Gestational Diabetes Mellitus and Exercise
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 alternative 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
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/m², 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 for GCT at 24–28 weeks. 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). RANZCOG accepted either approach [29].

### Table 1: Diagnostic criteria by various authorities

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<td>7 mmol/l</td>
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<td>1-h</td>
<td>10 mmol/l</td>
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<td>2-h</td>
<td>8.6mmol/l</td>
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<td>3-h</td>
<td>7.8mmol/l</td>
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*Diagnosis made if two or more glucose value met or exceeded.
**Diagnosis made if one or more glucose value met or exceeded.
*0.0 mmol/l by Australian criteria, 9.0 mmol/l by NZ criteria.

### 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 90th 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 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 alternative 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.
Gestational diabetes mellitus: challenges in diagnosis and management

Abstract
Gestational diabetes mellitus (GDM) is a well-characterized disease affecting a significant population of pregnant women worldwide. It has been widely linked to undue weight gain associated with factors such as diet, obesity, family history, and ethnicity. Poorly controlled GDM results in maternal and fetal morbidity and mortality. Improved outcomes therefore rely on early diagnosis and tight glycaemic control. While straightforward protocols exist for screening and management of diabetes mellitus in the general population, management of GDM remains controversial with conflicting guidelines and treatment protocols. This review highlights the diagnostic and management options for GDM in light of recent advances in care.

Keywords: Gestation diabetes mellitus, Glucose intolerance, Screening, Glycaemic control, Insulin, Oral agents

Introduction
Gestational diabetes mellitus (GDM), by definition, is any degree of glucose intolerance with onset or first recognition during pregnancy [1, 2]. This definition applies regardless of whether treatment involves insulin or diet modification alone; it may also apply to conditions that persist after pregnancy. GDM affects roughly 7 % of pregnancies with an incidence of more than 200,000 cases per year [2]. The prevalence, however, varies from 1–14 %, depending on the population and the diagnostic criteria that have been used [2].

GDM is the most common cause of diabetes during pregnancy, accounting for up to 90 % of pregnancies complicated by diabetes [2]. Women with GDM have a 40–60 % chance of developing diabetes mellitus over the 5–10 years after pregnancy [3].

Although GDM has been recognized as a disease for some time, it remains a controversial entity with conflicting guidelines and treatment protocols.

Review
Screening
The first screening test for GDM, proposed in 1973, consisted of the 1-h 50 gm oral glucose tolerance test [4]. While some guidelines recommend universal screening, others exempt those patients who are categorized as low-risk. Evidence suggests that universal screening improves pregnancy outcomes compared to selective screening [5]. However, other researchers argue that screening women based on their clinical characteristics allows for more efficient selective screening for GDM [6].

Low-risk patients include those women with the following characteristics: <25 years of age; normal body weight; no first-degree relatives with diabetes; no history of abnormal glucose metabolism; no history of poor obstetric outcomes; and not from an ethnic group with a high diabetes prevalence (Hispanic American, Native American, Asian American, African American, and Pacific Islander) [7, 8]. Although some experts recommend against screening these low-risk patients routinely [2], selective screening could miss approximately 4 % of patients with GDM [9].

Pregnant women with factors conferring a high risk of GDM (marked obesity, previous history of GDM, glycosuria, or family history of diabetes) should be screened for GDM as soon as possible, preferably during their first antenatal visit. If negative, they should be retested at the beginning of their third trimester between 24 to
28 weeks of gestation. Women who are categorized as average risk (neither high nor low risk) should also be screened between 24 and 28 weeks of gestation [2]. When universal screening is implemented, patients with no recognized risk factors for GDM also undergo a 1-h glucose challenge test at 24 to 28 weeks of pregnancy. The classification criteria are summarized in Table 1 [6].

Fasting plasma glucose and postprandial plasma glucose have been shown to have low sensitivity as screening tests for GDM [10, 11], and therefore they are not recommended for screening.

In general, there are two approaches to the evaluation of women for GDM: the one-step approach and the two-step approach. In the one-step approach, a diagnostic oral glucose tolerance test (OGTT) is performed without prior plasma or serum glucose screening. This approach may be cost effective in high-risk patients. In the two-step approach, initial screening involves the glucose challenge test, which measures the plasma or serum glucose concentration 1 h after a 50-gm oral glucose load. The diagnostic oral glucose challenge test is performed only in the subset of women found to have plasma or serum glucose concentration values exceeding the threshold for the glucose challenge test.

When the threshold for glucose challenge test is >140 mg/dl (7.8 mmol/l), the sensitivity is 80%; when it is 130 mg/dl (7.2 mmol/l), the sensitivity becomes 90% [1]. Whichever approach is used, the diagnosis of GDM is established only after performing an OGTT.

Diagnostic criteria
There are two major diagnostic criteria for the 3-h 100-gm OGTT used in the United States: the Carpenter-Coustan and the National Diabetes Data Group (NDDG) criteria. The Carpenter-Coustan criteria derive from the work of O’Sullivan and Mahan [4], which Carpenter and Coustan modified in 1982 [12]. In this method, diagnosis of GDM is based on exceeding two or more of the following threshold values:

- Fasting serum glucose concentration of 95 mg/dl (5.3 mmol/l)
- 1-h serum glucose concentration of 180 mg/dl (10.0 mmol/l)
- 2-h serum glucose concentration of 155 mg/dl (8.6 mmol/l)
- 3-h serum glucose concentration of 140 mg/dl (7.8 mmol/l)

The NDDG criteria, meanwhile, are slightly less inclusive than the Carpenter-Coustan criteria [13]. Furthermore, the NDDG criteria were found to be less sensitive in diagnosing GDM and in predicting incidence of perinatal morbidities [14]. The NDDG criteria are also based on exceeding two or more of the threshold values, which are as follows:

- Fasting serum glucose concentration of 105 mg/dl
- 1-h serum glucose concentration of 190 mg/dl
- 2-h serum glucose concentration of 165 mg/dl
- 3-h serum glucose concentration of 145 mg/dl

Alternatively, the American Diabetes (ADA) criteria for GDM diagnosis rely on a 75-gm glucose load and consider fasting serum glucose concentration, 1-h glucose concentration, and 2-h glucose concentration [15]. The glucose threshold values are, respectively, 95 mg/dl (5.3 mmol/l), 180 mg/dl (10.0 mmol/l), and 155 mg/dl (8.6 mmol/l). Again, two or more abnormal values are required for diagnosis. Although these major criteria all require two or more abnormal values for diagnosis, studies have shown that a single abnormal value is significantly associated with increased risk of perinatal morbidities [16].

The World Health Organization (WHO) recommends using a 75-gm glucose tolerance test for screening and diagnosis. The threshold values are a fasting glucose concentration of more than 126 mg/dl (7.0 mmol/l) and/or a 2-h glucose concentration of more than 140 mg/dl (7.8 mmol/l) [17]. When the WHO criteria are used, approximately twice as many patients will be diagnosed with GDM compared to other criteria. However, there is no proven additional clinical benefit with the use of WHO criteria [18]. The criteria for diagnosis of GDM are summarized in Table 2.

Treatment
Evidence shows that screening for and treating GDM lead to the reduction of perinatal morbidity and the
improvement of post-delivery outcomes [19]. As in other types of diabetes, the cornerstone of GDM management is glycaemic control [1]. Glycaemic control has been shown to reduce adverse outcomes in pregnant women with GDM [20, 21].

**Target glucose values**

Experts recommend that women with GDM should maintain the following capillary blood glucose values: preprandial glucose <95 mg/dl (5.3 mmol/l), 1-h postprandial glucose <140 mg/dl (7.8 mmol/l), and 2-h postprandial glucose <120 mg/dl (6.7 mmol/l) [1]. The American College of Obstetrics and Gynaecology (ACOG) has similar guidelines, the only exception being that both 130 mg/dl and 140 mg/dl 1-h postprandial glucose values are considered acceptable [22]. Other recommendations suggest maintaining fasting glucose levels of <90–99 mg/dl (5.0–5.5 mmol/l), 1-h postprandial glucose levels of <140 mg/dl (7.8 mmol/l), and 2-h postprandial glucose levels of <120–127 mg/dl (6.7–7.1 mmol/l) [23].

Even if it is not possible to achieve the recommended levels of glycaemic control, any improvement can be beneficial given that perinatal complications are linked to increasing serum glucose values [21, 24]. Despite the benefits of glycaemic control, however, studies have shown that very low target glucose values (<87 mg/dl) are associated with increased rates of intrauterine fetal growth retardation [20].

**Medical nutrition therapy (MNT)**

The first line of management for women with gestational diabetes mellitus is dietary modification, often called medical nutrition therapy [25]. Evidences indicate that nutrition therapy is effective in reducing pregnancy and perinatal complications and also in attaining glycaemic control [25].

According to ADA recommendations, carbohydrate intake should be approximately 40 % of total calorie intake and should be selected from foods with low glycaemic index values [26]. In pregnant women of normal body weight (BMI between 18.5–24.9), the recommendation is to consume 30–32 kcal/kg body weight, especially during the second half of pregnancy [27]. However, those who are overweight (BMI of 25 to 29.9) should ingest approximately 25 kcal/kg body weight [28]. Other guidelines recommend caloric intake based on BMI as follows: 30 kcal/kg for a BMI of 22–25, 24 kcal/kg for a BMI of 26–29, and 12–15 kcal/kg for a BMI of >30.

75–80 % of women with GDM become euglycaemic by following these caloric distribution guidelines. Assessing fasting ketonuria provides a method of confirming a woman’s caloric restriction, because caloric restriction of at least 50 % has been associated with ketogenesis [29]. On the other hand, moderate caloric restriction of about 33 % has been associated with controlled glucose levels without elevation of free fatty acids and ketonaemia [28, 29]. Caloric restriction should be approached cautiously, because studies show that elevated maternal ketone levels are associated with impaired psychomotor development [30].

Compared to diet alone, exercise with dietary modifications has been found to lead to improved glycaemic control in one study [31]. The proposed mechanism for such an improvement in glycaemic control is heightened sensitivity of peripheral tissues to insulin. A supervised home-based cycling program was helpful in maintaining normal postprandial glucose levels in pregnant women with diet-controlled GDM [32]. That said, another trial using a partially home-based exercise program found no reduction in blood glucose level [33]. This cohort did demonstrate improved cardiovascular fitness, however.

Based on the available evidence on the benefits of exercise in managing GDM, ADA recommends moderate exercise programs for women without medical or obstetrical complications [15]. There are no specific guidelines, however, on how to employ exercise regimes to achieve glycaemic control. For the general population, experts tend to recommend exercising 3 or more times a week for about 30 min.

