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Herbert Groeller
University of Wollongong, hgroell@uow.edu.au

Sandra Lowe
UNSW, s.lowe@unsw.edu.au

Anthony Worsley

Arthur Jenkins
University of Wollongong, ajenkins@uow.edu.au

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Abstract

Gestational diabetes mellitus (GDM) is associated with a marked increase in the long-term risk of type 2 diabetes and adverse pregnancy outcomes. Engaging in vigorous recreational physical activity prior to and during pregnancy significantly reduces the risk of developing GDM. In contrast, evidence of a therapeutic effect from participation in a structured exercise training regimen, although promising, is limited and requires further more substantial investigation. This paper briefly reviews the pathophysiology of GDM, the evidence related to physical activity participation and exercise regimen intervention on GDM, and the clinical considerations required for prescribing exercise. Key Words: gestational diabetes mellitus • exercise • physical activity • pregnancy • type 2 diabetes

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REVIEW ARTICLE

Does exercise have a role in the management of gestational diabetes mellitus?

Herbert Groeller PhD*, **Sandra Lowe** FRACP MD†, **Anthony Worsley** PhD‡ **and Arthur Jenkins** PhD‡

*Centre for Human and Applied Physiology, School of Health Sciences, University of Wollongong, Wollongong, NSW 2522;
†School of Women's and Children's Health, Royal Hospital for Women, University of New South Wales, Sydney, NSW;
‡School of Health Sciences, University of Wollongong, Wollongong, NSW 2522, Australia

Summary: Gestational diabetes mellitus (GDM) is associated with a marked increase in the long-term risk of type 2 diabetes and adverse pregnancy outcomes. Engaging in vigorous recreational physical activity prior to and during pregnancy significantly reduces the risk of developing GDM. In contrast, evidence of a therapeutic effect from participation in a structured exercise training regimen, although promising, is limited and requires further more substantial investigation. This paper briefly reviews the pathophysiology of GDM, the evidence related to physical activity participation and exercise regimen intervention on GDM, and the clinical considerations required for prescribing exercise.

Keywords: gestational diabetes mellitus, exercise, physical activity, pregnancy, type 2 diabetes

INTRODUCTION

Globally, an additional 195 million people (114% increase) are projected to have type 2 diabetes by 2030, with the prevalence estimated to increase from 2.8% to 4.4%, respectively, from 2000.[1] Existing data suggest that this rise in diabetes will be paralleled with a rise in gestational diabetes, with 2.2–8.8% prevalence during pregnancy.[2,3] Although gestational diabetes mellitus (GDM) is transient with glycaemic control often returning to normal postpartum, it does confer a four-fold risk of developing diabetes, and is associated with adverse pregnancy outcomes.[4,5]

The evidence is very strong that physical activity can prevent or delay the progression of type 2 diabetes in individuals at increased risk.[6] Indeed, a significant number of chronic diseases are directly associated with physical inactivity.[7] With only 50% of non-pregnant women meeting minimum levels of physical activity, and the rate of physical activity participation declining further during pregnancy, it appears likely that exercise may have an adjunct therapeutic role in the management of GDM.[8] This paper sets out to review the pathophysiology of GDM, the association of physical activity and exercise regimen on GDM, and finally the clinical implications of prescribing exercise for this group of women.

Correspondence to: Herbert Groeller, School of Health Sciences, Faculty of Health and Behavioural Sciences, University of Wollongong, Northfields Avenue, Wollongong, NSW 2522, Australia
Email: hgroell@uow.edu.au

PATHOPHYSIOLOGY OF GDM

Risk factors for GDM include older age, higher body mass index (BMI) and family history of diabetes, a pattern shared with type 2 diabetes.[9] Women who have had GDM are at markedly increased lifetime risk of developing type 2 diabetes, which may be as high as 70%.[10] For these reasons, and in light of the known similarities in pathogenesis discussed below, GDM can be seen as a transient form of type 2 diabetes, with rapid onset brought on by the metabolic and hormonal stresses of pregnancy.

