Effect of an exercise program, in addition to diet, to avoid insulin prescription in women with gestational diabetes: a randomized controlled trial

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Abstract

Objective: To evaluate the efficacy of an exercise intervention, in addition to usual care, to prevent or delay insulin prescription in women with gestational diabetes mellitus (GDM). Design: Randomised controlled trial Setting: University hospital Population: Women at 25-35 weeks pregnancy upon diagnosis of GDM. Methods: In the intervention arm, women had weekly, supervised, 30-45 min long exercise sessions and were encouraged to accumulate more than 5000 steps per day, monitored by a pedometer, in addition to usual care. Women in the control group had usual care only. Main outcome measure: Insulin prescription. Results: From February 2008 through April 2013, 109 women were randomized into intervention (n=57) or usual care (n=52). Two women, both in the intervention group, were excluded from the analysis (one randomised in error and one lost to follow-up). Six women never attended the exercise sessions and two women participated to less than two sessions, while two-third of women were considered as compliant to the intervention. Incidence of insulin prescription was not significantly different between groups: 31 (56%) in the intervention and 24 (46%) in the control group (RR 1.22, 95% CI 0.84 to 1.78); the median time between randomization and insulin prescription was not different between groups (14 and 13 days, respectively). Conclusion: We were unable to show that an exercise program reduces or delays insulin prescription. Low compliance with the intervention, small sample size and the short duration of the program may explain the apparent lack of benefit.

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Short running title: Exercise for women with gestational diabetes

ABSTRACT

Objective: To evaluate the efficacy of an exercise intervention, in addition to usual care, to prevent or delay insulin prescription in women with gestational diabetes mellitus (GDM).

Design: Randomised controlled trial

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Main outcome measure : Insulin prescription.

Results: From February 2008 through April 2013, 109 women were randomized into intervention (n=57) or usual care (n=52). Two women, both in the intervention group, were excluded from the analysis (one randomised in error and one lost to follow-up). Six women never attended the exercise sessions and two women participated to less than two sessions, while two-third of women were considered as compliant to the intervention. Incidence of insulin prescription was not significantly different between groups: 31 (56%) in the intervention and 24 (46%) in the control group (RR 1.22, 95% CI 0.84 to 1.78); the median time between randomization and insulin prescription was not different between groups (14 and 13 days, respectively).

Conclusion: We were unable to show that an exercise program reduces or delays insulin prescription. Low compliance with the intervention, small sample size and the short duration of the program may explain the apparent lack of benefit. (registered at clinicaltrials.gov, NCT03174340)

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Keywords : exercise, gestational diabetes, randomised trial, insulin

Tweetable abstract: A small RCT failed to show a benefit from exercise sessions in women with gestational diabetes

FUNDING

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INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy[1]. Prevalence ranges from 1 to 14% of all pregnancies, depending on the population and the diagnostic tests and criteria [1, 2]. In Geneva, Switzerland, 11% of pregnant women are currently diagnosed with GDM according to the IADPSG criteria [3]. Initial management of GDM consists of diet and monitoring glucose levels. When euglycemia is not achieved by diet alone, insulin therapy is prescribed [2].

There is good evidence that exercise improves insulin sensitivity in non-diabetic patients [4]. The benefit of exercise is best seen in milder forms of type 2 diabetes [5], which is usually the case with GDM. A systematic review of observational studies showed that women exercising before pregnancy or in early gestation have a lower risk of GDM [6]. Results of randomised trials evaluating the effects of programs in early pregnancy have shown that exercise can prevent GDM [7].

In women who develop GDM, increasing the daily time spent in moderate physical activity may be a useful therapeutic approach to improve the control of glycaemia and decrease the need for prescription of insulin. Women see the need for insulin as a failure of their initial efforts to control GDM. Injections, careful glucose monitoring and adjustment of the doses are perceived as an additional burden. Increased physical activity in pregnant women with GDM could improve the general health, decrease the risk of caesarean section, and of mother and child morbidity associated with GDM [8].

The effects of exercise programs for women diagnosed with GDM were evaluated in 11 trials including 638 women. The systematic review of these trials showed that exercise programs reduce fasting and post-prandial glycaemia, but there were no apparent benefits on clinically significant outcomes [9]. One study proposing three exercise sessions per week (one supervised, two at home) suggested a reduction in insulin prescription [10]. Other trials tested more intensive exercise interventions, and showed a benefit on glycaemia control [10]. For many women consulting in our clinic such intensive schedules are unfeasible because of travel and time constraints. Given that in our setting women generally consult on a weekly basis, we designed a voluntary, lightweight, easily implemented and low-cost once-weekly exercise program. Our objective was to evaluate the effect of this program on insulin prescription in women with GDM.

METHODS

Study design and participants

We conducted a randomized controlled trial in the Geneva University Hospitals (Switzerland) from February 2008 through April 2013. Women recently diagnosed with gestational diabetes using standard criteria[11] and referred to a multidisciplinary team of diabetologists, specialised nurses, dieticians, obstetricians and midwives, were invited to participate. In our setting, from 2008 until 2010, GDM was diagnosed with a 50g OGTT (O'Sullivan test:[12]). A 50g OGTT [?] 11 mmol/L was considered as gestational diabetes. If the result was [?] 7.8 mmol/L but less than 11 mmol/L, a 100g OGTT was undertaken, and the results interpreted using the Carpenter and Coustan criteria [11]. From 2011 onward, GDM was diagnosed with a 75g OGTT using the IADPSG criteria[13].