**Pharmacotherapy**

Pharmacological intervention in the management of GDM is usually employed when women fail to meet established goals with conventional therapy of diet and exercise. It is also indicated when elevated fasting glucose levels occur while on conventional therapy, because dietary modification has limited effect on these levels. Although most women achieve adequate glycaemic control

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**Table 2** Diagnostic criteria for gestation diabetes mellitus with their respective glucose values

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<th>Diagnostic criteria</th>
<th>Fasting (mg/dl [mmol/l])</th>
<th>1-h (mg/dl [mmol/l])</th>
<th>2-h (mg/dl [mmol/l])</th>
<th>3-h (mg/dl [mmol/l])</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-gm OGTT Carpenter/Coustan (two or more abnormal)</td>
<td>95 (5.3)</td>
<td>180 (10.0)</td>
<td>155 (8.6)</td>
<td>140 (7.8)</td>
</tr>
<tr>
<td>100-gm OGTT NDDG (two or more abnormal)</td>
<td>105 (5.8)</td>
<td>190 (10.6)</td>
<td>165 (9.2)</td>
<td>145 (8.1)</td>
</tr>
<tr>
<td>75-gm OGTT WHO (one or more abnormal)</td>
<td>92-125 (5.1-6.9)</td>
<td>≥180 (10.0)</td>
<td>153-199 (8.5-11.0)</td>
<td>-</td>
</tr>
<tr>
<td>75-gm OGTT ADA</td>
<td>95 (5.3)</td>
<td>180 (10.0)</td>
<td>155 (8.6)</td>
<td>-</td>
</tr>
</tbody>
</table>

OGTT = Oral glucose tolerance test, NDDG = National Diabetes Data Group, WHO = World Health Organization 2013, ADA = American Diabetes Association
with conventional therapy, 30–40 % do require the addition of pharmacologic therapy at some point during their pregnancies [34]. The pharmacological options in this case include insulin or oral hypoglycaemic agents (metformin and glyburide) [35, 36].

**Insulin**

Insulin therapy is the most commonly used pharmacotherapy once MNT fails to achieve desired outcomes. Insulin regimens often include intermediate-acting insulins such as isophane and short-acting agents such as regular recombinant insulin (Humulin R). Pharmacotherapy can also involve the insulin analogues aspart and lispro. Insulin therapy decreases the frequency of fetal macrosomia and the risk of perinatal morbidity [37]. Positive history of diabetes mellitus in a first-degree relative and multiple abnormal values in the OGTT were strongly found to predict the need for insulin management in women with GDM [38].

Studies have shown that insulin analogs (lispro and aspart) are more effective than regular human insulin in achieving targeted glucose values and minimizing the risk for macrosomia [39, 40]. There is limited data on the use of long-acting insulins in pregnancy. For women with GDM who require insulin, isophane is therefore the intermediate-acting insulin of choice [23]. Insulin analogues lispro and aspart have been widely studied and found to be clinically effective with minimal transfer across the placenta; these agents have similar safety profiles to human insulin [39]. Because the insulin analogues have shorter durations of action and more rapid onsets of action than regular insulin, they are associated with improved postprandial glycaemic control and less postprandial hypoglycaemia [41]. Glucose values that necessitate initiation of insulin are summarized in Table 3.

**Oral hypoglycaemics**

Oral hypoglycaemic agents used in the management of GDM should be both effective and safe for the woman and developing fetus. With the exception of glyburide and metformin, oral hypoglycaemic drugs are generally not recommended due to concerns about potential teratogenicity or prolonged neonatal hypoglycaemia from drug transport across the placenta [42].

**Glyburide**

Glyburide, one of the two oral hypoglycaemic drugs used for the management of GDM, acts primarily to enhance insulin secretion by the pancreas. It can be used as an alternative for women who are unable or unwilling to take insulin or, in some cases, as a first-line pharmacological therapy. Studies have shown that glyburide, unlike other sulphonylureas, does not cross the placenta in vivo or in vitro [43, 44].

Studies examining the use of glyburide and insulin for the management of GDM have found comparative maternal and neonatal outcomes [45, 46]. Regarding glyburide therapy, certain factors are associated with higher rates of success, including initiation after 30 weeks gestation or fasting blood glucose levels <110 mg/dl and 1-h postprandial glucose levels <140 mg/dl [47]. Despite several studies supporting the efficacy and safety of glyburide for women with GDM, ACOG and ADA guidelines do not recommend its use until larger randomized controlled trials are completed on the subject [15, 22]. However, a survey conducted by ACOG found that up to 13 % of American fellows prescribe glyburide as a first-line pharmacological agent in women with GDM [48].

**Metformin**

Metformin is another oral hypoglycaemic agent considered a potential substitute for insulin in GDM management. In a randomized controlled trial involving women with GDM, the use of metformin, whether alone or with supplemental insulin, was not associated with increased perinatal complications compared to insulin alone [49]. Meanwhile, a 2013 meta-analysis found that metformin is comparable to insulin regarding glycaemic control and neonatal outcomes [50]. In another recent study, metformin use was associated with similar desirable outcomes when compared to MNT and insulin use; its use was not associated with a higher risk of maternal or neonatal complications [51].

**Glucose monitoring**

In patients requiring insulin, the ideal frequency for glucose monitoring has not been established. In common practice, the patient generally checks glucose levels four times a day [23]: once upon waking in the morning, before meals, before bed and one or two hours postprandially to ensure adequate glycaemic control. Postprandial glucose levels are preferable to fasting glucose levels, because they are more strongly associated with macrosomia [52]. Insulin dose adjustments based on postprandial glucose levels rather than preprandial levels were shown to be associated with improvement in glycaemic control and reduction of both maternal and fetal adverse outcomes [53].

**Table 3** Glucose level cut-off points requiring insulin initiation in gestation diabetes mellitus

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Fasting (mg/dl [mmol/l])</th>
<th>1-h postprandial (mg/dl [mmol/l])</th>
<th>2-h postprandial (mg/dl [mmol/l])</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOG(22)</td>
<td>&gt;95 (5.3)</td>
<td>&gt;130-140 (7.2-7.8)</td>
<td>&gt;120 (6.7)</td>
</tr>
<tr>
<td>ADA(15)</td>
<td>&gt;90-99 (5.0-5.5)</td>
<td>&gt;140 (7.8)</td>
<td>&gt;120-127 (6.7-7.1)</td>
</tr>
</tbody>
</table>

ACOG = American College of Obstetrics and Gynecology, ADA = American Diabetes Association
In ill patient with DM and other comorbid conditions, Sliding Scale Insulin (SSI) is recommended to maintain tight glycemic control and avoid glycemic events (i.e. hypoglycemia and hyperglycemia) [54]. The sliding scale insulin regimen consists of short acting insulin 4 to 6 times a day based on regularly obtained capillary blood glucose measurements. However, studies have noted that use of SSI regimen is not improving glucose control in hospitalized patient [55-58]. In addition there is no standard SSI regimen and dosage vary widely between patients, providers and institutions [59].

For women with diet-controlled GDM, there are no clinical guidelines or controlled trials addressing the issue of monitoring frequency. In this case, the general practice involves checking levels four times per day at least two days per week [23]; when two values exceed the limits over the course of a week, pharmacotherapy is recommended.

Urine glucose monitoring is not useful in patients with GDM. However, urine ketone monitoring can be used in patients who are restricting calories to detect insufficient caloric or carbohydrate intake [15].

**Intrapartum management**

During labor, women on pharmacological therapy require hourly evaluations of their glucose values, while those with diet-controlled GDM do not require active glucose management. Patients on insulin usually have normal levels of glucose at the time of labor and also do not need active management [23].

**Delivery**

There is no definitive data on the timing and mode of delivery for pregnant women with GDM. If the patient has normal or near normal glucose values, it is recommended that she should deliver at term. The general recommendation is that pregnancies complicated by GDM should not extend beyond term. Elective cesarean section has not been associated with significant reduction of birth trauma and has not been found to be cost effective [60]. Earlier delivery was associated with reduction of macrosomia but not with reduction of other neonatal complications [61].

**Postpartum management**

After delivery, insulin resistance usually resolves quickly, as does the need for pharmacological management. However, approximately 40–60% of affected women will develop type 2 DM later in life. They are also at an increased risk of recurrent GDM that presents earlier in future pregnancies. In these women, regular screening for type 2 DM is strongly encouraged, beginning at 6 weeks post-delivery and annually thereafter. An OGTT should be performed postpartum, 1 year post-delivery, and every 3 years thereafter [23].

**Conclusion**

Despite GDM being one of the most common conditions during pregnancy, the lack of data from well-designed studies leaves some uncertainty surrounding the need for screening and management of this condition. Because the condition is associated with both maternal and fetal complications, screening and managing women at appropriate gestational age is important to minimize adverse outcomes. Glycemic control can safely be achieved with a combination of nutritional and pharmaceutical interventions. Metformin and Glyburide have been shown to be as effective as insulin in management of GDM. Effective communication between physician, patient and primary care provider is essential, as patients experience increased rates of GDM in subsequent pregnancies and a higher lifetime risk of developing non-gestational diabetes. Further studies are required to clarify the remaining controversies surrounding diagnosis and nuanced management practices.
Exercise improves glycaemic control in women diagnosed with gestational diabetes mellitus: a systematic review

Introduction

Gestational diabetes mellitus (GDM) is carbohydrate or glucose intolerance of variable severity that has its onset during pregnancy.\(^1\,^2\) It is diagnosed through laboratory screening, using a pregnancy oral glucose tolerance test that is performed between 24 and 28 weeks gestation.\(^3\,^4\) GDM is a common complication of pregnancy, with an incidence ranging from 3.5 to 12%; it also has an increasing prevalence.\(^1\,^4\,^5\) If poorly controlled, GDM results in hyperglycaemia,\(^6\,^7\) which affects both the mother and the developing baby. The short-term adverse consequences of hyperglycaemia may include hypertension and pre-eclampsia for the mother, and birth trauma from macrosomia (ie, excessive birth weight) for the baby.\(^7\,^8\) GDM also has longer-term health implications. For the mother, these include a 35 to 50% increase in risk of recurrence of GDM in subsequent pregnancies,\(^9\) with a seven-fold increased risk of developing type 2 diabetes mellitus.\(^9\) For the child of a GDM pregnancy, there is an increased risk of obesity and type 2 diabetes mellitus later in life,\(^10\,^11\) and those born with macrosomia have an increased lifetime risk of cardiovascular disease\(^12\) and an increased risk of leukaemia.\(^13\)