The characteristic feature and basis of diagnosis of GDM, like type 2 diabetes and all other forms of diabetes mellitus, is an abnormally high blood glucose concentration in the fasting state and/or in response to glucose ingestion. Blood glucose concentration is normally tightly controlled by complex endocrine and autonomic feedback loops acting on tissues that produce or consume circulating glucose. However, in the context of clinical diabetes these complex processes can be represented by a simple model, in which blood glucose concentration is determined by two processes: (i) glucose-stimulated insulin secretion from pancreatic β cells and (ii) insulin-sensitivity of glucose utilizing and producing tissues.[11] The hyperglycaemia of GDM and of type 2 diabetes is associated with a partial failure of insulin secretion and with reduced insulin sensitivity (or insulin resistance) but the sequence and relative importance of the events leading to hyperglycaemia are unclear. A broad consensus has developed over the last two decades that the primary insult is insulin resistance which, in susceptible individuals, leads to slow progressive failure of insulin secretion.[12] The molecular mechanisms responsible for insulin resistance are not yet clear, but it is predominantly associated with excess adiposity and there is currently great interest in the potential roles of adipose tissue

derived signals (i.e. adipokines).[13] Out of this consensus has come the theory that impairments in insulin secretion in GDM and type 2 diabetes represent the failure of a postulated feedback loop between insulin secretion and insulin sensitivity, which in non-diabetic individuals stimulates insulin secretion to compensate for reductions in insulin sensitivity, thus preserving normoglycaemia. As a practical consequence of this theory it is recommended that measures of insulin secretory function must be corrected for the prevailing level of insulin resistance in order to assess the operation of this postulated feedback loop.[12,14] However, it is now clear that the result of this correction (the so-called Disposition Index) is no more than an alternative way of expressing the level of glycaemia, and its use has the effect of obscuring the crucial independent role of impaired insulin secretion in the pathogenesis of GDM and type 2 diabetes.[11,15,16] So far there is little evidence for beneficial effects on insulin secretion in any of the existing diabetes therapies, and some evidence that some drugs exacerbate its decline.[17]

GDM differs from type 2 diabetes in its rapid onset and usual reversal, postpartum, consistent with a triggering role of the metabolic and hormonal stresses associated with pregnancy. These stresses include a developing insulin resistance, detectable in the second trimester, and more marked in the third.[10] The mechanism of this pregnancy-induced insulin resistance is not clear but changes in steroid and/or lactogenic hormone levels may play a role.[18] Elevated insulin secretion accompanies this insulin resistance, as in other insulin resistant states, and it has been argued that this is a consequence of the postulated feedback loop described above by which insulin resistance stimulates insulin secretion. However, it is now clear that pregnancy in rodents induces increased insulin secretion by a mechanism dependent on hormones acting through lactogen receptors on β cells, and although the usual caution must be exercised when extrapolating from animal models, it seems likely that similar mechanisms operate during pregnancy in humans.[19] Hypersecretion of insulin is an early response to pregnancy, and is most likely to account for the small but significant decline in fasting blood glucose that accompanies pregnancy in women who do not develop GDM.[20,21] GDM can therefore be seen as the result of a partial failure of this hypersecretory response. Given the close similarities between GDM and type 2 diabetes it may be hoped that a better understanding of this defect in GDM will shed light on the nature of impaired insulin secretion in type 2 diabetes.

Whatever the primacy and relative importance of insulin secretion and insulin resistance to the hyperglycaemia of GDM, it remains true that improvements in either process can reduce glycaemia and improve maternal and fetal outcomes. It has recently been shown in a systematic review of the literature that diagnosis of GDM is associated with increased body fatness as indexed by prepregnancy BMI[22] – for each one unit increase in BMI, prevalence of GDM increased by 0.92%. Elevated BMI is strongly associated with insulin resistance and therefore may account for increased insulin resistance before and during pregnancy which is reported in some women who develop GDM.[10] Any therapies that reduce insulin resistance, including lifestyle-induced weight loss, and the independent effects of physical activity on insulin resistance would be expected to improve glycaemia and maternal and fetal outcomes in women with GDM.