Consenting women with a singleton pregnancy, a positive GDM test, and not treated with insulin were invited to participate. Exclusion criteria were age less than 18 years, insulin already started or prescribed during the first visit, pre-existing diabetes and a contraindication for physical activity.

The protocol complied to the principles of the Helsinki declaration, the study was approved by the Geneva University Hospital Research Ethics Committee (reference ndeg 07-080 MATPED 07-021) and registered at clinicaltrials.gov (NCT03174340). All participating women provided written informed consent.

Randomisation and masking

Women were randomized in the intervention arm or usual care based on a list of randomly permuted blocks (block size of four to eight), distributed in opaque consecutively numbered sealed envelopes. Clinicians and participants had no access to the list, but were not masked to group allocation, which was made known after inclusion of the participant. The diabetologists responsible for the decision to prescribe insulin during follow-up were, as much as possible, kept blinded to the assignment.

Procedures

The research staff approached pregnant women during their first prenatal consultation after the diagnosis of GDM. Women had either follow-up for their pregnancy in the hospital or were referred by their private practitioner. Eligible women were informed of the trial procedures during that first visit, in addition to information of the management of GDM. Consenting women were randomly allocated to one of the two arms. Women in both groups had the usual care provided in this multidisciplinary prenatal consultation by diabetologists, dieticians, obstetricians and midwives. Initial management included dietary advice and four times daily capillary blood glucose self-testing[14]. In the intervention group, an exercise program was proposed, in addition to usual care. This program included a weekly, supervised, in-hospital exercise session,

at the same time the women had an appointment at the clinic for GDM management. The duration of the exercise session was 30-45 minutes and consisted of a mix of physical therapist supervised endurance effort (stationary cycling, arm-cranking) and light resistance exercise (elastic bands and free weights), personalized taking into account individual preferences and tolerance. The women warmed up for a few minutes with light load arm-cranking, followed by 10 minutes of arm-cranking targeting a heart rate >130 bpm. After a 5 minutes rest, they then engaged in exercise on a recumbent cycle-ergometer for 20 minutes, also targeting a heart rate >130 bpm. In case recumbent cycling was not bearable, this exercise was replaced by stepping exercise targeting a heart rate >130 bpm. During the training sessions the women wore a thoracic belt (Suunto Smartbelt, Vantaa, Finland) for heart rate monitoring. Session intensity was quantified by the average heart rate of the session and peak heart rate reached.

Using motivational interviewing techniques, the physical therapist coached the women to engage in more regular physical activity in daily life. They were encouraged to accumulate 5000 or more steps per day, monitored by a pedometer (HJ 112, Omron, Hoofddorp, Netherlands). Women were given diaries to record their physical activities, total number of steps per day and blood sugar levels.

Outcomes

We defined "compliance" with the exercise program as participation to at least 50% of the scheduled weekly exercise sessions between randomization and delivery and/or recording more than 5000 steps per day on average.

The primary outcome was the incidence of insulin prescription. Women who did not achieve the following glycaemic goals were treated with basal and/or prandial insulin: [?]5.3 mmol/l fasting, [?]8.0 mmol/l one hour after the beginning of each meal. This was in line with the recommendations of the Swiss Society for Endocrinology and Diabetes, adapted from the American Diabetes Association (ADA) [1]. Insulin regimen consisted of intermediate-acting NPH insulin, usually initiated at bedtime at a dose of 0.1 U/kg/day, and short-acting insulin aspart or lispro at mealtime. Oral antidiabetic agents were not used.

Secondary outcomes included suboptimal glycaemic control, time to insulin, maximum dose of insulin, mode of delivery, birthweight and neonatal morbidity.

Statistical Analysis

Analysis was based on the "intention to treat". We report baseline characteristics and outcomes as mean (SD), median (IQR), or number and percentage. We report the effects of the intervention as relative risks (RRs), with their 95% confidence intervals (CI). The statistical significance of the differences was tested using the Fisher exact test. Differences in means of continuous variables were tested with the Student T-test. We used SPSS (versions 18 and 20, IBM, Chicago, USA) and Stata (version 15, StataCorp, College Station, USA) for data management and statistical analysis.

Based on data from our clinic, we expected an incidence of 40% of insulin prescription in women with gestational diabetes treated initially with diet only (control group). For a clinically relevant reduction in insulin prescription with exercise to 20% (number-needed to treat of 5), the sample size (α=0.05 and power of 80%) was 91 patients in each group. We had to stop the trial before reaching the complete sample size because of low recruitment, low compliance to the exercise sessions and lack of funding for the physical therapist salary.

RESULTS

From February 2008 through April 2013, 109 consenting women were randomized, 57 in the exercise group and 52 in the usual care group (Figure 1). One woman was excluded because of diabetes type 1 (randomised in error) and another was lost to follow-up (was not followed in our unit and delivered in another hospital), leaving 107 women for the analysis.