For these reasons, the increasing rate of GDM has public health ramifications.\(^14\,^15\) Glycaemic control is a critical factor in combatting the adverse effects associated with poorly controlled GDM.\(^6\) Management of GDM typically consists of dietary modifications, regular self-monitoring of postprandial (ie, post-meal) acute capillary blood glucose levels\(^7\) and – where diet modification does not achieve euglycaemia – insulin therapy.\(^16\,^17\) There is strong evidence that exercise, particularly structured aerobic and/or resistance training, is a beneficial adjunctive therapy in the management of type 2 diabetes mellitus through its ability to increase glucose uptake and improve insulin sensitivity.\(^18\,^24\) Exercise, particularly activation of large muscles such as the quadriceps, stimulates glucose uptake in muscle, increases energy expenditure and improves glucose transportation, which results in improved glucose tolerance.\(^22\,^25\) Exercise is associated with a reduction of glycated haemoglobin (HbA1c), a measure of the average plasma glucose in the longer term (2 to 3 months), in people with type 2 diabetes mellitus;\(^26\,^27\) it is optimised by training of 150 minutes or more per week at moderate intensity.\(^7\,^28\) Exercise is also recommended as beneficial for women with uncomplicated pregnancies.\(^29\,^31\)

Question: Does exercise improve postprandial glycaemic control in women diagnosed with gestational diabetes mellitus? Design: A systematic review of randomised trials. Participants: Pregnant women diagnosed with gestational diabetes mellitus. Intervention: Exercise, performed more than once a week, sufficient to achieve an aerobic effect or changes in muscle metabolism. Outcome measures: Postprandial blood glucose, fasting blood glucose, glycated haemoglobin, requirement for insulin, adverse events and adherence. Results: This systematic review identified eight randomised, controlled trials involving 588 participants; seven trials (544 participants) had data that were suitable for meta-analysis. Five trials scored ≥ 6 on the PEDro scale, indicating a relatively low risk of bias. Meta-analysis showed that exercise, as an adjunct to standard care, significantly improved postprandial glycaemic control (MD –0.33 mmol/L, 95% CI –0.49 to –0.17) and lowered fasting blood glucose (MD –0.31 mmol/L, 95% CI –0.56 to –0.05) when compared with standard care alone, with no increase in adverse events. Effects of similar magnitude were found for aerobic and resistance exercise programs, if performed at a moderate intensity or greater, for 20 to 30 minutes, three to four times per week. Meta-analysis did not show that exercise significantly reduced the requirement for insulin. All studies reported that complications or other adverse events were either similar or reduced with exercise. Conclusion: Aerobic or resistance exercise, performed at a moderate intensity at least three times per week, safely helps to control postprandial blood glucose levels and other measures of glycaemic control in women diagnosed with gestational diabetes mellitus.
However, to date, the evidence regarding the benefits of exercise for the management of GDM has been equivocal – largely due to small sample sizes and heterogeneity of exercise type and outcome measures. In addition, the synthesis of the evidence on the benefits of exercise for the management of GDM has been limited to a review completed almost a decade ago.22 Several international guidelines and reviews recommend exercise in the management of GDM.4,16,33–35 While these guidelines recommend exercise as an adjunct to standard GDM care, there has not been supporting evidence from a systematic review with meta-analysis of the effects of exercise on postprandial blood glucose levels. There is good justification for postprandial glucose levels to be the main outcome of interest among this population due to the continuous relationship with macrosomia and birth defects.1,2,7,16 Fasting blood glucose levels and HbA1c are, however, important as secondary outcomes because, other than their established physiological relevance to complications of diabetes, 15 some trials may only include these measures rather than an oral glucose tolerance test (OGTT).

Therefore, the research questions for this systematic review were:

1. Can adjunctive exercise improve the acute postprandial control of blood glucose in women diagnosed with GDM when compared with standard GDM care?
2. Does adjunctive exercise improve fasting blood glucose levels and the longer-term measure, HbA1c, in women diagnosed with GDM when compared with standard GDM care?
3. What are the characteristics of exercise programs that are effective in lowering postprandial blood glucose levels for women with GDM and the variables affecting adherence to exercise?

Method

The review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.36

Identification and selection of studies

One reviewer (AH) performed a search of the following electronic databases from the earliest possible date (ie, from database inception) until November 2015: AMED, CINAHL, Medline, Embase, PsycINFO, Cochrane Library, PEDro, SPORTDiscus, Joanna Briggs Institute and Trip. To ensure full representation of the evidence, no search limitations were used. The search strategy consisted of four key concepts: GDM, physical activity, blood glucose and randomised, controlled trials. For each concept, key words and MeSH search terms were combined with the ‘OR’ operator. The results of the searches of the four key concepts were combined with the ‘AND’ operator. An example of the search strategy is presented in Appendix 1 on the eAddenda. Reference lists from the included studies were manually searched and relevant articles were screened and reviewed for possible inclusion. Using Google Scholar and Web of Science, citation tracking was also performed on the included articles to identify any additional, relevant articles.

Two reviewers (AH and HF or NT) independently reviewed the title and abstracts of the articles yielded by the search, according to the inclusion criteria presented in Box 1 and the exclusion criteria outlined below. If eligibility was unclear from the review of title and abstract, full text was obtained and reviewed by two researchers working independently. Disagreements were resolved by discussion between reviewers.

Assessment of characteristics of studies

Participants

Trials were excluded if the participants had existing type 1 or type 2 diabetes. This was because the aetiologies are somewhat different or, at least, the aetiology may be only transient in GDM and because the chronic physiological effects of longer-term diabetes could confound findings.13,35

Intervention

As the minimum level of exercise to improve self-monitored postprandial blood glucose levels is not well established, the inclusion criteria for this review were set broadly to include trials of interventions with exercise frequency greater than weekly. If individual studies provided an exercise intervention dosage that met the recommended guidelines,9,10 then it was considered that the exercise intervention would provide sufficient stimulus to achieve aerobic effect or changes in muscle metabolism. It was acceptable for the exercise intervention to be combined with dietary modification and insulin, as required, along with self-monitoring of blood glucose; this is considered standard care for women diagnosed with GDM.7,16,33,35

Outcome measures

As outlined in Box 1, postprandial glucose levels, fasting blood glucose levels and HbA1c were the outcome measures chosen to reflect treatment of existing GDM. Because the primary aim of this review was to evaluate the treatment effect of exercise on postprandial control of glycaemia in women with GDM, not to prevent it, trials were excluded if prevention of GDM was an outcome measure.

Risk of bias

Risk of bias was assessed using the Physiotherapy Evidence Database (PEDro) scale.57 This scale scores the risk of bias of studies out of 10, providing a comprehensive description for each item to improve inter-rater reliability57 and is considered a valid and reliable tool for measuring methodological quality.38,39 For the purposes of this review, trials achieving a PEDro score of ≥ 6 were considered as being at low, or slightly greater than low, risk of bias.39 Two reviewers (AH and NS) assessed the risk of bias independently. Disagreements between allocated scores were resolved by discussion.

<table>
<thead>
<tr>
<th>Box 1. Inclusion criteria.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
</tr>
<tr>
<td>- Randomised, controlled trial</td>
</tr>
<tr>
<td>- Full-text articles published in English in a peer-reviewed journal</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
</tr>
<tr>
<td>- Pregnant women diagnosed with GDM during the current pregnancy</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>- Cardiovascular exercise or strengthening exercises sufficient to achieve aerobic effect or changes in muscle metabolism</td>
</tr>
<tr>
<td>- Exercise performed more than once a week</td>
</tr>
<tr>
<td>- Exercise in any setting</td>
</tr>
<tr>
<td><strong>Primary outcome measure</strong></td>
</tr>
<tr>
<td>- Self-monitored postprandial blood glucose levels</td>
</tr>
<tr>
<td><strong>Secondary outcome measures</strong></td>
</tr>
<tr>
<td>- Fasting blood glucose levels</td>
</tr>
<tr>
<td>- HbA1c</td>
</tr>
<tr>
<td>- Requirement for insulin</td>
</tr>
<tr>
<td><strong>Comparisons</strong></td>
</tr>
<tr>
<td>- Standard care of GDM, including diet and/or insulin</td>
</tr>
</tbody>
</table>

Note: GDM, gestational diabetes mellitus; HbA1c, haemoglobin A1c.
A random-effects model was used to ensure a conservative common, a mean difference (MD) measure of effect was calculated. As the units of the measure within each outcome were different, the units of the measure within each outcome were converted into mmol/L using an online blood sugar conversion calculator from mg/dL units into mmol/L for glucose levels and fasting blood glucose levels, glycated haemoglobin levels, adverse events, adherence rates, and study conclusions.

The exercise interventions were all low impact, but the type of exercise varied. Two trials used circuit-type resistance training, and for more detailed data about the characteristics of the interventions, see Table 4 on the eAddenda). Two trials used cycling on upright cycle ergometers (one of which combined walking) and one trial used a recumbent cycle ergometer and another trial used an arm ergometer. Of the two remaining trials, one used brisk walking and the other used yoga as the exercise intervention.

### Results

#### Flow of studies through the review

The initial search yielded 351 articles (Figure 1). The yield included three papers that were published in languages other than English; however, as titles and abstracts for all three papers were available in English, they were included in the screening process. None of these three papers was a randomised, controlled trial and therefore all were ineligible. Through reference checking and citation tracking, four additional articles were identified by title. On review of these abstracts, all were excluded: two because they were not randomised, controlled trials, one because the outcomes were not related to the foetus, and the other because the intervention was a single bout of exercise. Following the screening process, eight trials were included in the review (Figure 1).

#### Characteristics of included studies

**Risk of bias**

Table 1 provides the details of the PEDro scoring for risk of bias. These trials involved an exercise intervention, so it was not anticipated that it would be possible to blind either participants or therapists; therefore, the maximum score expected was 8/10. Five of the eight trials scored > 6 on the PEDro scale, representing a low, or slightly greater than low, risk of bias.

**Participant characteristics**

The mean age of participants in the included trials ranged from 31 to 33 years (Table 2, and for more detailed data about the characteristics of the participants, see Table 3 on the eAddenda). Consistent with standard diagnostic testing for GDM occurring between 24 to 28 weeks, participants were recruited from 24 weeks gestation through to 31 weeks gestation. Parity and past history of GDM (with previous pregnancies) were reported in two of the trials. Five trials provided mean pre-pregnancy body mass index with a range of 23.4 to 27.6 kg/m².

**Intervention characteristics**

The exercise interventions were all low impact, but the type of exercise varied. Table 2, and for more detailed data about the characteristics of the interventions, see Table 4 on the eAddenda. Two trials used cycling on upright cycle ergometers (one of which combined cycling with walking), one trial used a recumbent cycle ergometer and another trial used an arm ergometer. Of the two remaining trials, one used brisk walking and the other used yoga as the exercise intervention.

