Does exercise during pregnancy impact on maternal weight gain and fetal cardiac function? A Randomized controlled study.

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Short Tittle: Impact of exercise during pregnancy on maternal weight gain and fetal cardiac function

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Abstract

Objective: to evaluate differences in maternal weight gain and fetal cardiac function according to exercise during pregnancy

Methods: A randomized controlled trial was performed at Hospital de Torrejón, Madrid, including 120 pregnant women, allocated into Exercise Group (EG) and Control Group (CG). The primary outcome was maternal weight. Secondary outcomes included caesarean section, preterm delivery, induction of labor, birth weight and fetal cardiac function parameters. A sample size of 45 (90 both groups) was planned to detect differences in maternal weight gain of at least 1 Kg, with a power of >80% (>0.8) and α of .05.

Results: From November 2014 to June 2015, 205 women were interested in the study and 120 were randomized into EG (n=75) and CG (n=45). Characteristics of the study participants were similar across groups (maternal age, pre-pregnancy BMI, parity, In Vitro Fertilization (FIV), Caucasian, previous to pregnancy physical exercise and smoking). No differences were found in maternal weight gain in both groups at 38 weeks (11.4±4 vs. 11.2±6, p = .82). The rate of a weight loss at 6 weeks postpartum was higher in the EG *vs.* CG (68.2% vs. 42.8%, RR 1.593, p < .05). When analyzing fetal cardiac function parameters, the Ductus Arteriosus Pulsatility Index (DA PI) was higher at 20 weeks in the EG compared to CG (2.43±0.40 vs. 2.26±0.33, p < .05) and the Ejection Fraction (EF) at 36 weeks was higher in the EG vs. CG (0.85±0.13 vs. 0.81±0.11, p < .05).

Conclusions: Performing exercise during pregnancy is not associated with a reduction in maternal weight gain but a higher weight loss 6 weeks postpartum. When studying fetal cardiac parameters, performing exercise is associated with an increased DAPI at 20 weeks and EF at 36 weeks, which could translate into adaptive mechanisms.

Clinical Trial Registration: Exercise during Pregnancy and Perinatal Outcome. URL:https://clinicaltrials.gov/ct2/show/NCT02756143?cond=exercise+and+pregnancy&draw=2&rank=15. Registration Number: NCT 02756143.

Introduction

Maternal pre-pregnancy weight, body mass index (BMI), pattern of gestational weight gain, and total gestational weight gain are factors determining birth weight. In addition, birth weight and adiposity are important because they have a major impact on neonatal morbidity and mortality, and appear to affect early adult weight and long-term health{Fraser, 2010, Association of maternal weight gain in pregnancy with offspring obesity and metabolic and vascular traits in childhood}.

The increased gestational weight gain has also been associated with an increased risk of cesarean section delivery, pregnancy-related hypertension (gestational hypertension, preeclampsia), gestational diabetes[1, 2], neonatal adiposity, and childhood overweight or obesity.

Performing exercise during pregnancy has been proved a preventive factor for developing hypertension during pregnancy, and there is controversy regarding the reduction on excessive gain weight during pregnancy. It may control offspring size at birth while reducing comorbidities related to chronic disease risk.

Regarding the fetus, practicing exercise during pregnancy might increase fetal and infant heart rate variability, determine the fetal overall health and the development of fetal autonomic nervous system. Fetal cardiac function parameters might also change according to the performance of exercise during pregnancy, but so far, it has not yet been studied. Also, there are no studies evaluating the association between gestational weight gain and fetal cardiac function parameters. During perinatal period, fetal heart

could be sensitive to remodeling by environmental factors as has been shown in the Intrauterine Growth Restriction (IUGR) fetuses affected by placental insufficiency[3].

The present study aims to clarify if performing a supervised controlled exercise program throughout the pregnancy prevents from a gestational weight gain that could be associated with a reduction in other pregnancy or birth complications. *S*econdary objective was to analyse caesarean section, preterm delivery, induction of labor, birth weight and fetal cardiac function parameters in women performing exercise vs. women who do not perform exercise during pregnancy.

