

## REVIEW

# Effect of exercise modality on markers of insulin sensitivity and blood glucose control in pregnancies complicated with gestational diabetes mellitus: a systematic review

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Received 29 December 2017; revised 24  
May 2018; accepted 27 May 2018

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## Summary

### Background/aim

Exercise can be used as a strategy to attenuate hyperglycaemia experienced during gestational diabetes mellitus (GDM). To maximize its use for clinical management, the most effective modality should be identified. The purpose of this review is to elucidate the most effective modality of exercise on insulin sensitivity and blood glucose control in pregnant women with or at risk of GDM.

### Methods

A search was undertaken in MEDLINE, PubMed, Scopus, CINAHL, the Cochrane Library, Embase and the Maternity & Infant Healthcare Database. Studies that met inclusion criteria were randomized controlled trials and case-controlled studies, which compared exercise interventions with standard care during pregnancy in women with or at risk of GDM.

### Results

Two interventions using resistance training, eight using aerobic exercise and two using a combination of both modalities were included. The interventions showed consistently that requirements of insulin therapy, dosage, and latency to administration were improved in the exercise groups. Less consistent results were observed for capillary blood glucose measurements; however, both modalities and combination of modalities were effective at improving blood glucose control in already diagnosed patients and pregnant women with obesity. Discrepancies in the timing of intervention, GDM diagnostic criteria, and the different measures used to assess glucose metabolism make it difficult to draw clear recommendations.

### Conclusion

Exercising three times per week for 40–60 min at 65–75% age-predicted heart rate maximum using cycling, walking or circuit training as a modality improved glycaemic control in GDM patients and reduced incidence of GDM in pregnant women with obesity. Further studies looking specifically at the effects of different modalities of exercise on glucose metabolism with combined strategies to enhance insulin sensitivity should be explored to maximize benefits for GDM pregnancies. Consistency in design and delivery of exercise-only interventions is required to make recommendations on a suitable exercise prescription in this population. In practice, adherence to consensus in diagnostic cut-offs for GDM diagnosis is fundamental for standardizing future research.

**Keywords:** Exercise, gestational diabetes mellitus, glycaemic control, insulin sensitivity.

## List of abbreviations

GDM	gestational diabetes mellitus
RCT	randomized controlled trial
HAPO	Hyperglycaemia and Adverse Pregnancy Outcomes
GLUT-4	glucose transporter type 4
OGTT	oral glucose tolerance test
HRR	heart rate reserve
HRmax	heart rate maximum
OGIS	Oral Glucose Insulin Sensitivity index
HOMA-IR	homeostatic model assessment-insulin resistance
MET-h/week	metabolic equivalent hours per week
HbA1c	glycated haemoglobin
RT	resistance training
AER	aerobic exercise
IADPSG	International Association of the Diabetes and Pregnancy Study Groups

## Introduction

Gestational diabetes mellitus (GDM) is a carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy and with resolution post-partum (1). It is recognized that overt diabetes during pregnancy is associated with significant levels of perinatal morbidity, such as macrosomia, neonatal hypoglycaemia, shoulder dystocia and other birth injuries (2), as well as more recently respiratory, neurological, digestive and cardiac disorders such as cardiac malformations and hypertrophic cardiomyopathy (3).

In addition, exposure to GDM pregnancy *in utero* has also been shown to induce long-term effects in offspring (4,5), such as increased incidence of type II diabetes, cardiovascular alterations such as hypertension (6), metabolic syndrome (7) and obesity (8) in the offspring later in adulthood, as well as increased risk of developing long-standing diabetes in the mother (9). Complications for pregnancies subsequent to GDM are well established and carry serious consequences (10).

Stringent new diagnostic criteria have been adopted as usual practice in centres globally following findings from the prominent Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study (11), which showed that small degrees of hyperglycaemia have significant effects on pregnancy and neonatal outcomes. These findings have led to improved uniformity in the diagnosis of GDM internationally. Use of the newly established criteria (12) has also resulted in a rise of prevalence of GDM from 2.7% using previous criteria for diagnosis (13) to figures

between 9.3% and 25% across the continents using the newly adopted and more stringent diagnostic criteria (14,15). This threefold increase in prevalence is accompanied by a concurrent rise in specialist medical referrals and has therefore become a significant burden on the healthcare system.

Medical therapy during gestation, through nutritional therapy and pharmacological intervention to obtain glycaemic control, has had positive results in the management of this condition and attenuation of complications (16). The importance of prenatal glycaemic control and weight management through exercise and nutrition manipulation is recognized in practice. The Royal College of Obstetricians and Gynaecologists and the American College of Obstetricians and Gynaecologist both endorse the participation of pregnant women in aerobic and strength-conditioning exercise, with the goal of maintaining a good fitness level, as part of a healthy lifestyle during pregnancy (17,58). Despite multiple interventions over the last decade, the most effective form of lifestyle management composed of dietary and physical activity behaviours for the prevention of GDM remains undetermined (18). A Cochrane review of lifestyle interventions for the treatment of GDM reported that women exposed to lifestyle interventions were less likely to have post-natal depression and were more likely to achieve post-partum weight goals (19). Exposure was also associated with a decreased risk of the neonate being born large for gestational age and decreased neonatal adiposity. Despite these positive findings, the contribution of individual components of lifestyle could not be assessed owing to study design limitations (19).