### Table 1

<table>
<thead>
<tr>
<th>Trial</th>
<th>Random allocation</th>
<th>Concealed allocation</th>
<th>Groups similar at baseline</th>
<th>Participant blinding</th>
<th>Therapist blinding</th>
<th>Assessor blinding</th>
<th>&lt;15% dropouts</th>
<th>Intention-to-treat analysis</th>
<th>Intergroup comparison reported</th>
<th>Point estimate and variability measures</th>
<th>Total Score (0 to 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avery57</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>4</td>
</tr>
<tr>
<td>Be50</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Brankston55</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Bung58</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>de Barros44</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Hultie46</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Jovanovic-Peterson50</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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</tr>
<tr>
<td>Youngswanichsetha51</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7</td>
</tr>
</tbody>
</table>
The frequency of exercise ranged from three to seven sessions per week. Exercise intensity was variable: four trials used an age-predicted heart rate maximum varying from 50 to 70%, 46–49 two trials used Borg exertional scale ratings of 12 to 14, 47,50,51 and one trial used the OMNI exertional scale 44,45 and one trial did not state the exercise intensity. 35 When descriptors of exertion were used, they were generally between ‘moderate’ and ‘somewhat hard’. Exercise session durations ranged from 20 to 45 minutes, which included short warm-up and cool-down periods. Where specified, all of the session durations ranged from 20 to 45 minutes, which included short warm-up and cool-down periods. Where specified, all of the session durations ranged from 20 to 45 minutes, which included

### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avery 47 USA</td>
<td>n = 29</td>
<td>Exp = cycle ergometer, indiv, superv, 30 min x 2/wk x 6 wk (70% predHRmax) and walking, indiv, superv, 30 min x 2/wk x 6 wk (70% predHRmax via Borg Scale)</td>
<td>Postprandial BGL</td>
</tr>
<tr>
<td></td>
<td>Age (yr) = 31 (SD 5)</td>
<td>Con = usual activity</td>
<td>Fasting BGL</td>
</tr>
<tr>
<td></td>
<td>BMI (kg/m²) = 26.5 (SD 6.3)</td>
<td>Both = usual diet</td>
<td>Need for insulin</td>
</tr>
<tr>
<td></td>
<td>BGL (mmol/L) = 10.3 (SD 1.1)</td>
<td>Con = usual activity</td>
<td>Fasting BGL</td>
</tr>
<tr>
<td></td>
<td>Bo 48 Italy</td>
<td>Exp = brisk walking, indiv, unsuperv 5, 20 min x 7/wk x 25 wk (Borg 12 to 14) ± behavioural advice 45</td>
<td>Postprandial BGL</td>
</tr>
<tr>
<td></td>
<td>n = 200</td>
<td>Con = ± behavioural advice 45</td>
<td>Fasting BGL</td>
</tr>
<tr>
<td></td>
<td>Age (yr) = elig 18 to 50</td>
<td>Both = individually prescribed diet</td>
<td>HbA1c</td>
</tr>
<tr>
<td></td>
<td>Gestation (wk) = elig 24 to 26</td>
<td>Both = prescribed diet</td>
<td>Need for insulin</td>
</tr>
<tr>
<td></td>
<td>BMI (kg/m²) = 27.6 (SD 4.2)</td>
<td>Both = prescribed diet</td>
<td>Fasting BGL</td>
</tr>
<tr>
<td></td>
<td>BGL (mmol/L) = n/s</td>
<td>Both = prescribed diet</td>
<td>Need for insulin</td>
</tr>
<tr>
<td></td>
<td>Brankston 45 Canada</td>
<td>Exp = circuit resistance ex, indiv, superv for 3 sessions then unsuperv 5, 2 to 3 sets x 15 to 20 reps x 3/wk x 8 wk ('somewhat hard')</td>
<td>Postprandial BGL</td>
</tr>
<tr>
<td></td>
<td>n = 32</td>
<td>Con = usual activity</td>
<td>Fasting BGL</td>
</tr>
<tr>
<td></td>
<td>Age (yr) = 31 (SD 5)</td>
<td>Both = prescribed diet</td>
<td>Need for insulin</td>
</tr>
<tr>
<td></td>
<td>Gestation (wk) = 29 (SD 2)</td>
<td>Con = usual activity</td>
<td>Fasting BGL</td>
</tr>
<tr>
<td></td>
<td>BMI (kg/m²) = 26.5 (SD 4.1)</td>
<td>Both = prescribed diet</td>
<td>HbA1c</td>
</tr>
<tr>
<td></td>
<td>BGL (mmol/L) = 9.8 (SD 1.2)</td>
<td>Both = prescribed diet</td>
<td>Need for insulin</td>
</tr>
<tr>
<td></td>
<td>Bung 46 USA</td>
<td>Exp = recumbent cycle ergometry, indiv, superv, 45 min x 3/wk x 3/wk x 10 wk (50% VO₂max)</td>
<td>Fasting BGL</td>
</tr>
<tr>
<td></td>
<td>n = 34</td>
<td>VO₂max</td>
<td>Postprandial BGL</td>
</tr>
<tr>
<td></td>
<td>Age (yr) = 31 (SD 5)</td>
<td>VO₂max</td>
<td>Postprandial BGL</td>
</tr>
<tr>
<td></td>
<td>Gestation (wk) = 30 (SD 2)</td>
<td>VO₂max</td>
<td>Postprandial BGL</td>
</tr>
<tr>
<td></td>
<td>BMI (kg/m²) = n/s</td>
<td>VO₂max</td>
<td>Postprandial BGL</td>
</tr>
<tr>
<td></td>
<td>BGL (mmol/L) = n/s</td>
<td>VO₂max</td>
<td>Postprandial BGL</td>
</tr>
<tr>
<td></td>
<td>de Barros 44 Brazil</td>
<td>Exp = circuit resistance ex, indiv, superv 2/wk and unsuperv 1/wk, 30 to 40 min x 3/wk x 8 wk (‘somewhat heavy’)</td>
<td>Postprandial BGL</td>
</tr>
<tr>
<td></td>
<td>n = 64</td>
<td>Con = usual activity</td>
<td>Need for insulin</td>
</tr>
<tr>
<td></td>
<td>Age (yr) = 32 (SD 5)</td>
<td>Con = usual activity</td>
<td>Fasting BGL</td>
</tr>
<tr>
<td></td>
<td>Gestation (wk) = 31 (SD 2)</td>
<td>Both = prescribed diet</td>
<td>HbA1c</td>
</tr>
<tr>
<td></td>
<td>BMI (kg/m²) = 25.4 (SD 4.0)</td>
<td>Both = prescribed diet</td>
<td>Need for insulin</td>
</tr>
<tr>
<td></td>
<td>BGL (mmol/L) = 9.1 (SD 1.4)</td>
<td>Both = prescribed diet</td>
<td>Fasting BGL</td>
</tr>
<tr>
<td></td>
<td>Halse 46 Australia</td>
<td>Exp = home cycle ergometer, indiv, superv 3/wk and unsuperv 2/wk, 25 to 45 min x 5/wk x 8 wk (55 to 85% predHRmax)</td>
<td>Postprandial BGL</td>
</tr>
<tr>
<td></td>
<td>n = 40</td>
<td>Con = usual activity</td>
<td>Fasting BGL</td>
</tr>
<tr>
<td></td>
<td>Age (yr) = 33 (SD 4)</td>
<td>Both = dietary advice</td>
<td>HbA1c</td>
</tr>
<tr>
<td></td>
<td>Gestation (wk) = 29 (SD 1)</td>
<td>Both = dietary advice</td>
<td>Need for insulin</td>
</tr>
<tr>
<td></td>
<td>BMI (kg/m²) = 25.8 (SD 6.9)</td>
<td>Both = dietary advice</td>
<td>Fasting BGL</td>
</tr>
<tr>
<td></td>
<td>BGL (mmol/L) = 8.8 (SD 1.1)</td>
<td>Both = dietary advice</td>
<td>HbA1c</td>
</tr>
<tr>
<td></td>
<td>Jovanovic-Peterson 49 USA</td>
<td>Exp = arm ergometer 5, 20 min x 3/wk x 6 wk (70% predHRmax) 5, n/s</td>
<td>Postprandial BGL</td>
</tr>
<tr>
<td></td>
<td>n = 19</td>
<td>Con = usual activity</td>
<td>Fasting BGL</td>
</tr>
<tr>
<td></td>
<td>Age (yr) = 32 (SD 5)</td>
<td>Both = diet</td>
<td>HbA1c</td>
</tr>
<tr>
<td></td>
<td>Gestation (wk) = n/s</td>
<td>Both = diet</td>
<td>Need for insulin</td>
</tr>
<tr>
<td></td>
<td>BMI (kg/m²) = n/s</td>
<td>Both = diet</td>
<td>Fasting BGL</td>
</tr>
<tr>
<td></td>
<td>BGL (mmol/L) = 10.2 (SD 0.9)</td>
<td>Both = diet</td>
<td>HbA1c</td>
</tr>
<tr>
<td></td>
<td>Youngwanichsetha 51 Thailand</td>
<td>Exp = yoga breathing, postures and movements, indiv, some superv, 15 to 20 min x 5/wk x 8 wk (intensity n/s) + mindfulness eating</td>
<td>Postprandial BGL</td>
</tr>
<tr>
<td></td>
<td>n = 170</td>
<td>Con = usual care, including dietary advice</td>
<td>Fasting BGL</td>
</tr>
<tr>
<td></td>
<td>Age (yr) = 32 (5)</td>
<td>Con = usual care, including dietary advice</td>
<td>HbA1c</td>
</tr>
<tr>
<td></td>
<td>Gestation (wk) = elig 24 to 30</td>
<td>Con = usual care, including dietary advice</td>
<td>Fasting BGL</td>
</tr>
<tr>
<td></td>
<td>BMI (kg/m²) = n/s</td>
<td>Con = usual care, including dietary advice</td>
<td>HbA1c</td>
</tr>
<tr>
<td></td>
<td>BGL (mmol/L) = 9.5 (SD 1.1)</td>
<td>Con = usual care, including dietary advice</td>
<td>HbA1c</td>
</tr>
</tbody>
</table>

BGL = blood glucose level. BMI = body mass index. con = control group. elig = eligibility range. ex = exercise. exp = experimental group. indiv = individual. superv = supervised. unsuperv = unsupervised.

- Age and gestation are at enrolment. BMI is pre-pregnancy, and BGL is postprandial at enrolment. Where participant characteristics are not stated but similar measures were reported (eg, BMI at enrolment instead of pre-pregnancy), these are reported in Table 3 on the eAddenda.
- For more detailed characteristics of the interventions, see Table 4 on the eAddenda.
- Occasional phone call and/or visit.
- This trial was factorially randomised, meaning that half the participants in the exp and con groups were randomly allocated behavioural recommendations.
- It was unclear whether the arm ergometry was individual or group exercise and whether it was supervised or unsupervised.