PHYSICAL ACTIVITY

Links between physical activity and GDM

There is substantial associative evidence that women who carry out vigorous recreational activities before and during pregnancy have much lower chances of developing GDM than sedentary women. The most robust evidence comes from two American cohort studies.[23,24] Project Viva followed a cohort of 1805 women in eastern Massachusetts.[23] It showed that women who had engaged in any vigorous activity in the year prior to pregnancy had an odds ratio (OR) of 0.56 for GDM (95% CI 0.33–0.95). Walking and total physical activity (the sum of walking, light to moderate and vigorous activity) were associated with lesser benefits. Similar findings were found in the Nurses Health Study, a prospective cohort study of 21,765 women who reported at least one singleton pregnancy between 1990 and 1998.[24] The multivariate relative risk (RR) of GDM was 0.77 (highest versus lowest quintile of physical activity; 95% CI 0.69–0.94). Among those who did not perform vigorous activity, those who engaged in regular brisk walking had a much lower risk of GDM (RR 0.66, 95% CI 0.46–0.95). Similar positive effects of physical activity on GDM risk have been shown in case-control studies. Dempsey *et al.*[25] showed that women who took part in any form of physical activity during the first 20 weeks of pregnancy were 48% less likely to develop GDM than inactive women (OR 0.52, 95% CI 0.33–0.80). Women who took part in recreational physical activity in the year before pregnancy also had reduced risk of GDM and those who undertook physical activity in both periods had the greatest reduction in risk (OR 0.40, 95% CI 0.23–0.68).

It would appear from these investigations that additional benefit is afforded to women who engage in vigorous physical activity prior to or during pregnancy.[23–25] These observations are consistent with findings in type 2 diabetes.[26]

Lui *et al.*[27] investigated whether the introduction of increased levels of physical activity during pregnancy among women who had been inactive prior to pregnancy provides benefits for their health. They examined records from 4813 women in the 1988 National Maternal and Infant Health Survey and found that the 11.8% of previously inactive women who became active in pregnancy experienced a reduced risk of GDM (OR 0.43, 95% CI 0.20–093); women who undertook brisk walking in pregnancy had an OR of 0.44 (95% CI 0.19–1.02) and those who had a physical activity index score above the median had an OR of 0.38 (85% CI 0.15–0.96) compared with inactive women. Of course those who took up physical activity may have been predisposed in some way to have lower risk of GDM.

Measurement: validity and reliability issues

Most investigations of physical activity use questionnaires to estimate participation in endurance activities, such as walking, running and sport; quantitated as METs (units of resting metabolic rate). The MET value of an activity is an indication of the energy required per kilogram of body mass to perform the activity, divided by the energy needed per kilogram of body weight at rest. For example running may incur a 10 MET value, indicating the energy requirement for the activity is 10-fold higher than resting. There are several questionnaires which have been used to estimate physical activity

in pregnancy such as the Kaiser Physical Activity Survey (KPAS),[28] and the Pregnancy Physical Activity Questionnaire (PPAQ).[29] Both instruments appear to provide reliable and valid indices of physical activity. Schmidt *et al.*[30] administered the KPAS along with the PPAQ and conducted accelerometer measurements for seven days on 63 pregnant women. They showed that the reproducibility of the KPAS was moderately high (the intraclass correlation for total activity was 0.84) and Spearman correlations between the accelerometer data and reported total activity ranged from 0.49 to 0.59, with scores derived from the KPAS and PPAQ being highly intercorrelated. Earlier work showed that correlations between accelerometer measures and PPAQ total activity scores ranged from 0.08 to 0.43 for total activity, i.e. the scores exhibited low to moderate validity.[29] It should be emphasized that there is relatively little evidence about possible effects of flexibility or strength exercise (for example, upper body resistance exercise) on the risk of GDM, despite the possible utility of resistance exercise in the management of type 2 diabetes in adults (discussed below).[31] Physical activity may have broader effects on pregnant women than reduction of GDM risk alone. For example, a retrospective Canadian case-control study showed that women who performed regular leisure time physical activity in the first 20 weeks of pregnancy had much lower risks of pre-eclampsia (RR 0.67, 95% CI 0.46–0.96) and gestational hypertension (RR 0.75, 95% CI 0.54–1.05).[32] Retnakaran *et al.*[33] showed that vigorous/sports activity was associated with improved glucose tolerance status ($P = 0.02$) and was weakly correlated with an index of insulin sensitivity ($r = 0.21$ $P < 0.001$).