Exercise has long been accepted as an adjunctive therapy in the management of type II diabetes mellitus in non-pregnant individuals, owing to its ability to improve insulin sensitivity and insulin-stimulated muscle glucose uptake, both of which improve glycaemic control (35). The adaptations to exercise occur at the skeletal muscle level, and owing to similarities with GDM, the findings may translate to this population group (36). Modality, frequency, and duration of exercise are important components of exercise prescription and need to be defined in order to be of practical use to be prescribed in pregnancies both 'at risk' and those with a clear diagnosis of GDM.

The purpose of this literature review was threefold: (1) to identify exercise intervention studies implemented specifically during pregnancies complicated by diagnosed GDM or 'at risk' of GDM, (2) to determine which exercise modality was the most effective at improving insulin sensitivity and glycaemic control and (3) to make recommendations for future exercise intervention studies in this population.

## Methods

### Data sources and search strategy

A systematic search of the literature was performed to identify journals articles that examined the insulin and glycaemic effects of exercise intervention during pregnancy on women at risk or diagnosed with GDM. The search strategy 'gestational diabetes' AND 'exercise' AND 'intervention' AND 'glycaemic control' NOT 'type II diabetes' was applied to the following seven databases: MEDLINE (EBSCO), PubMed (NCBI), Scopus, CINAHL, the Cochrane Library, Embase and the Maternity and Infant Healthcare Database (Ovid). No date or limits were set; language limits were set for English. RSS notifications were set up for each database. In addition, bibliographies of existing reviews, eligible studies, key journals and conference proceedings were manually scanned. Scholars of various articles were contacted to enquire about protocol. Publications that did not have follow-up publication of the corresponding trial results were followed-up. The literature search was conducted in April 2018.

### Study selection

All journal articles retrieved from the databases were independently reviewed in a two-stage process by three reviewers. In the first stage, the titles and abstracts of articles from the database search were merged into EndNote™ and duplications removed. Studies that met review inclusion criteria and studies where there was uncertainty about meeting inclusion criteria were reviewed in full text by the main author. In the second stage, the full text of the study was read to determine if the study would be included in the review. The eligible studies were then reviewed by a second independent reviewer. Ambiguity was resolved by discussion with a third reviewer (A. D.). Inclusion criteria consisted of the following: (1) a study population of women diagnosed with GDM or considered at risk, with clearly defined risk factors; (2) an intervention of exercise (on multiple occasions) including any modality (aerobic, resistance, aquatic, etc.); (3) comparisons of exercise interventions with standard care; (4) outcome measures of insulin sensitivity or blood glucose control; and (5) a randomized controlled trial study design or (6) a case-controlled trial study design. Studies were excluded if they included a dietary aspect to the intervention (unless this was part of standard medical therapy), participants presented with co-morbidities or used medication to control hyperglycaemia, and they investigated the response to one bout of exercise.

### Data extraction

Data from articles were extracted onto an Excel® spreadsheet. Data extracted on the details of participants included the following: number of participants in each intervention and control; nature of intervention; and timing of intervention, duration and type. Outcome measures relevant to the review such as glycaemic measures and measures of insulin sensitivity were included. Other reported outcomes were listed. Inclusion/exclusion criteria, setting (supervised or home based) and compliance/adherence methods of objectively measuring intensity of exercise were included.

### Assessment of risk of bias, data synthesis, and analysis

The main author and a second assessor independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (23). Any disagreement was resolved by a third assessor (A. D.). When eligible studies did not have combinable outcomes for meta-analysis, a narrative review was thus undertaken. The eligible articles were summarized and discussed.