**Baseline comparability of the randomised groups**

Baseline data, where reported, showed that the control and intervention groups were similar at baseline (see Table 3 on the eAddenda). Baseline data were reported for mean postprandial blood glucose measures by six trials, 44–47,49,51 fasting blood glucose by seven trials, 44–49,51 and HbA1c by three trials. 44–46,49,50

**Effect of adding exercise to standard care**

**Postprandial blood glucose**

Data from seven trials, 44–47,49–51 with a total of 554 participants, compared the effect of exercise plus standard care with the effect of standard care alone on postprandial blood glucose levels (Figure 2, see Figure 3 on the eAddenda for a detailed forest plot). There was a significant between-group difference in postprandial glucose by seven trials, 44–47,49–51 fasting blood glucose by seven trials, 44–49,51 and HbA1c by three trials. 44–46,49,50
still significantly favoured exercise (Figure 4, see Figure 5 on the eAddenda for a detailed forest plot).

**Fasting blood glucose**

Data from six trials,45–47,49–51 with a total of 500 participants, compared the effect of exercise plus standard care with the effect of standard care alone on fasting blood glucose (Figure 6, see Figure 7 on the eAddenda for a detailed forest plot). There was a significant between-group difference in fasting blood glucose favouring exercise (MD –0.31 mmol/L, 95% CI –0.56 to –0.05, I² = 82%). A seventh trial measured fasting blood glucose, but did not report data with standard deviations and so was unable to be included in the meta-analysis.44

**Glycated haemoglobin**

Data from four trials,46,49–51 with a total of 439 participants, compared the effect of exercise plus standard care with the effect of standard care alone on glycated haemoglobin (Figure 8, see Figure 9 on the eAddenda for a detailed forest plot). There was a significant between-group difference in glycated haemoglobin favouring exercise (MD –0.33%, 95% CI –0.48 to –0.18, I² = 60%).

**Need for insulin therapy**

Data from six trials44–47,49,50 with a total of 384 participants, compared the effect of exercise plus standard care with the effect of standard care alone on the proportion of participants requiring insulin therapy (Figure 10, see Figure 11 on the eAddenda for a sensitivity analysis excluding the study by Jovanovic-Peterson et al49 due to heterogeneity.

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**Figure 2.** Mean difference (95% CI) in effect of exercise plus usual care versus usual care only on postprandial blood glucose (mmol/L) in women with gestational diabetes mellitus.

**Figure 4.** Mean difference (95% CI) in effect of exercise plus usual care versus usual care only on postprandial blood glucose (mmol/L) in women with gestational diabetes mellitus.

**Figure 6.** Mean difference (95% CI) in effect of exercise plus usual care versus usual care only on fasting blood glucose (mmol/L) in women with gestational diabetes mellitus.

**Figure 8.** Mean difference (95% CI) in effect of exercise plus usual care versus usual care only on glycated haemoglobin (%) in women with gestational diabetes mellitus.

**Figure 10.** Odds ratio (95% CI) for insulin requirement with exercise plus usual care versus usual care only in women with gestational diabetes mellitus.

*a* An odds ratio and 95% CI for the study by Jovanovic-Peterson et al49 could not be calculated because there was no insulin use in either group.
Effect of exercise versus insulin therapy

Significant worsening of maternal/neonatal outcomes. Exercise caused a significant increase in adverse events or a reduction in maternal/neonatal complications due to exercise (OR 0.50, 95% CI 0.28 to 0.89). Some trials reported no adverse events in either group.

No adverse events in either group.

No significant difference between groups.

‘No adverse effects were reported in response to exercise’.

No complications in either group.

No adverse events occurred during practice.

Adherence

Adherence was defined and analysed in varying detail in the included trials, as presented in Table 5. One trial reported significantly reduced maternal/neonatal complications due to exercise (OR 0.50, 95% CI 0.28 to 0.89). Some trials reported no adverse events in either group. Other trials reported that maternal and neonatal outcomes were similar or not significantly different between the randomised groups. None of the trials reported that exercise caused a significant increase in adverse events or a significant worsening of maternal/neonatal outcomes.

Effect of exercise versus insulin therapy

One trial evaluated the effect of exercise and diet compared with insulin therapy and diet. There was no statistical difference in the weekly fasting blood glucose levels between the exercise group and the insulin group. This trial reported a similar rate of complications (premature rupture of membranes, premature labour, birth weights) in each group.

Adherence

All of the included trials reported some information about the level of adherence to exercise in the experimental group (Table 6), although the method of collecting these data was not well described. Two trials reported ‘satisfactory’ adherence, with participants exercising 2 to 2.4 times a week. Another trial stated ‘good’ adherence, as reported by participants in surveys; however, actual exercise attendance was 66%. Three trials reported a specific percentage of adherence with exercise: one trial reported > 90% attendance for centre-based exercise; one trial reported 96% attendance to home-based stationary cycling; and one trial reported 100% adherence to the home-based yoga exercise program.

Discussion

Evidence from seven randomised, controlled trials found that exercise as an adjunct to standard care significantly improved postprandial control of glycaemia in women diagnosed with GDM. This evidence is likely to be robust because it relies on multiple meta-analyses; the included studies examined various exercise types, and the studied populations were representative of the wider target population of women with GDM. The current systematic review therefore provides strong new comprehensive evidence to support the many recommendations in the literature to use exercise in this population; the recommendations were based on other forms of evidence such as narrative reviews, physiological rationales, consensus opinion or systematic reviews of fewer studies.

Lower postprandial blood glucose levels are associated with fewer perinatal complications. These results are clinically important because they indicate the potential of exercise to assist in reducing acute blood glucose levels to within the normal range: postprandial blood glucose (MD –0.45 mmol/L, 95% CI –0.68 to –0.22) and fasting blood glucose levels...
Glucose uptake is also influenced by the duration in a decrease in blood glucose levels for up to 72 hours improves insulin sensitivity, promotes glucose uptake and results in lower levels of GDM, 4–7. Improved management of GDM is important. As women with GDM, 56 poor control leads to fasting and/or postprandial control of glycaemia is maintained normal postprandial glycaemic levels and optimising control of glycaemia in women with GDM. Although dietary therapy.

insulin levels, as occur in hyperglycaemia, may be associated with vascular damage; so the lower the dose of insulin required, the better. In the exercise intervention groups, it was observed that there were fewer women requiring insulin (26 out of 194, 13%) compared with those receiving standard care (39 out of 190, 21%), although the meta-analysis of the studies contributing to these pooled data did not identify a statistically significant difference. A larger cohort would provide greater power to determine whether exercise decreases the number of women requiring insulin. One trial 53 found that participants who exercised were prescribed less insulin (p = 0.01) and another 54 concluded that adjunctive exercise was as effective as insulin in maintaining normoglycaemia and could therefore be useful in obviating the need for insulin therapy.

There is a plausible physiological explanation to support exercise as a therapeutic adjunct for improving postprandial control of glycaemia in women with GDM. Although dietary modification is the basis of standard GDM management for maintaining normal postprandial glycaemic levels and optimising maternal and foetal outcomes, postprandial control of glycaemia is not maintained with diet therapy alone in as many as 38% of women with GDM. Poor control leads to fasting and/or postprandial hyperglycaemia triggering the prescription of insulin. 55 However, insulin administration does not address insulin resistance per se. In contrast, an acute bout of exercise increases insulin action by stimulating glucose uptake in muscle, via activation of intracellular glucose transporters, and increasing use of intracellular fatty acids. Exercise training also alters expression of muscle proteins involved in insulin responsiveness. 56 Activation of large muscles, such as the quadriceps, improves glucose uptake. 22,23 In type 2 diabetes, the acute effects of a bout of aerobic exercise are to regulate fat and glucose metabolism. 24 This improves insulin sensitivity, promotes glucose uptake and results in a decrease in blood glucose levels for up to 72 hours afterwards. 25 Glucose uptake is also influenced by the duration and intensity of exercise performed; the more intense the exercise, the stronger the glycaemic lowering effect. 60

The variation of exercise prescription across the trials hinders the identification of an optimal exercise regimen. However, the results from these trials suggest that a program of either aerobic exercise or resistance training appears equally effective, as long as it is performed at least at a moderate intensity or greater, for 20 to 30 minutes, three to four times a week, to provide a repeated stimulus that facilitates improved blood glucose uptake and induces increases in insulin sensitivity. Consistent with the findings of a previous systematic review on type 2 diabetes, 61 this suggests that as long as the dosage is similar, there is flexibility in type of exercise. This is relevant to translation into a person-centred model of care. This would enable exercise programs to be tailored to suit an individual’s preference, which may help adherence.

Although the ideal situation is prevention, a recent review investigating the effect of exercise combined with diet for the prevention of GDM reported that there was little difference between the exercise plus diet group and the control group who received no intervention; however, limitations with the available evidence were acknowledged. 62 Therefore, with increasing prevalence of GDM, 63–67 improved management of GDM is important. As maintaining acute postprandial blood glucose levels within the recommended targeted range is associated with improved perinatal outcomes in women diagnosed with GDM and as exercise appears to improve HbA1c in the longer-term, 46,49–51 this suggests that commencement of adjunctive exercise as early as possible in pregnancies complicated by GDM may be beneficial. Larger and more rigorous studies are needed to further investigate the effect of exercise earlier in pregnancy in relation to GDM onset and blood glucose control.

The prevention of GDM and the achievement of optimal clinical benefit, 62 none of the trials systematically investigated or evaluated adherence determinants, mediators or adherence strategies. Level of exercise adherence appeared to be collected through attendance and participation, but this was not consistently or well described. Participants in the trial of Bo et al. 21 self-reported good adherence, but attendance was 60%. This highlights that self-reporting is liable to overestimation due to the possibility of social desirability bias; this reduces the level of confidence in the actual adherence to the intervention and, thereby, the certainty of the optimal exercise dosage required to achieve the physiological effect. Greater supervision, either face-to-face or via phone follow-up, appeared to be associated with higher levels of adherence. 46,48,49,51 The convenience of a supervised, home-based exercise program was suggested as a reason for good adherence. 46,51 Home-based exercises involving little or no equipment, such as brisk walking, 50 resistance exercises with exercise bands, 44,45 or yoga, 51 are more accessible for most women and less expensive in terms of access costs compared with clinic attendance; and they have equivalent beneficial effects on blood glucose control. All interventions were individually delivered, which has the advantage of tailoring to the individual, thereby facilitating adherence. Future research is needed to explore determinants of exercise adherence in women with GDM and to subsequently evaluate the effect of exercise adherence strategies on glycaemic control outcomes.