Baseline characteristics are summarised in Table 1. There were more obese women (BMI 30 kg/m^2 or more) randomized in the intervention group and more nulliparous women in the usual care group. In the

intervention group, six women (11%) never attended the exercise sessions and two women (4%) had minimal participation (one session only). We considered as compliant to the intervention 35 women (64%), 32 because they attended more than 50% of the scheduled sessions between randomisation and delivery and 3 because they did not, but reached on average more than 5000 steps per day during the same period. Average duration of the exercise sessions was 43 (SD 5) minutes, the average heart rate during the exercise sessions was 114 (SD 12) bpm, and the average peak heart rate was 142 (SD 17) bpm.

The incidence of insulin prescription was not significantly different between groups: 31 women (56%) in the exercise group compared with 24 (46%) in the control group (relative risk 1.22, 95% CI 0.84 to 1.78; P=0.39) (Table 2). Days between randomization and start of insulin treatment were not significantly different: 16 (SD 13) and 17 (SD 15) in the exercise and usual care group, respectively (P= 0.62). The means of the maximal dose of insulin were similar in the two groups.

Between 26 and 32 weeks, mean postprandial glucose was 9.4 (SD 1.8) mmol/L in the exercise group, compared to 8.9 (SD 2.0) mmol/L in the usual care group, (P=0.22). The number of postprandial glucose values per week above 8.0 mmol/L was similar (4.1, SD 3.4 and 3.8, SD 3.1; P= 0.77). Between 32 and 36 weeks, mean postprandial glucose was 9.0 (SD 2.1) mmol/L in the exercise group, compared to 8.9 (SD 1.8) mmol/L in the usual care group, (P=0.75). The number of postprandial glucose values above 8.0 mmol/L was also similar (3.9, SD 3.4 and 4.1, SD 3.4; P=0.84).

Secondary outcomes, including gestational weight gain, caesarean section, maternal complications, did not differ significantly between groups. Neonatal outcomes were also similar between groups.

DISCUSSION

We were unable to show that a voluntary, lightweight, once-weekly exercise program improves glycaemic control sufficiently to prevent or delay insulin prescription in women with GDM.

Exercise before, during and after pregnancy has important health benefits for the mother, including cardiovascular function, prevention of preeclampsia, gestational diabetes, varicose veins, deep vein thrombosis, lower back pain, and better mood and psychological wellbeing[15]. Regular exercise also limits weight gain during pregnancy and fat retention after delivery [16]. There further is decreased risk of preterm delivery, labour is shorter and there are less perinatal complications [15]. The off-spring from physically active mothers have lower birth weight, lower fetal body fat, and do well during their early life years[17]. Women who were physically active prior to pregnancy are at lower risk of GDM, and engaging into regular exercise early in pregnancy can prevent GDM [18].

Some studies implemented 3 exercise sessions per week and reported some clinically relevant effects [9]. In our setting, women consulting for the follow-up of the GDM are limited by time and travel constraints to attend at more than a weekly session. Thus, we evaluated if a lightweight intervention, combined with the advice to accumulate at least 5000 steps a day would be enough for a clinically relevant effect. The absence of a benefit may be due to the low volume of exercise sessions.

Although some centers use oral drugs to treat GDM, the current approach in our center is the use of insulin. Insulin does not cross the placenta and is therefore the safest medication used to treat diabetes in pregnancy, but is associated with some risks, as hypoglycemia, is costly, requires specific teaching by specialized nurses and women are reluctant to perform the injections. Therefore, if women with GDM could avoid the use of insulin, not only by a strict dietary management, but also by physical activity, as suggested by previous studies, this could ease and reduce the costs of GDM management. In our setting, insulin was generally prescribed only a few weeks after starting the exercise program, which limited the potential benefit.

The limitations of our study may explain the apparent absence of benefit. We had to stop the recruitment before completing the calculated sample size. The exercise program was light and of short duration, and some women attended infrequently the sessions.

CONCLUSION

Our results suggest that a light physical activity intervention, chosen on purpose in order to allow large-scale application without important resources, is not sufficient once GDM is diagnosed. Since beginning regular exercise earlier in pregnancy can successfully prevent GDM, we may conclude that starting an exercise program once gestational diabetes is diagnosed is too late and that physical activity promotion should be encouraged before and throughout pregnancy.

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Contribution to authorship:

Design: MB, BK, FJ, VOG

Recruitment and data collection: MB, VOG

Analysis: MB, BK, VOG

Writing: MB, BK, FJ, VOG

All authors approved the final version of the manuscript

Details of ethics approval:

The protocol complied to the principles of the Helsinki declaration, the study was approved by the Geneva University Hospital Research Ethics Committee (reference n° 07-080 MATPED 07-021) and registered at clinicaltrials.gov (NCT03174340). All participating women provided written informed consent.

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Table/Figure caption list

Figure 1: Flow diagram

Table 1: Maternal characteristics at randomisation

Table 2: Maternal and neonatal outcomes. Results are presented as n (%), except when stated otherwise

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