## Results

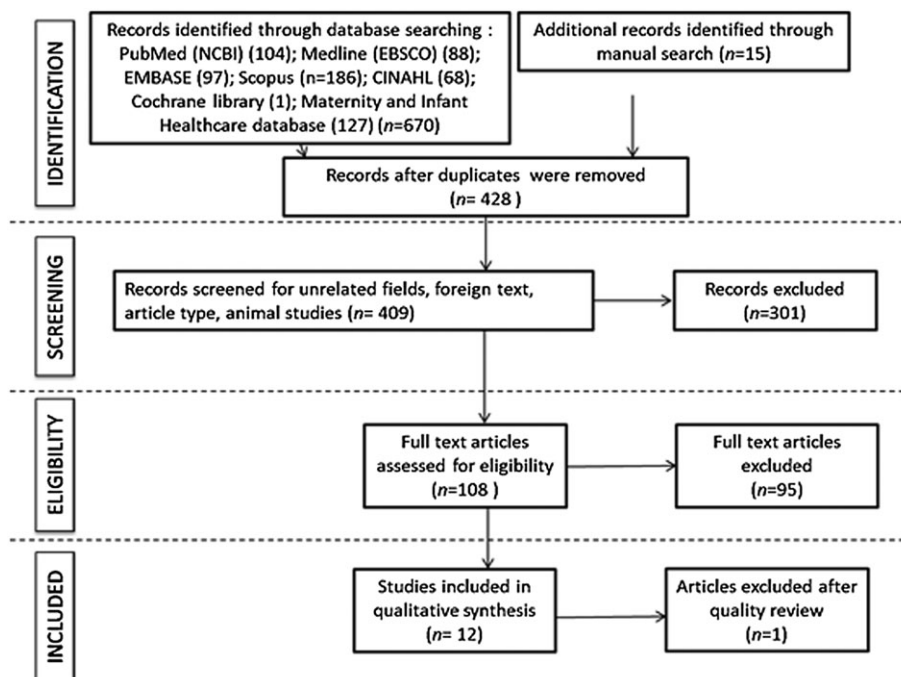
### Description of the studies

The initial search yielded 685 abstracts, of which 13 studies met inclusion and exclusion criteria (Figure 1). Twelve of these were included in this review after reviewing for quality (a summary is shown in Tables S1a and b): two interventions looked at resistance exercise (24,25), eight studies looked at the effect of an aerobic exercise intervention (26–30,62,64,68) and two studies utilized a combination of aerobic and resistance exercises (63,65). One study was omitted owing to poor adherence to the intervention, with only 16.4% of people attending half the sessions (31). This study was therefore not included, as the results did not reflect the effect of the exercise trial, which was a combination of resistance and aerobic training.

### Risk of bias

#### Allocation

Methods to generate the random sequence were judged to be adequate in 10 of the 12 included randomized controlled trials, and two were unclear risk (see Table S1a). Various techniques were used for randomization;



**Figure 1** PRISMA showing inclusion/exclusion of journal articles throughout screening procedures.

these methods included use of random number table (24), computer-generated random series produced by a person not related to the protocol (25) and block randomization (32); others stated they randomized participants but did not detail how this was performed (26,29,30).

Five trials were judged to have used adequate methods for allocation concealment (24–26,30,68,65). Of these five trials, three used concealed opaque envelopes; a separate researcher allocated patients according to a randomization list and one trial allocation was conducted by a third party at another location outside the hospital (30). For the remaining four trials, the risk of bias was judged to be unclear owing to inadequate allocation concealment as no methods were detailed (29,32,62,64).

### Blinding

For 10 trials, the risk of performance bias due to inadequate blinding of participants and personnel was judged to be high (24,26,27,29,62–64,68); one trial did not state details of blinding (30), and one study successfully blinded the personnel (25). However, owing to the nature of the interventions, blinding participants is not possible (participants are required to perform exercise).

All trials were considered at high risk of detection bias owing to patient-reported outcomes being self-monitored and also the end-point being insulin administration.

### Outcome data

All studies were considered at low risk of attrition bias with clearly reported attrition rates, and all trials had low risk of reporting bias as they included data from these participants in their analysis, with the exception of one trial (24). Oostdam *et al.* (31) had a low adherence of 16.5%, and as a result, much of the follow-up data were missing. They used a statistical technique, bootstrapping, to analyse estimates of missing data.

### Case-controlled trial

One included study was a case-controlled trial (28) that was assessed using a tool specific for its design (23). The risk of bias was judged to be minimal. Details of this can be seen in Table S1b.

### Characteristics of studies

Table 1 summarizes the studies selected, showing author, number of participants (*n*), nature of the population diagnosed or at risk of GDM, the exercise modality and details of the timing of the intervention.

### Resistance exercise

Two studies examining the effects of a resistance exercise programme during GDM pregnancy were identified

Table 1 Characteristics of studies meeting inclusion criteria

Article	n		Population		Timing of intervention			Duration (weeks)
	Intervention	Control	Diagnosed with GDM	At risk of GDM	Start point	End point	End point	
Brankston et al. (24)	16	16	X		From GDM diagnosis (26–32)	Till end of gestation	~5	
De Barros et al. (25)	32	32	X		From GDM diagnosis (24–34 weeks)	Till end of gestation	~5	
Halse et al. (26)	20	20	X		From GDM diagnosis (week 28.8 ± week of gestation)	Till week 34 gestation	~5	
Ruchat et al. (27)	6	6		X	Between 16 and 20 weeks	34–36 weeks' gestation	14–20	
Davenport et al. (28)	10	20	X		From diagnosis (24–28 weeks)	To delivery	≥6	
Ong et al. (29)	6	6		X	From week 18 gestation	28 weeks' gestation	10	
Callaway et al. (30)	25	25		X	From 12 weeks' gestation	36 weeks' gestation	24	
Avery et al. (62)	16	17	X		From GDM diagnosis (from 34 weeks or less)	Till end of gestation	4–6	
Gueffi et al. (64)	85	87		X	Between 13 to 15 weeks' gestation	28 weeks' gestation	14	
Wang et al. (68)	150	150		X	<12 <sup>16</sup> weeks' gestation	36 weeks' gestation	~24	
Garnaes et al. (63)	46	45		X	12–18 weeks' gestation	36 weeks' gestation	18–24	
Sklempe Kokic et al. (65)	20	22	X		28 weeks	Till end of gestation	6–10	

AER, aerobic exercise; COMB, combination; GDM, gestational diabetes mellitus; RT, resistance training.