No trials reported using group exercise interventions, which may provide social support and be a cost-effective healthcare option. In the reviewed trials, neither socio-economic status nor cultural characteristics were well reported. These factors may influence a woman’s attitude, health literacy level and acceptability of the intervention, which may affect clinical outcomes and are therefore important considerations in future research. One trial 51 provided culturally appropriate exercise, and when combined with supervision achieved good compliance and positive results across the reported outcomes. Although reporting of cultural background and socio-economic details was scant, the geographical breadth of the trial locations (Canada, United States of America, Brazil, Thailand and Australia) and reported cultural backgrounds (Caucasian, South-East Asian and Spanish) improve the generalisability of the findings.

The differing types of exercise among the included studies could be seen as a potential limitation. A previous systematic review 68 concluded that aerobic or resistance exercise, or a combination, were similarly effective in improving glycaemic control in people with type 2 diabetes mellitus; therefore, the present study deemed it acceptable to combine different types of exercise, provided they were similar in dosage. As no trial included a follow-up phase, the lasting effects of exercise and lifestyle modification on long-term prevention of type 2 diabetes mellitus in this population is unknown.

In conclusion, the results of this review provide evidence to support the recommendation that exercise, as an adjunct to standard GDM care, is beneficial in controlling postprandial blood glucose levels and in glycaemic control in women diagnosed with GDM. Programs of either aerobic or resistance exercise appear effective. Characteristics of effective exercise programs for management of GDM appear to be exercise performed at a moderate intensity and for a minimum of three times a week.
Exercise intervention during pregnancy can be used to manage weight gain and improve pregnancy outcomes in women with gestational diabetes mellitus

Abstract

Background: The study aimed to evaluate whether exercise intervention can be applied to pregnant women with gestational diabetes mellitus (GDM) for controlling gestational weight gain (GWG) and combating GDM-related outcomes.

Methods: Retrospective six months analysis of 14,168 single pregnant women without diabetes from 15 hospitals in Beijing in 2013. Each participant’s demographic data, interventions condition and medical information were collected individually by questionnaires and relying on medical records. The level of statistical significance was set equal to 0.05.

Results: 2750 (19.4 %) pregnant women were diagnosed with GDM, 74.9 % of them received exercise intervention during pregnancy, and the starting time was 25.8 ± 3.7 gestational weeks. Women with GDM with exercise intervention (GDM-E) had the lowest BMI increase during late and mid-pregnancy than women with GDM without exercise intervention (GDM-nE) (2.05 ± 1.32 kg/m² vs. 2.40 ± 1.30 kg/m², p < 0.01) and non-GDM women (2.05 ± 1.32 kg/m² vs. 2.77 ± 1.21 kg/m², p < 0.01). Moreover, GDM-E group experienced a significantly lower risk of preterm birth (5.58 % vs. 7.98 %, p < 0.001), low birth weight (1.03 % vs. 2.06 %, p < 0.001) and macrosomia (9.51 % vs. 11.18 %, p > 0.05) than GDM-nE group. After including dietary factors in the analysis, women with GDM without either dietary or exercise intervention (GDM-nDnE) had the highest risk of preterm birth (OR = 1.64, 95 % CI, 1.14–2.36), while women with GDM with dietary intervention only (GDM-DnE) had the highest risk of low birth weight (OR = 3.10, 95 % CI, 1.23–7.81). However, women with GDM with both dietary and exercise intervention had the lowest rate of macrosomia.

Conclusion: Exercise intervention is a suitable non-invasive therapeutic option that can be readily applied to manage weight gain and improve pregnancy outcomes in women with GDM.

Keywords: Pregnancy, Gestational diabetes mellitus, Exercise intervention, Dietary intervention, Gestational weight gain, Preterm birth, Macrosomia, Low birth weight, Caesarean delivery
Background

Gestational diabetes mellitus (GDM) is a common complication of pregnancy. The prevalence of GDM has been reported to be as high as 16.1%, and this rate is increasing worldwide [1].

A higher body mass index (BMI) before or in the first trimester of pregnancy and excessive gestational weight gain (GWG) during early and mid-pregnancy are both considered prominent early markers of GDM [2]. In women with both high pre-pregnancy BMI and excessive GWG, the risk of GDM increases by 2.2–5.9-fold [3]. Meanwhile, excessive GWG is one GDM-related complication [4]. Moreover, GDM and excessive GWG are strong predictors of mothers and offspring being overweight/obese a decade or more after the birth [5, 6]. Thus, there is a vicious cycle of excessive GWG, overweight/obesity and GDM. Certainly, pregnancy-related weight problems must be addressed and be paid adequate attention.

In addition, maternal overweight status and obesity [7], excessive GWG [8] and GDM [9] are all independently associated with an increased risk of adverse pregnancy outcomes, such as preterm birth, macrosomia and cesarean delivery, particularly when these three factors occur simultaneously [10]. American scholars determined that excessive GWG was the strongest contributor (33.3–37.7 %) to large-for-gestational-age neonates, more than GDM (2.0–8.0 %) or maternal pre-pregnancy overweight status and obesity (9.5–22.4 %) [11]. Similar results were published in two other studies [12, 13], which suggested that GWG outside the Institute of Medicine (IOM) recommendations after a diagnosis of GDM is associated with a 36–83 % increase in the risk of GDM-related perinatal adverse outcomes. Thus, we hypothesized that targeting gestational weight problems, particularly excessive GWG, which is a modifiable risk factor during pregnancy, would contribute to improving adverse GDM-related pregnancy outcomes.

Physical exercise is one of the best ways to control weight and stay healthy [14]. Currently, experts and obstetricians increasingly emphasize the role of exercise in preventing and managing GDM. A recent meta-analysis showed that high levels of activity before pregnancy (OR = 0.45, 95 % CI, 0.28–0.75) or in early pregnancy (OR = 0.76, 95 %, CI 0.70–0.83) were both significantly associated with a lower risk of GDM [15]. Previous observational studies also showed that women with GDM who undergo exercise intervention had superior blood glucose control and required a lower dose of insulin [16, 17].

However, studies that focus on pregnancy outcomes related to the use of exercise intervention are very limited. Therefore, to better understand the effects of exercise on GDM, the aim of this analysis was to examine whether exercise intervention is a suitable non-invasive therapeutic option that can be readily applied to pregnant women with GDM to control GWG and combat potential GDM-related adverse outcomes, including preterm birth, low birth weight, macrosomia and cesarean delivery, thus interrupting the GDM-centred vicious cycle.

Methods

Data source

This present analysis was part of a large retrospective study. In that study, based on the number of deliveries, 15 hospitals in Beijing were chosen as clusters by a systematic cluster sampling method; 15,194 pregnant women delivered from June 20th to November 30th, 2013, at these hospitals. The study was reviewed and approved by the Institutional Review Board of the First Hospital, Peking University (Reference number: 2013[578]). All participants provided written informed consent, and the ethics committee approved this consent procedure.

Women in our study were excluded for the following reasons: pre-existing diabetes, multiple births, and missing data on major items, such as 75 g oral glucose tolerance test (OGTT) results, birth weight, gestational age, delivery mode and whether women with GDM had exercise or dietary intervention during pregnancy.

Data collection

A questionnaire was designed to obtain information by interviewing all the pregnant women and collecting medical records the day after they gave birth. The questionnaire had two primary parts as follows: a demographic information part that needed to be completed via a face-to-face interview in the patient’s room, and case data part that included information such as the woman’s weight at different gestational weeks, 75 g OGTT values, the neonatal’s birth weight, gestational age at delivery and similar parameters; the investigator was required to review and extract these data from each medical record. Certainly, information such as “whether you exercised or had dietary intervention during pregnancy” and “what time did you start to exercise or have dietary intervention” were self-reported and also need investigators to collect individually. Only women with GDM or diabetes mellitus (DM) were asked about exercise and dietary interventions, for these two items acted as two major methods in their treatment.

Exercise intervention means sit less, take more steps, be more active, incorporate light and moderate PA as much as possible into their daily life et al., and diet intervention means reduce intake of sugar, eat more vegetables, reduce fat intake, and the total energy intake 1800 calories a day in all.

All the investigators in each hospital were trained before the survey. Each completed questionnaire was verified by an inspector. Data were coded and entered into a specially designed data software system that automatically checked
for out-of-range values and logical mistakes. Moreover, all
the questionnaires were entered independently by two
persons and were verified by a third person.

Definitions

(1) GDM: The GDM diagnostic criteria followed the new
criteria amended in August, 2014, in China, which
recommend a diagnostic 75-g OGTT performed after
the 24th week of gestation. GDM was diagnosed when
any one value met or exceeded 5.1 mmol/L at 0 h,
10.0 mmol/L at 1 h, or 8.5 mmol/L at 2 h. Values of
7.0 mmol/L at 0 h or 11.1 mmol/L at 2 h should be
always be diagnosed as DM [18].

(2) GWG: Each participant’s GWG was represented
by BMI increases, which were calculated using
pre-pregnancy weight (within three months before
pregnancy), mid-pregnancy weight (around the
time of the 75-g OGTT), late-pregnancy weight
(within the last week before giving birth) and
height. Thus, we obtained the patients’ BMI
increases between mid and pre-pregnancy, late
and mid-pregnancy and late and pre-pregnancy.
This necessitated that pre-pregnancy weight was
self-reported, whereas mid and late-pregnancy
weight were obtained from medical records.

(3) BMI categories: The BMI categories were classified
based on the following recommendation of the
Group of China Obesity Task Force of the Chinese
Ministry of Health: overweight, 24 ≤ BMI < 28 kg/m²;
obese, BMI ≥ 28 kg/m² [19].

(4) Guidelines for GWG during pregnancy: underweight
women should gain 12.5–18 kg; normal weight
women, 11.5–16 kg; overweight women, 7–11.5 kg;
and obese women, 5–9 kg [20].

(5) Preterm birth: Gestational age at delivery less than
37 weeks.

(6) Macrosomia: Foetal birth weight ≥ 4000 g, regardless
of gestational age.

(7) Low birth weight: Foetal birth weight < 2500 g with
gestational age ≥ 37 weeks.

(8) Physical activity during pregnancy: Light: No work or
sitting while working, walking less than 60 minutes a
day. Moderate: Activities that require moderate
physical effort and make a pregnant woman breathe a
little harder than normal (such as cooking, sweeping
the floor, washing clothes, average daily commute
longer than 60 minutes or walking more than
60 minutes a day, carrying light loads, or bicycling at a
regular pace). High: Activities that require considerable
physical effort and make a pregnant woman breathe
much harder than normal (such as heavy lifting,
aerobics, fast bicycling, dancing or swimming).