Methods

Participants and trial design:

A prospective randomized clinical trial was undertaken in Hospital de Torrejón, Madrid, Spain. Pregnant women with singleton pregnancies who had a pregnancy follow-up at the hospital from the first trimester of pregnancy were given the option of participating in the study. Inclusion criteria were: (I) no obstetric or medical complications (based on the American college of obstetricians and gynaecologists guidelines (ACOG) [4]; (II) time of pregnancy <16 weeks; (III) not exercising regularly for more than 30 min (3 d·week−1); (IV) able to communicate in spanish. Exclusion criteria were: non-availability to attend to the exercise program during pregnancy.

*R*ecruitment was performed from November 2014 to June 2015. The trial was ended because the sample size was achieved.

Gestational age was judged from the menstrual history and confirmed by measurement of fetal crown-rump length at a first trimester scan, which was done routinely in all *participating women*.

Trial coordinators regularly undertook quality control of data handling, and verification of adherence to protocols.

All patients gave written consent. The study was approved by the Local Research Ethics Committee of the Hospital (CEIC Hospital Universitario Severo Ochoa) (19/07/2013) (Madrid, Spain) and was in accordance with the ethical guidelines of the Declaration of Helsinki (modified in 2008).

The present study has been registered at clinicaltrials.gov identifier NCT 02756143.

Randomization and masking

After written informed consent was obtained from women, they were randomly allocated to the Exercise Group (EG) or Control Group (CG). A randomization process in a 3:5 proportion (for each 3 in the control group, 5 were in the intervention group) was used to allocate the study participants. A computer-generated list of random numbers was used to allocate the participants into two groups: exercise and control. For this EPIDAT 3.1 option of balanced groups (similar but not equal size) was used. M.V. was the researcher in charge of generating the random allocation sequence, enrolling participants and assigning participants to interventions.

Intervention

The EG women undertook a supervised physical conditioning program of three 60 minutes sessions per week during whole pregnancy (from week 9-38). Each session included 10 min of warming up, 25 minutes of cardiovascular exercise, 10 minutes of strengthening exercises, 5 minutes of coordination and balance, 5 minutes of pelvic floor exercises, and 5 minutes of stretching and relaxation. Aerobic activity was prescribed at light to moderate intensity, aiming for 55-60% of maximum heart rate. All

subjects wore a heart rate (HR) monitor (Polar FT7) during the training sessions to ensure that exercise intensity was *mild*-moderate.

The CG women were advised not to attend to any exercise program during pregnancy, and in every clinical appointment, women from the CG were interrogated about the exercise practice, and was assess that they were not performing a more than 30 minutes, 3 times per week exercise program. The women were not discouraged from exercising on their own. They reported no regular exercise during their pregnancies (by telephone interviews).

The clinical team of the trial in a routine antenatal clinic managed both groups. Obstetric Ultrasound was performed at 20, 28 and 36 weeks, including a specific fetal echocardiography. The scans were performed by three blind researchers (I.F.B., M.B.S y A.M.A.), and data were collected prospectively. An ultrasound system (Voluson s8; GE Healthcare) was used accorded with the guidelines of the International Society of Ultrasound in Obstetrics and Gynaecology. Women participating in the study received general recommendations of nutrition and exercise.

The following variables were measured by ultrasound in the fetal heart:

- MPI (Myocardial Performance Index, Tei Index): (ICT + IRT/ET)
- TAPSE (Tricuspid Annulus Plane Systolic Excursion)
- MAPSE (Mitral Annulus Plane Systolic Excursion)
- Tricuspid and Mitral E/A ratios
- Ejection Fraction (EF)

MPI or Tei Index has been assessed using a 2-10 MHz probe. In a four chamber view, the calliper was placed in the basal area of left ventricular wall (mitral annulus), interventricular sept and right ventricular wall (tricuspid annulus). The insonation angle was always < 30º to the ventricular wall. Angle was not corrected. MPI was calculated

as following: MPI = (ICT + IRT) / ET. ICT was isovolumetric contraction time, IRT isovolumetric relaxation time and ET, cardiac ejection time[5].