(24,25). The interventions both took place from diagnosis at circa week 24 until the end of gestation, for a period of at least 10 weeks. Details of the design of the intervention, outcome measures taken and their main findings are summarized in Table 2, with a more comprehensive table in Table S2a.

Both studies had similar exercise interventions, each consisting of a circuit format of eight exercises working up to 15 repetitions of each exercise using a resistance band, three times a week. Both showed positive results, and these differed; Brankston et al. (24) showed that the exercise group required less insulin during gestation (43.8%) in comparison with diet alone (56.3%), but this was not statistically significant ( $p = 0.48$ ). The amount of insulin required (in units per kilogram) was less in the exercise intervention group,  $0.22 \pm 0.2$  vs.  $0.48 \pm 0.3$  ( $p < 0.05$ ), and women in the intervention group required insulin later in pregnancy,  $3.71 \pm 3.1$  vs.  $1.11 \pm 0.8$  weeks after diagnosis ( $p < 0.05$ ). No detectable difference in blood glucose levels, with the exception of pooled post-meal (2 h) glucose, which was lower in the exercise group,  $6.0 \pm 0.29$  vs.  $6.4 \pm 0.81$  mmol L<sup>-1</sup> ( $p < 0.05$ ). De Barros et al. (25) found that fewer patients in the exercise group 21.9% vs. 56.3% required insulin during gestation ( $p = 0.005$ ). Moreover, patients in the exercise intervention who used insulin continued to present adequate glycaemic control according to the target established for a longer percent period of weeks compared with control patients who used insulin ( $0.63 \pm 0.30$  vs.  $0.41 \pm 0.30$  [ $p = 0.006$ ]). No difference was detected between groups in mean glucose levels, amount of insulin required and latency to insulin requirement in those patients requiring insulin. Mean glucose levels were observed between patients of the two groups who used insulin; however, these were not found to be different (control:  $5.9 \pm 0.4$  vs. intervention:  $6.1 \pm 0.5$  mmol L<sup>-1</sup>;  $p = 0.342$ ).

### Aerobic exercise

Eight intervention studies were identified that used aerobic exercise as their exercise intervention (26–30,62,64,68). The details of the design and findings of the outcome measures are summarized in Table 3 with a more comprehensive table in Table S2b.

The exercise interventions were completely supervised in some cases (27–29,64,68), partially supervised in others (26,62) and not supervised at all in one study (30). The methods used and outcome measures taken vary greatly in each trial, making it difficult to compare them directly (see Table S2b); however, there seems to be a positive impact of exercise in outcome measures of insulin sensitivity and glycaemic control across those studies that had at least three supervised sessions per

**Table 2** Abridged summary table for resistance exercise interventions, their main outcomes and findings

Article	Intervention	Main outcome measures	Main findings (intervention group vs. control)
Brankston <i>et al.</i> (24)	Circuit session: 3× per week. 3 rounds of 8 exercises × 15 repetitions	Requirement for insulin Amount of insulin Latency of administration of insulin Pooled post-meal glucose	↔ No difference ↓ Improved ↑ improved ↓ improved
De Barros <i>et al.</i> (25)	Circuit session 3× per week: 3 rounds of 8 exercises × 15 repetitions	Requirement for insulin Amount of insulin Latency of administration of insulin Pooled capillary glucose levels	↓ Improved ↔ No difference ↔ No difference ↔ No difference

week lasting 40–45 min. Two studies found no differences in various measures of blood glucose control and surrogate measures of insulin sensitivity between intervention and control groups. The first study (62) had two supervised sessions lasting 20 min, and outcome measures were limited to fasting glucose, glycated haemoglobin (HbA1c) and use of insulin therapy. The second study (64) started at 20 min and increased in duration; the outcome measures used were oral glucose tolerance test (OGTT), homeostatic model assessment-insulin resistance (HOMA-IR), Oral Glucose Insulin Sensitivity and HbA1c.

Three of these studies recruited a population already diagnosed with GDM, two of which reported improvements in outcome measurements (26,28), whereas Avery *et al.* (62) did not detect any changes in outcome measures. The difference between these studies was the type of exercise: Halse *et al.* (26) used cycling as a modality and Davenport *et al.* (28) walking, whereas Avery *et al.* (62) used an arm ergometer. Frequency and duration of exercise were also less: twice per week for 20 min (62) as opposed to three times per week for 40 min (26,28).