(9) Statistical analysis.

We divided participants into the following three groups
based on their diagnosis of GDM and whether they
received exercise interventions during pregnancy: the
non-GDM (normal) group, the GDM without exercise
intervention group (GDM-nE) and the GDM with exercise
intervention group (GDM-E). Because pregnant women
with GDM should also receive dietary intervention during
pregnancy, we further divided participants into subgroups
to examine the role of exercise intervention separate from
dietary intervention. The subgroups were the following:
pregnant women with GDM without either dietary or
exercise intervention (GDM-nDnE), pregnant women
with GDM with dietary intervention only (GDM-DnE),
pregnant women with GDM with exercise intervention
only (GDM-EnD) and pregnant women with GDM with
both dietary and exercise intervention (GDM-DE).

Data management was performed using the SPSS 13.0
statistical software package (Peking University Clinical
Research Institute). Continuous variables are expressed
as the mean ± standard deviation, and categorical variables
are presented as numbers and percentages. Differences
in the means between groups were evaluated using an
independent samples T-test and analysis of variance
(ANOVA). Pearson’s chi-square test was used for cat-
egorical variables. The level of statistical significance
was set at 0.05. Odds ratios (ORs) were used as estimates
of the effect of exercise intervention on improving preg-
nancy outcomes. Pregnant women in the Non-GDM
group and GDM-DE group were used as the reference,
and ORs with 95 % confidence intervals were calculated.

Results

In total, 14168 pregnant women were recruited into this
study. Among these women, 2750 (19.4 %) were diag-
nosed with GDM, of whom 2061 (74.9 %) stated that
they had undergone exercise intervention during preg-
nancy. The mean time at which they began the exercise
intervention was 25.8 ± 3.7 gestational weeks. The base-
line characteristics of the study population are summa-
rized in Table 1. Overall, the majority of the participants
included in our study were between 22 and 35 years of
age (89.8 %), and most had at least a high school educa-
tion (81.7 %). Approximately 70.4 % of the participants
were nulliparous, and 13.9 % reported a family history of
diabetes. Based on their pre-pregnancy BMI and the
2009 IOM recommendations, 19.1 % were overweight or
obese, and nearly half of the women (48.0 %) experi-
enced excessive GWG. Age, pre-pregnancy BMI and a
family history of diabetes in the current pregnancy were
all higher among the pregnant women with GDM. The
pregnant women’s physical activity during pregnancy is
also shown in Table 1. Pregnant women with GDM with
exercise intervention had the highest level of physical
activity during pregnancy.
Pre-pregnancy BMI and the BMI increase between mid and pre-pregnancy were both much higher in pregnant women with GDM compared with pregnant women without GDM (22.67 ± 3.60 kg/m² vs. 21.36 ± 3.16 kg/m² for pre-pregnancy BMI; 3.54 ± 2.02 kg/m² vs. 3.31 ± 1.87 kg/m² for the BMI increase between mid and pre-pregnancy, \( p < 0.001 \)), especially in the GDM-E group (22.71 ± 3.57 kg/m² for pre-pregnancy BMI; 3.59 ± 1.92 kg/m² for the BMI increase between mid and pre-pregnancy). However, findings for the BMI increase between late and mid-pregnancy were quite the opposite. The BMI increases among the non-GDM, GDM-nE and GDM-E groups are shown in detail in Table 2. The BMI increases during late and mid-pregnancy were lower in the GDM-E group than in the GDM-nE group (2.05 ± 1.30 kg/m² vs. 2.40 ± 1.30 kg/m², \( p < 0.001 \)) and the non-GDM group (2.05 ± 1.32 kg/m² vs. 2.77 ± 1.21 kg/m², \( p < 0.001 \)); the total BMI increase, which was defined as the BMI increase from pre-pregnancy to late pregnancy, was lowest in the GDM-E group and highest in non-GDM group (GDM-E, 5.64 ± 2.22 kg/m² vs. GDM-nE, 5.71 ± 2.55 kg/m² vs. non-GDM, 6.05 ± 2.19 kg/m²).

Overall, 5.17 % of births occurred at a gestational age less than 37 weeks, and the mean gestational age was 39.0 ± 1.7 weeks. A total of 7.86 % of newborn infants had a low birth weight. Each outcome was worse among GDM pregnant women. However, Table 3 shows that compared with the GDM-nE group, women in the GDM-E group had an apparent lower risk of GDM-related adverse outcomes. Using the non-GDM group as a reference, women in the GDM-E group experienced a significantly lower risk of preterm birth than women in the GDM-nE group (5.58 %, OR = 1.14, 95 % CI, 1.04–1.24; \( p < 0.001 \)) and of low birth weight (1.03 %, OR = 1.02, 95 % CI, 0.93–1.12; \( p < 0.001 \)) of GDM patients in the GDM-E group compared with the GDM-nE group (49.4 %, OR = 1.43, 95 % CI, 1.30–1.57; \( p < 0.001 \)) of GDM patients in the GDM-E group compared with the GDM-E group (49.4 %, OR = 1.43, 95 % CI, 1.30–1.57; \( p < 0.001 \)).

After including dietary factors in the analysis, the results remained the same, and they are shown in Tables 4 and 5. Because only 5 pregnant women stated that they had exercise intervention without dietary intervention, we excluded them. Women in the GDM-DE group had a higher pre-pregnancy BMI and a greater BMI increase between mid and pre-pregnancy but a smaller BMI increase between late and mid-pregnancy.

### Table 1 Baseline characteristics of pregnant women enrolled in this study

<table>
<thead>
<tr>
<th></th>
<th>Total sample N = 14,168</th>
<th>Non-GDM N = 11,418</th>
<th>GDM-nE N = 689</th>
<th>GDM-E N = 2061</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>28.12 ± 4.28</td>
<td>27.86 ± 4.21</td>
<td>28.70 ± 4.38</td>
<td>29.38 ± 4.40</td>
</tr>
<tr>
<td>Pre-pregnancy BMI* (kg/m²)</td>
<td>21.62 ± 3.29</td>
<td>21.36 ± 3.16</td>
<td>22.53 ± 3.69</td>
<td>22.71 ± 3.57</td>
</tr>
<tr>
<td>Exceeds recommended GWG</td>
<td>6303(48.0)</td>
<td>5092(48.3)</td>
<td>281(46.0)</td>
<td>930(47.3)</td>
</tr>
<tr>
<td>Family history of diabetes*</td>
<td>1969(13.9)</td>
<td>1392(12.2)</td>
<td>117(17.0)</td>
<td>460(22.3)</td>
</tr>
<tr>
<td>Physical labor during pregnancy*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light</td>
<td>10398(73.4)</td>
<td>8414(73.7)</td>
<td>530(76.9)</td>
<td>1454(70.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>3561(25.1)</td>
<td>2830(24.8)</td>
<td>154(22.4)</td>
<td>577(28.0)</td>
</tr>
<tr>
<td>High</td>
<td>75(1.2)</td>
<td>147(1.3)</td>
<td>4(0.6)</td>
<td>24(1.2)</td>
</tr>
</tbody>
</table>

Continuous variables were expressed as means ± SD and categorical variables were expressed as n (%)

Abbreviations: BMI body mass index (calculated as weight in kilograms divided by the square of height in meters), GWG gestational weight gain

*Indicates a significant difference among Non-GDM, GDM-nE and GDM-E group, \( p < 0.001 \)

### Table 2 The BMI increases among the non-GDM, GDM-nE and GDM-E groups

<table>
<thead>
<tr>
<th></th>
<th>Total sample</th>
<th>Non-GDM</th>
<th>GDM-nE</th>
<th>GDM-E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-pregnancy BMI (kg/m²)</td>
<td>21.62(3.29)</td>
<td>21.36(3.16)*</td>
<td>22.53(3.69)*</td>
<td>22.71(3.57)*</td>
</tr>
<tr>
<td>Δ Mid-Pre BMI (kg/m²)</td>
<td>3.35(1.90)</td>
<td>3.30(1.87)*</td>
<td>3.35(2.29)*</td>
<td>3.59(1.92)*</td>
</tr>
<tr>
<td>Δ Late-Mid BMI (kg/m²)</td>
<td>2.64(1.26)</td>
<td>2.77(1.21)*</td>
<td>2.40(1.30)*</td>
<td>2.05(1.32)*</td>
</tr>
<tr>
<td>Δ Late-Pre BMI (kg/m²)</td>
<td>5.96(2.22)</td>
<td>6.04(2.19)*</td>
<td>5.71(2.55)*</td>
<td>5.64(2.22)*</td>
</tr>
</tbody>
</table>

Data expressed as mean (Standard Deviation)

Abbreviations: BMI body mass index, Δ Mid-Pre BMI BMI increase between mid and pre-pregnancy, Δ Late-Mid BMI BMI increase between late and mid-pregnancy, Δ Late-Pre BMI BMI increase between late and pre-pregnancy

*Indicates a significant difference between Non-GDM group and GDM-nE group; **Indicates a significant difference between Non-GDM group and GDM-E group; &Indicates a significant difference between GDM-nE group and GDM-E group. * & \( p \) values were based on Independent Samples T test, \( p < 0.05 \)
increase between late and mid-pregnancy compared with the GDM-nDnE and GDM-DnE groups. Moreover, compared with the GDM-DE group, women in the GDM-nDnE group had a significantly increased risk of preterm birth (OR = 1.64, 95% CI, 1.14–2.36), and women in the GDM-DnE group had a considerably increased risk of low birth weight (OR = 3.10, 95% CI, 1.23–7.81). Furthermore, the rate of macrosomia was lower in the GDM-DE group compared to the GDM-DnE and GMD-nDnE groups (9.53% vs. 10.34% vs. 11.52%, respectively).

Discussion

One important novel finding of our study was that exercise intervention during pregnancy significantly reduced BMI increases in women with GDM. The results stood after we combined the analysis of dietary intervention and exercise intervention.

The association between exercise intervention and GWG identified in our study was consistent with published literature. Shericka T. Harris et al. found that women who reported exercising ≥3 times a week were more likely to meet GWG recommendations (32.7% vs. 18.7%), and the OR of excessive GWG was lower (aOR = 0.43, 95% CI, 0.24–0.78) than that for women who did not have the same intensity of exercise [21]. Likewise, Ronnberg A and colleagues found that total GWG was lower in the moderate-intensity (14.9 ± 3.8 kg) group compared with the low-intensity (15.3 ± 2.9 kg) and control groups (18.3 ± 5.3 kg). In addition, excessive GWG was prevented in 70% of the women in the low-intensity group and 77% of those in the moderate-intensity group [22]. A Chinese cohort study with 862 participants suggested that physically active pregnant women experience less weight gain during pregnancy, and the OR of excessive GWG decreased with an increased level of physical activity (p < 0.05) [23]. However, it should be noted that all of these studies were focused on healthy pregnant women. To the best of our knowledge, the participants in most existing studies of GWG and related issues were healthy overweight or obese pregnant women; therefore, our study is unique in its focus. Furthermore, we assessed the effect of exercise separately from that of dietary intervention.