Influence of physical activity in pregnancy

Few studies have examined factors that influence performance of physical activity in pregnancy. Pereira *et al.*[34] identified the factors which appear to inhibit women from undertaking physical activity in pregnancy. These included the onset of pregnancy (13% were inactive before pregnancy and 22% in the postpartum period) and the presence of at least one child (OR 1.58, CI 1.07–2.32). Postpartum factors associated with inactivity included weight retention, working longer hours in the first trimester and reported lack of child care. Dinallo *et al.*[35] used accelerometry to show that pregnant women slowed down their walking pace in a treadmill walking condition as pregnancy progressed. The authors observed that less than 12% of women in the study's free-living condition met recommended physical activity guidelines consistent with the findings of other investigations.[36] With only 50% of non-pregnant women meeting current minimum physical activity levels, and levels of participation declining during pregnancy, there appears considerable scope to increase levels of physical activity undertaken by pregnant women.[8]

While there is strong suggestive evidence that vigorous and habitual physical activity can reduce the risk of GDM, many women are inactive both before and increasingly during pregnancy. More randomized controlled trials are required to investigate the effects of different forms of exercise during pregnancy.

Acute and chronic effects of exercise

A single bout of exercise results in a marked rise in insulin-stimulated glucose uptake in insulin-resistant individuals.[37] When individuals with type 2 diabetes performed postprandial exercise for 45 minutes at a moderate intensity, a significant reduction in glycaemic excursion and plasma insulin levels were observed.[38] However, although distinct, the effect of exercise was transient with glycaemia and plasma insulin returning to original levels after four hours with the consumption of a second meal.[38] Interestingly, although the mechanism differed, a reduction in caloric intake had the same effect as exercise on postprandial glycaemia and plasma insulin levels. The mechanism for this exercise response may be attributed to enzymatic changes in the regulation of non-oxidative disposal of glucose, elevated skeletal muscle blood flow and a decline in muscle glycogen.[39] The complexity of the systemic response to acute exercise is underscored by recent observations of an exercise and metformin interaction.[39] When metformin and acute exercise were combined, insulin sensitivity remained unchanged. In contrast, the exercise-only condition caused insulin sensitivity to significantly increase (54%). Given that metformin and exercise target different tissues (liver and skeletal muscle, respectively), the authors had proposed an additive effect associated with combined acute exercise and metformin administration.[39] These findings are preliminary and warrant further investigation, but highlight the complex systemic effects exercise has on human physiology.

As with type 2 diabetes, in women with GDM, a single bout of 30-minute low- or moderate-intensity exercise caused plasma glucose levels to decline significantly for up to 15 minutes after the completion of exercise.[40] Other investigations have reported a more prolonged (60 min) decline in postprandial plasma glucose upon cessation of exercise.[41] However, in all investigations the effect of a single bout of exercise in GDM individuals is short-lived with no residual effect observed on glycaemic control or insulin levels in the day following.[41–43] Thus, for exercise to have a sustained influence on glycaemic control through these mechanisms, a chronic exercise regimen is required.[44,45]

There is strong evidence that physical training has a beneficial effect in the treatment of type 2 diabetes.[46] Furthermore, a measurable improvement in glycaemic control has been observed after one to 12 weeks of physical training in a variety of populations.[47–50] These findings suggest that glycaemic control can adapt in a time period clinically relevant for implementation with GDM patients. However, direct evidence in GDM participants is sparse. Only five investigations have been published; they are characterized by small cohort size, disparate treatment regimens and primary outcome measures.[40,44,45,51,52]