TAPSE and MAPSE were calculated in a four chamber apical view, placing the caliper in the tricuspid annulum on the right ventricular wall (TAPSE) and in the mitral annulum on the left ventricular wall (MAPSE) with an angle of insonation of 0^{o}[6].

In a four chamber view, using Pulsed Doppler though the A-V valves, it was measured early (E) and late peaks (A) just underneath the valve outflow and tricuspid and mitral E/A ratios were calculated.

Ejection Fraction was calculated according to the formula EF = (end diastolic ventricular volume – end systolic volume) / end diastolic volume. This **measure was** calculated in M-Mode tracing a perpendicular line to the inter-ventricular septal wall in 2D ultrasound.

Those women not attending at least 70% of assistance to the program were excluded **from** the final analysis (n=33) in the EG. Women having late miscarriage (n=1) and high-risk pregnancy follow–up due to anti –Kell antibodies, were also excluded from the CG for the final analysis.

Outcome measures

The primary outcome was the maternal weight gain during pregnancy. It was stratified as Maternal Weight Gain at 20, 28, 36, and 38 weeks and 6 weeks postpartum. Secondary outcomes were: gestational and labour outcomes (Cesarean Section, Gestational Age at delivery < 37 weeks, Induction of labor, Birth weight and Perineal Tear), perinatal outcome (Birth weight, Apgar score < 6 5th minute, Arterial cord pH and Admission to neonatal unit-NNU) and fetal cardiac function parameters (MPI, TAPSE, MAPSE, mitral and tricuspid E/A ratios, Aortic and Pulmonary Velocity, Ductus Arteriosus PI, Aortic Isthmus PI and Ejection Fraction).

Statistical analysis

Regarding the calculation of sample size, a conservative approach was used. We performed a power calculation for the primary outcome, maternal weight gain, assuming a bilateral alternative and considering a standard deviation of 2.2 Kg, based on the IOM recommendation for pregnancy normal weight 11.5–16 Kg women[7]. Additionally, we wanted to detect differences in maternal weight gain of at least 1 Kg with a power of >80% (>0.8) and α of .05. Assuming a maximum loss at follow-up of 15%, we decided to recruit at least 45 participants for each study group.

SPPS software package (version 23.0) was used for all statistical analyses. Quantitative variables were expressed in mean and standard deviation for EG and GC groups and qualitative variables in frequencies and percentages. Comparisons between groups were made with the Mann-Whitney U test. Univariate comparisons of dichotomous data were done with Fisher's exact test.

Results for all hypotheses were two sided, with p-values <0,05 were considered statistically significant.

Results

Baseline characteristics of the study participants

From November 2014 to June 2015 women were enrolled and randomly assigned to perform and supervised exercise program during the pregnancy (EG) or not to perform it (CG). From the total eligible population 840 woman, 24.4% women were interested on the participation on the study, and 41.4% of them were excluded mainly because of non-availability to attend to the exercise program. The baseline characteristics of the study eligible women were: maternal age 31,8±5 years old, pre-pregnancy BMI

24,8±4,4, nulliparous 54,9%, In Vitro Fertilization (IVF) pregnancies 4,4%, Caucasian ethnic 95,7% and smokers 21,7%.

A total of 120 women were recruited and randomized. Two women were excluded from the CG group: a woman because of late miscarriage at 20 weeks and the other because of high-risk pregnancy (anti Kell antibody). Also, 33 women from the EG group were not compliant with the program, and did not attend to more than 70% of the program as requested by the study, and were excluded for the final analysis. Finally, the analysis groups were EG (N = 42) and CG (N = 43) shown in the Trial Profile (Figure 1). The baseline characteristics were similar between both groups. Regarding maternal age, pre-pregnancy BMI, parity, IVF pregnancy, ethnic, previous to pregnancy physical exercise and smoking, both groups were homogeneous (Table 1).