Another main finding of our study was that exercise intervention during pregnancy could substantially combat GDM-related adverse outcomes, notably, preterm birth, low birth weight and macrosomia.

In our study, women with GDM had a higher risk of preterm birth, macrosomia and caesarean delivery compared to non-GDM pregnant women. However, we were delighted that exercise intervention could significantly reduce the risks of these adverse outcomes. Recently, Spanish scholars indicated that moderate exercise intervention performed over the second and third trimesters of pregnancy reduced the GDM-related risk of having a newborn with macrosomia and a caesarean delivery by 58% and 34%, respectively [24]. An earlier intervention study also showed that women who performed moderate aerobic activities three times per week during the entire pregnancy period had a lower frequency of macrosomia in newborn infants (6.0% vs 12.5%, P = 0.048) than those who performed little exercise [25].

**Table 3** Birth outcomes among the non-GDM, GDM-nE and GDM-E groups

<table>
<thead>
<tr>
<th></th>
<th>Preterm birth</th>
<th>Macrosomia (birth weight ≥ 4000 g)</th>
<th>Low birth weight (birth weight &lt; 2500 g)</th>
<th>Caesarean delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) OR 95% CI</td>
<td>n (%) OR 95% CI</td>
<td>n (%) OR 95% CI</td>
<td>n (%) OR 95% CI</td>
</tr>
<tr>
<td><strong>Total Sample</strong></td>
<td>732(5.17) 1113(7.86) 142(1.06) 6009(42.4)</td>
<td>562(4.92) 840(7.36) 109(1.00) 4647(40.7)</td>
<td>55 (7.98) 77(11.18) 13(2.05) 343(49.8)</td>
<td>115(5.58) 196(9.51) 20(1.03) 1019(49.4)</td>
</tr>
<tr>
<td><strong>Non-GDM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDM-nE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDM-E</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Preterm birth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Indicates a significant difference between GDM-nDnE and GDM-DnE group; *Indicates a significant difference between GDM-nDnE and GDM-DE group; &amp;Indicates a significant difference between GDM-DnE and GMD-nDnE group.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data expressed as mean (Standard Deviation)

Abbreviations: BMI body mass index, Δ Mid-Pre BMI increase between mid and pre-pregnancy, Δ Late-Mid BMI increase between late and med-pregnancy, Δ Late-Pre BMI increase between late and pre-pregnancy.
Notably, in our study, women with GDM with only dietary intervention had a considerably increased risk of neonatal low birth weight; however, when the treatment was combined with exercise intervention as an adjunct therapy, other pregnancy outcomes improved, and the rate of low birth weight neonates significantly decreased.

Therefore, exercise must have had an extraordinary or independent effect on controlling the GWG of women with GDM and combating GDM-related adverse outcomes. As we mentioned above, scholars have already noted that excessive GWG after a diagnosis of GDM worsens GDM-related adverse pregnancy outcomes [13], perhaps because GDM pregnant women who exercise have the best GWG control. Indeed, exercise might have some general basic mechanism of action [26].

In this study, we also found that the overall percentage of overweight or obese pregnant women in Beijing was 19.1 %, far higher than the percentage in 2009 [27]. This might be because China is now experiencing rapid economic, social and cultural changes. Therefore, an increasing number of women of reproductive age enter pregnancy overweight or obese, and this is associated with a heightened risk of GDM [28].

Accordingly, the rate of overweight/obese women in our study was as high as 30.7 % among pregnant women who developed GDM later, which is far higher than the overweight/obese rate among normal pregnant women (16.5 %). Similarly, the data from our study showed that pregnant women with GDM had much greater BMI increases between mid and pre-pregnancy, especially those who required exercise interventions later in pregnancy.

IOM guidelines provide specific pregnancy weight recommendations according to a woman’s pre-pregnancy BMI [20]. Though some published studies have been critical of the IOM recommendations [29] and have, in particular, questioned the guideline for GWG for obese pregnant women [30, 31], many studies have indicated that exceeding the IOM recommendations for GWG is associated with an increased risk of developing GDM [32]. Hedderson et al., noted that a woman’s risk of GDM increased with the rate of GWG, especially the rate of GWG in early pregnancy. Compared with GWG of less than 0.27 kg/week, GWG of 0.27–0.40 kg/week and more than 0.41 kg/week were associated with an increased risk of GDM (OR = 1.43, 95 % CI 0.96–2.14; OR = 1.74, 95 % CI 1.16–2.60, respectively) [32]. A more recent matched case–control study found that women with GDM gained significantly more weight by 24 weeks than those with normal glucose tolerance [33]. Similarly, a Chinese study with 90 GDM cases and 165 normal cases showed that compared with GWG of less than 0.28 kg/week, GWG of 0.28 kg/week or more was associated with an increased risk of GDM (OR = 2.03; 95 % CI 1.15–3.59) [34]. Additionally, all these studies emphasized that excessive GWG in the first trimester is the chief contributor to increasing a woman’s risk of GDM. Thus, this could be one reason to explain the result of our study that pregnant women with GDM with exercise intervention during pregnancy had the highest GWG between mid and pre-pregnancy. Perhaps these women have more severe and resistant blood glucose conditions.

Therefore, we are inclined to believe that exercise intervention initiated at the very beginning of pregnancy could decrease the risk of excessive GWG in the first and early second trimester and then possibly reduce the incidence of GDM among the entire population.

The American College of Obstetricians and Gynecologists (ACOG) recommends that pregnant women should exercise moderately for 30 minutes on most days of the week. However, very few women meet the minimum recommendations [35]. The data in our study also showed that only a small proportion of pregnant women performed moderate (25.1 %) to high (1.2 %) physical activity during pregnancy. The reasons for this might be that pregnancy is a very special period in a woman’s life; pregnant women are very careful about their actions during pregnancy [36], and they might not receive adequate advice and information concerning exercise from professionals [37]. Considering the prominent role of exercise during pregnancy in previous research and in our study, strengthening the research on pregnancy exercise-related issues, such as the optimal forms of exercise and intensity, will be of great value in improving pregnant women’s physical exercise level.

This study was conducted by trained staff who performed face-to-face interviews with pregnant women the day after they gave birth, and most of the items in the questionnaire were based on medical records. This method ensured the standardization of data collection.

### Table 5 Birth outcomes among GDM-nDnE, GDM-DnE and GDM-DE groups

<table>
<thead>
<tr>
<th></th>
<th>GDM-DE</th>
<th>OR (95% CI)</th>
<th>Reference</th>
<th>GDM-DnE</th>
<th>OR (95% CI)</th>
<th>Reference</th>
<th>GDM-nDnE</th>
<th>OR (95% CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth</td>
<td>115 (5.59)</td>
<td>1.00</td>
<td>Reference</td>
<td>196 (9.53)</td>
<td>1.00</td>
<td>Reference</td>
<td>20 (1.03)</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Macrosomia (birth weight ≥ 4000 g)</td>
<td>21 (10.34)</td>
<td>1.10 (0.68–1.76)</td>
<td></td>
<td>6 (3.14)</td>
<td>3.10 (1.23–7.81)</td>
<td></td>
<td>7 (1.58)</td>
<td>1.49 (0.63–3.54)</td>
<td></td>
</tr>
<tr>
<td>Low birth weight (birth weight &lt; 2500 g)</td>
<td>56 (11.52)</td>
<td>1.24 (0.90–1.69)</td>
<td></td>
<td>7 (1.58)</td>
<td>1.49 (0.63–3.54)</td>
<td></td>
<td>235 (48.4)</td>
<td>0.96 (0.79–1.17)</td>
<td></td>
</tr>
<tr>
<td>Caesarean delivery</td>
<td>1017 (49.5)</td>
<td>1.00</td>
<td>Reference</td>
<td>108 (5.32)</td>
<td>1.16 (0.87–1.55)</td>
<td></td>
<td>235 (48.4)</td>
<td>0.96 (0.79–1.17)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: OR odds ratios, CI confidence interval
However, several limitations of this study should be noted. First, our study is a retrospective study, and items such as pre-pregnancy weight, physical activity during pregnancy and whether each woman had dietary or exercise intervention were self-reported; thus, it may contain recall bias. Second, information concerning the types of exercise intervention was not available in this study, so we could not examine the level and the duration of exercise intervention during pregnancy, nor could we specifically evaluate whether each woman really received an exercise intervention. However, to some extent, if pregnant women stated that they had exercise intervention during pregnancy, they should have at least been more active than not.

Conclusion
Our findings provide some insights into the association of exercise intervention with GDM and GDM-related adverse outcomes. Pre-pregnant overweight/obese status and excessive GWG during pregnancy are both high-risk factors for GDM. Poor GWG control can aggravate GDM-related pregnancy outcomes. Exercise intervention is a good way to increase pregnant women’s physical activity during pregnancy, and it can also play an effective and particular role in managing the GWG of pregnant women with GDM; moreover, exercise might combat GDM-related adverse pregnancy outcomes. However, the overall level of physical activity among pregnant women is low. Above all, it is vital to call for action to improve pregnant women’s physical activity or increase their exercise levels during pregnancy.

Abbreviations
GDM: Gestational diabetes mellitus; DM: Diabetes mellitus; GWG: Gestational weight gain; BMI: Body mass index; OGTT: Oral glucose tolerance test; OR: Odds ratios; GDM-E: GDM women without exercise intervention during pregnancy; GDM-E: GDM women with exercise intervention during pregnancy; GDM-DnE: GDM women without either dietary or exercise intervention; GDM-DnE: GDM women with dietary intervention only; GDM-EnD: GDM women with exercise intervention only; GDM-DE: GDM women with both dietary and exercise intervention; Δ Mid-Pre BMI: BMI increase between mid and pre-pregnancy; Δ Late-Mid BMI: BMI increase between late and med-pregnancy; Δ Late-Pre BMI: BMI increase between late and pre-pregnancy.
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“This course was developed from the open access article: Exercise intervention during pregnancy can be used to manage weight gain and improve pregnancy outcomes in women with gestational diabetes mellitus - Wang et al. BMC Pregnancy and Childbirth (2015) 15:255 (doi: 10.1186/s12884-015-0682-1), used under the Creative Commons Attribution License.”