Notwithstanding the contrasting methodologies, several investigations have observed a significant change in glycaemic control or exogenous insulin requirement following a 4–8-week regimen of exercise in the final trimester of pregnancy.[44,45,51] Jovanovic-Peterson *et al.* observed a significant decline in glycosylated haemoglobin (~10%), fasting glucose (~20%) and one hour plasma glucose (~40%) in GDM women following a six-week arm ergometry exercise intervention compared with treatment with diet alone. These marked changes were achieved with an exercise regimen that required 20 minutes of endurance exercise three times per week, a training duration and frequency significantly less than that recommended for diabetic or gravid populations.[53,54]

In contrast, Bung *et al.*[51] utilized a more demanding exercise regimen requiring subjects to exercise at 50% of estimated $\dot{V}O_{2peak}$ for 45 minutes three times per week during

semirecumbent cycling. The authors deliberately selected GDM subjects who were unresponsive to dietary therapy. After eight weeks of supervised exercise no change in glycaemic control was observed compared with the insulin only group. However, only the exercise group was able to maintain euglycaemia without the need of insulin therapy. These findings suggest that regular endurance exercise was as effective as exogenous insulin therapy in maintaining euglycaemia.[51] These findings were not supported by Avery *et al.*,[40] who observed no change in HbA1c, incidence of exogenous insulin therapy and fasting or postprandial blood glucose levels compared with a diet-only control group. With less than ~25% (4) of the experimental group completing the eight-week supervised and home-based exercise regimen, the results of this investigation should be interpreted with caution given the significant reduction in statistical power. Similar caution should be applied to the results of a larger study ($n = 96$) that investigated the effect of semisupervised exercise in GDM women.[52] Subjects were not randomly allocated to experimental groups; they self-enrolled into either a treatment group (diet and exercise 7 days per week; $n = 39$) or control group (diet only; $n = 57$) and baseline levels of physical activity were not reported. The investigators observed exogenous insulin requirement was similar between the two groups and maternal weight gain was significantly lower in the treatment group compared with controls.

The effect of endurance exercise has been extensively investigated and shown to be effective in improving insulin resistance and glycaemic control in type 2 diabetes.[46] In contrast, resistance exercise has been less studied, but more recent evidence suggests that it should be an essential part of a treatment regimen in type 2 diabetes.[50] Although the mechanism is not yet clear, progressive resistance training may increase fat-free mass, reduce intramuscular triglycerides or change visceral fat deposits.[50,55,56] Importantly, the mechanism of adaptation may be different from endurance-based exercise suggesting that regimens that combine both endurance and resistance exercise may be synergistic.[57] Stair-climbing for example could be considered as combining both endurance and resistance components. Interestingly, in gravid women who did not engage in recreational physical activity, those who reported climbing one to four flights of stairs or greater than 10 flights daily had a 23% and 81% reduction in GDM risk, respectively.[25] Furthermore, a longitudinal resistance training regimen in GDM women showed that the number of women requiring insulin following the intervention did not change, but there was a significant change in insulin requirement.[45] The exercise regimen consisted of whole-body exercise using rubber tubing performed in a continuous circuit-type workout, interspersed with short one-minute rest periods between each exercise station. Brankston and co-investigators[45] observed that resistance-trained subjects had a delay in the initiation of insulin therapy, were prescribed less insulin and those subjects with a BMI greater than 25 $kg \cdot m^2$ had a greater attenuation of exogenous insulin requirement compared with the diet only control group. However, this investigation also utilized a relatively small sample size ($n = 32$) with a significant difference observed between the experimental groups in prepregnancy body mass and hyperglycaemia, indicating matching of subjects was less than optimal.