Five of the studies engaged a population at risk of gestational diabetes (27,29,30,64,68). The duration of these interventions ranged from 10 to 20 weeks in comparison with the 4–6 weeks' duration of intervention in those studies that engaged a population diagnosed with GDM (26,28,62). Improvements were found in capillary blood glucose levels (27), blood glucose response to OGTT (29,68), insulin resistance (68) and gestational weight gain; and incidence of GDM was reportedly improved in one study (68). One study in particular (64) reported no difference in all outcome measures, despite similar frequency, intensity, type and duration of exercise intervention. This study differed from the aforementioned studies in the population recruited, where women with previous GDM were recruited as opposed to women with obesity. These women had a lower body mass index (BMI) than those women engaged in the other studies, with 44% in the exercise group and 55% in the control

group within a healthy BMI. It is also worth noting that this had a sample size powered to gestational weight gain and not measure of glucose control or insulin sensitivity.

### Combined aerobic and strength exercise

Two studies included both aerobic and resistance training modalities of exercise (63,65). A summary can be found in Table 4 and more in-depth details in Table S2b. Both studies had supervised and non-supervised elements. Garneas and colleagues (63) reported that an incidence of GDM was less in exercise group vs. control group (6.1% vs. 27.3%,  $p = 0.04$ ); however, no difference was observed in OGTT, insulin, HbA1c, and HOMA2-IR. Sklempe and colleagues (65) found an improvement in post-intervention average of three postprandial measures ( $4.66 \pm 0.46$  vs.  $5.30 \pm 0.47$ ,  $p < 0.001$ ), but no difference in fasting glucose between the two groups. The two interventions varied in duration and population characteristics, with Garnaes *et al.* (63) intervening for 18–24 weeks in pregnant women at risk of GDM ( $BMI \geq 28 \text{ kg m}^{-2}$ ) and Sklempe *et al.* (65) between 6 and 10 weeks following a GDM diagnosis.

## Discussion

Twelve intervention studies met the inclusion criteria for this systematic review and were included in this review (24–30,62,68,63–65). Modalities of these interventions were resistance exercise (24,25) and aerobic exercise (26–30,62,64,68). Some interventions showed that requirement of insulin therapy (25,28), dosage (24,28) and latency to administration (24) improved in the exercise groups. Capillary blood glucose measurements also improved (26–28), as well as post-meal glucose (24) and blood glucose response (29). Other outcomes measured showed no difference in insulin sensitivity (26,29,64), insulin resistance (30,68), requirement of insulin (24), amount of insulin required (25) and latency of administration (25). Of note is that no studies reported any negative

**Table 3** Abridged summary table for aerobic exercise interventions, their main outcomes and findings

Article	Intervention	Main outcome measures	Main findings (control vs. intervention group)
Halse <i>et al.</i> (26)	Cycling 5× per week. 3× a week: supervised 45 min moderate intensity and short bouts of higher intensity, 2× a week 30 min moderate cycling unsupervised	Mean capillary blood glucose pre-exercise and post-exercise ( <i>exercise group only</i> ) HbA1c OGTT Insulin sensitivity Pooled capillary glucose levels	↓ Improved  Increased in both groups, with no difference between groups ↔ No difference ↔ No difference ↓ Improved
Ruchat <i>et al.</i> (27)	Supervised walking programme 3–4× per week: 40 min in total with 30 min at target HR of 30 or 70% HRR according to group allocation	Capillary blood glucose pre-exercise and post-exercise	↓ Improved in all groups and durations. Longer durations of exercise (40 min). Improvements in capillary glucose attenuated with longer durations of exercise
Davenport <i>et al.</i> (28)	3–4 walking sessions a week of 40 min at 30% HRR	Capillary blood glucose Requirement for insulin Amount of insulin	↓ Improved ↓ Improved ↓ Improved
Ong <i>et al.</i> (29)	3× per week 45 min cycling ergometer at 50–60% HRmax	Blood glucose response (OGTT) Insulin sensitivity (OGIS)	↓ Improved OGTT at 1 h ↔ No difference
Callaway <i>et al.</i> (30)	Individualized exercise plan, to reach recommendation of 7.5–12.5 MET-h/week of moderate to vigorous intensity activity	Insulin resistance (HOMA-IR) Fasting glucose Fasting insulin	↔ No difference ↓ Improved ↓ Improved
Avery <i>et al.</i> (62)	2 supervised session per week 30- and 5-min warm-up, 20 min 70% HRmax, 5-min cool down on cycle ergometer. In addition, 1–2 unsupervised sessions at the same intensity walking	Fasting glucose HbA1c Use of insulin therapy	↔ No difference ↔ No difference ↔ No difference
Guelfi <i>et al.</i> (64)	3× per week at home supervised on cycle ergometer. Warm-up for 5 min at 55–65% HRmax, intervals alternating between 65 and 75% HRmax and 75–85% HRmax. Sessions progressed by increasing in duration by 5 min every 2–3 weeks so that they started at 20 min up to a maximum of 60 min	Pre-intervention and post-intervention OGTT HOMA-IR OGIS HbA1c	↔ No difference ↔ No difference ↔ No difference ↔ No difference
Wang <i>et al.</i> (68)	3× per week supervised exercise sessions on cycle ergometer. 5-min warm-up (55–65% HRmax) 30-s sprint at 75–85% HRmax every 2 min for 3–5 intervals, followed by 5 min at 60–70% HRmax. 3 × 1 min at 75–85% HRmax (increased resistance) 2 min at 65–75% HRmax. 5-min cool down at 55–65% HRmax. Exercise period start at 45 min and increased to 60 min progressively	Incidence of GDM Gestational weight gain Insulin resistance OGTT: fasted 1 h post-ingestion 2 h post-ingestion	↓ Improved ↓ Improved Insulin levels ↓ Improved Insulin resistance ↔ remained the same ↓ Improved ↓ Improved ↓ Improved

