treat GDM. It was then shown by Crowther et al. and others that diagnosis and subsequent treatment were beneficial [5-7]. In 2005, the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) randomized 1000 women with diagnosed GDM using 75g OGTT into intervention group and control group between 24 and 34 weeks of gestation. The rate of serious perinatal outcomes among infants decreased significantly from 4% to 1% after intervention (P=0.01, adjusted relative risk 0.33, 95% CI, 0.14 to 0.75). 34 infants were needed to treat to prevent a serious outcome (95% CI, 20 to 103). The mean birth weight in the intervention group was lower (3482 g vs 3335 g, P<0.001, adjusted treatment effect -145, 95% CI -219 to -70) [5]. Similar to ACHOIS, in 2009, Landon et al. [6] randomized 958 subjects with GDM at 24 to 31 weeks of gestation into intervention group and control group. In the intervention group, there was a reduction in the incidence of shoulder dystocia (4% vs 1.5%, P=0.02, relative risk 0.37, 97% CI 0.14 to 0.97), macrosomia (14.3 vs 5.9%, P<0.001, relative risk 0.41, 97% CI 0.26-0.66) and caesarean delivery (33.8% vs 26.9%, P=0.02, relative risk 0.79, 97%CI 0.64–0.99) [6]. The mean birth weight (3408 g vs 3302 g, P<0.001) was lower when compared to the control group. In a meta analysis including five randomized controlled trials (RCT), the conclusion was mainly dominated by the above two mentioned trials, the risk of shoulder dystocia (odds ratio 0.40, 95% CI 0.21 to 0.75) and macrosomia (odds ratio 0.48, 95% CI 0.38 to 0.62) was reduced by specific GDM treatments [7]. It therefore would be justifiable to diagnose and treat GDM for its potential benefit.

The aim of treatment was to maintain maternal blood glucose concentration within an acceptable range in a normal pregnancy. Interventions included lifestyle modification, oral hypoglycaemic agents (OHAs) and insulin.

It was estimated that 70-90% of women diagnosed with GDM could achieve targeted glycaemic goals with lifestyle modification and nutrition therapy alone [46, 47]. Hyperglycaemia could be reduced by carbohydrate restriction or a low glycaemic index diet. The glycaemic index was introduced as a means to categorize the distinctly different glycaemic impact of specific carbohydrate foods [48]. The use of low glycaemic index diet might reduce postprandial glucose responses in non-pregnant adults living with diabetes and women with GDM [49, 50].

Traditionally, insulin was being used for better glycaemic control in which dietary adjustment alone had failed [4]. The rapid onset of action and the inability to cross the placenta made it the treatment of choice. It was usually prescribed as a few short acting forms together with and an intermediate acting form in order to achieve a relative stable glucose state. However, it required refrigerated storage thus making it expensive and not widely available in low resources countries. Patients needed to acquire the skill for injection and would face the risk of maternal hypoglycaemia. On the other hand, there were growing evidences that OHAs were equally safe and effective [51-57]. OHAs were cheaper and easier to be administered. They were more acceptable to patient and could improve compliance. The glyburide and metformin were the most frequently studied drugs. Glyburide was the second generation sulfonylurea which enhanced insulin secretion and insulin sensitivity of peripheral tissue. It was a United States Food and Drug Administration category C medication with minimal transplacental passage in vivo. Metformin was an insulin sensitizer which increased peripheral glucose uptake and decreased hepatic gluconeogenesis. It was a category B medication and it passed through the placenta. Its use in patient with PCOS during the first trimester and treatment for GDM so far did not reveal any teratogenicity [46]. A systemic review of four RCTs and five observational studies compared the maternal and neonatal outcomes in women with GDM treated with OHAs with all types of insulin. They found no substantial adverse maternal or neonatal outcome with the use of glyburide or metformin compared with insulin. The strength of evidence was not strong in view of small quantity of studies and their different study designs [52]. Another systemic review included six RCTs with 1388 subjects comparing OHAs with insulin, of which two studies were also included in the previous review. There were no significant differences in maternal fasting or postprandial glycaemic control. Use of OHAs was not associated with an increase risk of neonatal hypoglycaemia, caesarean delivery, and increased birth weight or large for gestational age infants [53]. Compared with insulin, metformin was associated with less weight gain, better satisfaction and acceptance, and a lower risk of maternal hypoglycaemia [51].Therefore, with the comparable short term outcomes, OHAs could be considered as a safe alternative for treatment of GDM.