Although the findings appear promising, given the limitations of the existing longitudinal GDM investigations, a definitive finding on the clinical significance of physical training as an adjunct therapy in GDM at this stage cannot be determined.[58] Indeed, it has been reported there are inadequate data to deduce the risks and benefits of exercise during normal pregnancies.[59] The methodology of two larger proposed investigations has been published, the results of which should shed some light on the efficacy of early exercise intervention during pregnancy on risk of GDM.[60,61]

The minimum level of physical activity recommended by the American College of Sports Medicine and American Heart Association for healthy adults aged 18–65 years is 30 minutes of moderate-intensity aerobic activity five days per week (or vigorous-intensity 20 minutes, three days per week) and activities that maintain or increase muscular endurance or strength two days per week.[62] Currently, 30 minutes or more of moderate-intensity exercise a day on most, if not all, days over a week is recommended for pregnant women without medical or obstetric complications.[54]

CLINICAL IMPLICATIONS

For the vast majority of pregnant women with gestational diabetes, exercise will be beneficial and recommended. When women are diagnosed with gestational diabetes and educated about the long-term risks of type 2 diabetes, many become highly motivated to achieve lifestyle changes. This should be taken as an opportunity to help women make potentially long-lasting changes to both their dietary and exercise habits.

There are a small number of situations where exercise in pregnancy must be restricted or limited in some way. The American College of Obstetricans and Gynecologists have itemized these contraindications in a Committee Opinion paper published in 2002 (Table 1).[54] It must be noted that there is no specific evidence to support these recommendations although physiologically they appear reasonable. These conditions are generally co-incident to the diagnosis of gestational diabetes and not caused by it. It would be prudent to include severe polyhydramnios in the list of absolute contraindications as these women have an increased risk of preterm rupture of membranes.

In women with relative contraindications, with appropriate assessment and counselling it may be possible to allow exercise in pregnancy. In fact many of these women may potentially benefit from exercise in terms of their underlying conditions and their pregnancy outcomes. With appropriate caution, women with chronic respiratory conditions, obesity and previous sedentary lifestyle can be introduced to an appropriate exercise programme during pregnancy that may motivate them to continue exercise after pregnancy.

Pregnant women frequently require modification of their exercise regimen because of musculo-skeletal or mechanical symptoms such as pubic symphysis dysfunction or back pain. The prescription of an upper body exercise programme, for example, cycle ergometry or water-based exercise programmes can overcome these limitations. Similarly, the demands of work, partners and other children may make planning and participating in exercise difficult. By including specific exercise advice in the management plan for gestational diabetes, it may help validate the women's requests for support in both the workplace and home to allow her to meet these recommendations. The building of social support networks and elevating confidence in the practice of physical activity are important determinants of increased levels of physical activity postpartum

Table 1 **ACOG recommendations regarding exercise in pregnancy**[54]

Absolute contraindications	Relative contraindications
Medical	
O Haemodynamically significant heart disease, e.g. mod-severe valvular heart disease, cardiomyopathy, cyanotic heart disease	O Severe anaemia
O Restrictive lung disease	O Unevaluated cardiac arrhythmia
O Preeclampsia	O Chronic bronchitis
	O Poorly controlled type 1 diabetes
	O Extreme morbid obesity
	O Extreme underweight (BMI <12)
	O history of extreme sedentary lifestyle
	O Poorly controlled hypertension
	O Orthopaedic limitations
	O Poorly controlled seizure disorder
	O Poorly controlled hyperthyroidism
	O Heavy smoker
Obstetric	
O Incompetent cervix/cerclage	O Intrauterine growth restriction in current pregnancy
O Multiple gestation at risk for premature labour	
O Persistent second or third trimester bleeding	
O Placenta praevia after 26 weeks gestation	
O Ruptured membranes	

BMI = body mass index

in women with recent GDM.[63] Such support practices may assist in reducing the risk of developing type 2 diabetes.

As gestational diabetes is a relatively common complication, it may be practical to offer supervised group exercise such as walking groups, antenatal exercise classes or aqua aerobics. This can also help develop the exercise habit in a positive, supportive environment for women who have often been marginalized from such activities, for example, by obesity.

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