GDM, gestational diabetes mellitus; HbA1c, glycated haemoglobin; HOMA-IR, homeostatic model assessment-insulin resistance (method to quantify insulin resistance (38)); HRmax, heart rate maximum established from predicted formula or sub-maximal exercise testing; HRR, heart rate reserve (target heart rate was determined using the HRR equation by Karvonen *et al.* (36)); MET-h/week, metabolic equivalents-hours per week; OGIS, Oral Glucose Insulin Sensitivity index, which determines insulin sensitivity from the OGTT (37); OGTT, oral glucose tolerance test (the specific test used is outlined in each study).

**Table 4** Abridged summary table for combined aerobic and strength exercise interventions, their main outcomes and findings

Article	Intervention	Main outcome measures	Main findings (intervention group vs. control)
Garnaes <i>et al.</i> (63)	3× per week supervised. 35-min aerobic exercise (walking/jogging) at ~80% HRmax. 3× 10 reps squats, push-ups, diagonal lifts, oblique abdominal crunches. 3× 30-s plank at the end. Pelvic floor exercise 10 sets of 6–8 s hold.  50-min home programme 1× per week (same structure as supervised session). Pelvic floor exercises daily	Gestational weight gain Incidence of GDM OGTT Insulin HbA1c HOMA2-IR	↔ No difference ↓ Improved ↔ No difference ↔ No difference ↔ No difference
Sklempe <i>et al.</i> (65)	2× per week supervised session. (50–55 min) 20-min treadmill walking at 65–75% HRmax. Resistance exercise using body weight, elastic bands and 0.5-kg handheld weight. 6 exercises × 3 sets of 10–15 reps. 3 different routines were used and interchanged. Exercise group was also asked to perform 30-min brisk walk per day	Post-intervention average of 3 postprandial measures Fasting glucose Insulin therapy	↓ Improved  ↔ No difference No participants required insulin therapy

HbA1c, glycated haemoglobin; HOMA-IR, homeostatic model assessment-insulin resistance; HRmax, heart rate maximum; HRR, heart rate reserve; OGTT, oral glucose tolerance test.

outcomes of exercise on blood glucose control. Discrepancies in the timing of intervention, GDM diagnostic criteria and the variety in outcome measures used to assess glucose metabolism make it difficult to draw clear recommendations but have useful considerations for the design of future exercise interventions in this patient population.

The details of the exercise (modality, time, intensity) are of high importance during GDM, as diagnosis occurs around weeks 24–28 of gestation, allowing for 8–10 weeks' opportunity for intervention before parturition. In the studies included in this review, the time frame exposed to the exercise intervention and degree of hyperglycaemia of the participants varied as a product of different GDM diagnostic criteria used by the study to define a starting point (37–40). These criteria are less stringent than the current guidelines by the World Health Organization (1) derived from the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) as a result of findings from the HAPO study. This could potentially have an effect of the outcomes of the exercise interventions, as it still needs to be established at which specific point prior or during GDM can an exercise intervention be most effective.

Interventions delivered in 'at risk' population (29,30,27,64,68,63) commenced earlier in gestation and lasted 10–24 weeks. Ong and colleagues (29) recruited pregnant women with obesity otherwise not at risk of

GDM, and the length of time of intervention was over 6 weeks. Commencing exercise intervention earlier gave positive results to glycaemic control in all cases, barring a population who had previous GDM. This is in line with exercise interventions in type II diabetic patients, where positive outcomes were attributed to the benefits of metabolic control and adaptation over 15 weeks or more (41), with even 1 week of aerobic training known to improve whole body insulin sensitivity in obese individuals with type II diabetes (42). In light of this, it is worth considering at which point to intervene with an exercise intervention, even though it is recognized that exercise prior to pregnancy is effective at reducing the risk of GDM (43); the most effective strategies to maximize results have not been identified.

The modality of exercise also needs to be considered in terms of the longer-term aspects of the effects that it may have. Most of the studies included in this literature review did not follow up the women or infants post-partum, with the exception of Halse *et al.* (26) who reported follow-up data separately (60). This is very valuable, as they reported a reduced incidence of macrosomia in the offspring and less maternal weight gain over the intervention period in the group who engaged in the exercise intervention. No other improvements in obstetric or neonatal outcomes were observed, despite that it is also positive that no adverse effects were reported as a result of the exercise intervention. These data are relevant in



understanding what benefits aerobic activity confer in the longer term. Specifically, this population group is at higher risk of developing type II diabetes following gestation (44), and the benefits of various exercise modalities can extend beyond the acute phase post-partum (22,45).