Two RCTs compared the use of metformin and glyburide in patients who failed dietary treatment. One study, which randomized 72 patients into two groups, showed no difference in terms of modes of delivery, gestational age at delivery, birth weight, macrosomia or neonatal hypoglycaemia. Women in the metformin group had lower weight gain during pregnancy [54]. The other study of 149 women also showed no difference in glucose control, gestational age at delivery, neonatal intensive care unit admission, neonatal hypoglycaemia, maternal hypoglycaemia and shoulder dystocia. However, in the latter study, metformin was associated with a statistically significant lower birth weight (3329 vs. 3103 g) but increased caesarean delivery [55]. Patient requiring insulin for glucose control was similar in glyburide group and metformin group (23.8% vs 25.0%) [54], while 34.7% in the metformin group and 16.2% in the glyburide group required insulin to achieve adequate control in the latter study [55]. A study that followed up the children of women treated with metformin during pregnancy found no effect of on weight, height, growth or motor social development up to 18 months old [58]. More upcoming studies demonstrated similar short term outcome between OHAs and insulin and provided clinician with confidence in using OHAs [56,57]. Due to its convenient administration, low cost and encouraging result, it may be expected that OHAs would become the first line treatment in GDM patient who failed dietary modification in the future. However, physician should also be aware that studies regarding the long term safety on children of

patients treated with OHAs were lacking. Adequate patients' counseling was important before starting OHAs.

Weight gain on GDM

Institute of Medicine set guideline on weight gain during pregnancy according to the pre-pregnancy BMI [59]. The gestational weight gain before 24 weeks was a risk factor for GDM in overweight and obese patients but not in patients with a normal BMI or who were underweight before pregnancy [60]. It was later shown that gestational weight gain above the recommendation by Institute of Medicine guideline would increase the risk of caesarean delivery, preterm delivery, and macrosomia [61-63]. However, weight gain below this would also increase the proportion of small for gestational age baby [62].

Delivery

With advancing gestation, the risk of macrosomia, shoulder dystocia and stillbirth increased. Management options included expectant management, induction of labour or elective caesarean delivery. The timing and the mode of delivery was not straight forward as well controlled prospective studies were lacking. For the timing of delivery, ADA in 2004 recommended delivery at 38 weeks unless obstetric considerations dictated alternative management [4], while ACOG did not recommend routine delivery before 40 weeks [64]. NICE in 2008 recommended pregnant women with diabetes should be offered elective birth through induction of labour after 38 completed weeks [26]. RCOG in 2012 recommended induction of labour at term to reduce the incidence of shoulder dystocia in women with gestational diabetes [7,65]. One systemic review included one RCT and four observational studies. The RCT suggested that active induction at 38 weeks could reduce birth weight and macrosomia without increasing caesarean delivery. The four observation studies suggested a potential reduction in macrosomia and shoulder dystocia with elective delivery. They found it difficult to draw conclusions based on the limited evidence [66]. A retrospective cohort study observed that expectant management may increase risk of mortality at 39 weeks when compared with delivery. 1500 deliveries would be needed to prevent one death at 39 weeks. However, the degree of glycaemic control of the subjects was not available [67]. For the mode of delivery, caesarean delivery would only be suggested for an estimated fetal weight of 4500g in mothers with diabetes to prevent brachial plexus injury by a decision analysis study [68]. The delivery option of well controlled GDM remained uncertain. Future prospective study would be needed.

Future Direction

Identifying a high risk group could potentially allow preventive measures before the development of GDM. Increase in the insulin level before 16-18 weeks was suggested to reflect the underlying insulin resistance. The measurement of fasting and 2-hours serum insulin level less than 16 weeks was shown to be useful to predict the chance of GDM [69]. The hyperinsulinaemia detected during the first trimester could predate the development of GDM [70]. Both trials focused on a high risk group, so its use in general population should be further evaluated. A recent cluster-randomized trial revealed a non significant decrease risk of GDM in the intervention group (intensified counseling on physical activity, diet and weight gain) than the usual care group [71]. Nutritional advice for weight gain during pregnancy could reduce the risk of GDM [72]. The future direction should focus on the early prediction and effective preventive measures before the development of GDM, so as to decrease the associated short term and long term complications.

Summary

Gestational diabetes remains a contentious issue for debate. Screening and subsequent treatment are beneficial for short term outcome and possibly long term outcome. With the generous effort by the IADPSG, a new criterion was proposed and re-instilled the focus to the optimal cut off for GDM diagnosis. It remains uncertain whether the new approach is cost effective or beneficial. The encouraging result and safety profile with OHAs provides a safe alterative to insulin in patient who fails lifestyle modification. While all the research related to management will need to be based on a well-defined criterion of GDM, a consensus is urgently needed.

Conflict of Interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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