The tests used to assess glycaemic control in the interventions are typically 75-g OGTTs at diagnosis and later in pregnancy, postprandial blood glucose, random blood glucose and insulin measures, HbA1c, indirect measures of insulin sensitivity (Oral Glucose Insulin Sensitivity) based on OGTT (33), HOMA-IR (34) and need for insulin treatment and others as indicators of progression of hyperglycaemia; however, additionally, treatment criteria depend on which criteria the health centre practises. Sensitivity of these measures needs to be considered (61,67), and can explain the variation in results, sometimes seeing a positive outcome in one outcome with no change in another, all within the same study. Postprandial plasma glucose excursions have been found to be as important (46) in achieving HbA1c goals in type II diabetic patients, and owing to the limited time frame of pregnancy, this may be a more relevant marker than HbA1c, as blood renews itself after 8–12 weeks, therefore missing out on the period of the acute intervention delivery. The lack of homogeneity in measurements across studies makes them difficult to compare.

Adherence was measured in each of the trials, with the use of attendance logs (24,26,27,29), pedometer readings (28), self-monitored exercise diaries (26) and a combination of attendance and logbook (24,27). All included trials reported high attendance with over 90% exercise sessions attended by intervention groups. Trials involving supervised components of at least three times per week with at least 40 min of exercise had better outcomes in glycaemic management than those who engaged in less.

When lifestyle changes do not normalize blood glucose levels, pharmacological treatment can be utilized, progressing to insulin treatment as a final course of action. Delaying and minimizing treatment with insulin are of clinical importance not only as an indicator of progression of hyperglycaemia but also owing to its association with vascular damage (47). Both resistance interventions took measures of insulin administration (24,25), and although these specific interventions were not statistically powered for this outcome measure, they showed improvements as a result of the intervention. Future studies should incorporate these measures within their trials.

The mechanisms behind impaired insulin sensitivity during GDM are not completely understood and, therefore, remain a very fertile ground for research. Exercise may be an effective strategy to optimize glucose homeostasis as it can lower blood glucose levels, thereby improving insulin sensitivity during pregnancy, reducing

the burden on the compensating  $\beta$ -cells (20). Exercise lowers blood glucose concentration via two distinct mechanisms: the contraction-mediated pathway and the insulin-stimulated pathway (21). The physiological mechanisms involved in increasing insulin sensitivity include increased number of insulin-sensitive glucose transporters (GLUT-4), enhanced response of GLUT-4 to insulin and increased glycogen synthase activity, all within the skeletal muscle. These work in combination to lower capillary glucose concentrations. The underlying mechanisms surrounding this are described in depth elsewhere (22). As the skeletal muscle is the major source of insulin-stimulated glucose uptake, any treatment targeted to improve glucose uptake in this tissue will improve whole-body insulin sensitivity. The metabolic benefits of exercise, specifically during GDM pregnancy, are thought to be due to changes affecting pathways, which influence insulin sensitivity, adipokines and reduction–oxidation reactions (22). Aerobic and resistance exercises trigger various metabolic pathways to elicit metabolic benefits when performed prior to pregnancy (18) and as part of medical therapy for glycaemic management in type II diabetic patients (48). Some research has shown that the metabolic benefits and protective effects are dose dependent (49), directing some studies to turn their focus to energy expenditure (30,59). However, studies investigating the effects of differing modality of exercise on several metabolic markers and compartmental changes in body composition show that the metabolic benefits are specific and diverse (50–54).

Aerobic exercise may work best for increased uptake of glucose into the muscle and reducing fat mass (reduced adipokine and leptin production). However, resistance exercise may be more effective at increasing lean muscle, and thus basal metabolic rate, and therefore may have its place in the management of GDM pregnancies, in terms of long-term maternal outcomes and their risk of developing type II diabetes mellitus (44). Previous studies have suggested that the maternal environment, in particular reduction in maternal insulin sensitivity, contributes significantly to foetal growth (69). Regular aerobic exercise, through an effect on maternal insulin sensitivity, may influence offspring size by regulating nutrient supply to the foetus.

The discrepancies in the results of the resistance exercise interventions (24,25) included in this review may be due to the higher numbers recruited in the study of De Barros *et al.* (25). Also of note is the difference in delivery of interventions. Brankston *et al.* (24) supervised three sessions per week, including a weekly phone call to ensure adherence. This was in contrast to De Barros *et al.* (25), where one session per week was supervised and phone contact was made with participants to

encourage adherence for the other two sessions that took place at participants' home unsupervised. In both trials, resistance was adjusted via the length of the elastic band to increase tension, and even though it is speculated that this modality is self-limiting unlike free weights, a short-term study in women has found elastic bands to produce the same benefits in body composition changes as free weights (55). The aerobic interventions had varying results, as the delivery of their intervention and outcome measures were different in each study. Therefore, as previously alluded to, it is suggested that future study designs be homogenized in order to make comparisons between effectiveness of exercise modality on glycaemic parameters.

Studies have previously shown that greater exercise intensity yields greater glucose uptake by skeletal muscle cells acutely, and over time through the contraction-mediated and insulin-stimulated pathways, to increase insulin sensitivity (56). Exercise prior to pregnancy is known to reduce the risk of developing GDM (35,43). In an overweight/obese non-diabetic population, it has been shown that aerobic exercise was more effective at reducing fat mass, and resistance training was more effective at increasing lean mass. However, performing both, and hence doubling the time committed to exercise by participants, did not double the benefits (57). This, as well as the limited time frame between diagnosis of GDM and parturition (~8 weeks), further highlights the importance of establishing the most effective modality of exercise as a treatment for hyperglycaemia in GDM patients during pregnancy, in order to maximize strategies for minimizing hyperglycaemia in the antenatal period.

## Conclusion for practice

This systematic review recommends that patients with GDM and pregnant women with obesity can improve glycaemic management and incidence of GDM during pregnancy through exercise. Evidence collated in this review suggests that women diagnosed with GDM benefit from exercise performed a minimum of three times per week, resistance exercise consisting of eight exercises of 15–20 repetitions each using major muscle groups or aerobic exercise using major muscle groups such as cycling and walking, performed at a rate of perceived exertion (RPE (66)) of 12–14 (equivalent to 65–75% age-predicted HRmax) for 40–60 min. For adherence purposes, supervising sessions and making these sessions interesting using brief intervals of increased intensity such as RPE 13–15 (75–85% age-predicted HRmax) using resistance or speed can be undertaken safely with suitable monitoring and realistic increments of time and intensity according to the patients' previous ability and progress.

Combinations of aerobic and resistance exercises also confer such benefits to glycaemic control, in line with the 7.5–12.5 MET-h/week (~900 kcal) of moderate to vigorous exercise guidelines set out for this population group. Women at risk of GDM due to high BMI ( $>28 \text{ kg m}^{-2}$ ) would benefit from a similar intervention; however, those at high risk of GDM due to previous exposure to GDM without obesity do not seem to have improvement in glycaemic control with such interventions.

Further research on the effectiveness of exercise interventions needs to take place, in a standardized manner, in order to compare results and answer what is the most effective exercise intervention in this population. This includes timing and duration of intervention, as well as methods of measuring glucose control and indices of insulin sensitivity. It is recommended that dietary intake and physical activity are measured as confounding factors, in order to isolate and observe the effects of specific exercise interventions. Future studies should also focus on measurements of hyperglycaemia, as confirmed by the large HAPO study, that small degrees of hyperglycaemia have a significant effect on pregnancy and neonatal outcomes. The clinical significance of the outcome measures used should be considered. Interventions should aim to follow up participants post-partum to understand longer-term benefits of antenatal exercise intervention.

Well-controlled exercise interventions, which are homogenous in the measures used, specific gestational period when intervention is implemented and clinical population (i.e. all diagnosed at the same diagnostic threshold) are required to understand which modality, intensity and duration of exercise are most effective in this population.

## Conclusions

There is a paucity of literature on exercise interventions during pregnancy on women with GDM, specifically including measures of glycaemic control. The studies included in this review showed an improvement in blood glucose measures in two modalities of exercise: aerobic and resistance exercises. Future studies looking at exercise strategies to maximize non-insulin stimulated uptake of glucose through are needed to counteract the increase in insulin resistance observed during pregnancy, and especially of GDM.

Studies examining specific exercise interventions in this particular population are of importance on several levels: to understand the mechanisms behind the exercise being performed; for public health policy, to discern which modality and duration are most effective in order to make recommendations and promote these to

this specific population; and economically, as effective interventions may reduce the medical burden this condition constitutes to both mother and infant.

There needs to be a shift in paradigm, similar to the nutrition adage of 'eating for two' having been dispelled in recent years through education. It is important to emphasize to pregnant women that moderate-intensity exercise during pregnancy is safe, healthy and indeed beneficial to both mother and child, when performed in line with guidelines (58). In recent years, nutrition has taken the role of being the 'cornerstone of therapy – also referred to as medical nutritional therapy'; however, exercise has not quite caught up to this reputation, despite the effects it has on multiple metabolic mechanisms in the body (56). In the months during pregnancy, mothers are known to be very receptive to behaviour change and have many 'teachable moments'. This is certainly supported by the studies included with high adherence rates in these studies and should be considered a good opportunity for behavioural change to be maximized by the allied health professions.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

## Acknowledgements

This research project was supported by the University of Limerick through an Education & Health Sciences Faculty Postgraduate Deans Scholarship, Graduate Entry Medical School Strategic Research Fund and Health Research Institute Seed Funding.

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## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1** (a) Cochrane assessment of risk of bias for randomized control trials summary figure. ‘+’ low risk, ‘–’ high risk ‘?’ unclear risk. (b) Quality assessment for case-controlled trial.

**Table S2** (a) Details of exercise intervention, the outcome measures taken and main findings for the interventions using a resistance exercise intervention. (b) Details of exercise intervention, the outcome measures taken and main findings for the interventions using an aerobic exercise intervention. (c) Details of exercise intervention, the outcome measures taken and main findings for the interventions using a combination of aerobic and resistance exercise intervention.