Pregnancy and Perinatal outcomes according to allocation group

Regarding the primary outcome, maternal weight gain, no differences were found in both groups at 20, 28, 36 and 38. However, maternal weight loss at 6 weeks postpartum was higher in the EG vs. CG (9.7±3 vs. 8.1±3.5 Kg, $p < 0.05$). When analysing weight loss higher than 9 Kg, the rates were higher for EG *vs*. CG (68.2% vs. 42.8%, RR 1.593, 95%CI 1.060-2.393, $p < .05$). In addition, pregnancy and delivery outcomes in both groups were similar in terms of caesarean section, preterm birth <37 weeks, induction of labour, fetal growth or vaginal tear (Table 2).

When comparing birth weights, adjusted to gestational age, and calculating centiles of birth weight, there were no differences in both groups in birth weight below 10^{th} centile in the EC vs. CG (16% vs. 18%), $p = 0.19$).

Fetal Echocardiography outcomes according to allocation group

MPI at 20, 28 and 36 weeks of gestation were similar in both groups. In addition, TAPSE, MAPSE and Tricuspid E/A Ratio at 20, 28 and 36 weeks were similar in both

groups. However, when comparing DA PI was higher in the EG vs. CG (2.43±0.40 vs. 2.23±0.33, p<.05) and EF at 36 weeks was higher in the EG vs. CG (0.85±0.13 vs. 0.81±0.11, p < .05). For the rest of the variables aortic artery velocity, pulmonary artery velocity, aortic arch PI, no differences were found in both groups in the gestational age studied (20, 28 and 36 weeks). Table 3 shows the results of secondary outcomes in both groups.

Discussion

Main Findings of the Study

First, the practice of exercise during pregnancy does not reduce maternal weight gain, but increases maternal weight loss after delivery. Second, practising exercise during pregnancy does not affect the fetal cardiac function. Third, there are changes in the DA and EF which could reflect an adaptation in the DA blood flow, increasing the DA PI at 20 weeks in women exercising compared to the control group, leading to a better EF at 36 weeks of pregnancy in the exercise group.

Comparison with previous studies

Few systematic reviews have studied gestational weight gain and postpartum weight loss related to physical activity. The overall findings of a meta-analysis of physical activity and weight management in pregnant women suggest that physical activity may restrict gestational weight gain. This reduction in maternal weight gain is variable according to different studies ranging from 0.50 to 0.80. It is not clear weather this reduction is higher in the obese, overweight or normal weight women. Since the present study includes mainly normal BMI pre-pregnancy women, this could be the rationale for not concordant results.

Regarding maternal weight loss in the postpartum period there is one study concluding no differences in both groups. The present study shows a higher maternal weight loss after delivery in those women exercising during pregnancy. The higher sample size could be an explanation for the statistically significant result.

Regarding the findings of the DA, this vessel is one of the most important vessels of the fetal circulation. In the normal developed fetus, 90% of the right ventricular stroke volume, is shunted via the DA towards the descending aorta. DA PI does not change with gestation, ranging between 1.9 and 3 (mean 2.46 ± 52)[8]. Under normal conditions, the DA has a high level of intrinsic tone during fetal life. The exact underlying mechanisms that cause premature constriction of the DA are still subject of investigation. Physiologically, the DA remains maximally dilated until term, actively sustained by regulatory control of prostaglandins and nitric oxide (NO), which are produced within the ductal tissue[9].

Recently, a variety of substances has been identified to exert vasoconstriction on the arterial duct, as established for non-esteroid anti-inflammatory drugs. Echocardiographic diagnosis of progressive ductal constriction is further based upon increased systolic and particularly diastolic peak velocities in the DA, resulting in a PI of less than 1.9**.**

Pathophysiological basis and insights

The present study shows that exercise during pregnancy may induce a higher PI in the DA at 20 weeks and this effect could be preventive for early closure of DA. This could be related to an interaction with the regulatory control of prostaglandins and nitric oxide, produced within the ductal tissue. It is reported that acute exercise (as opposed to exercise training) in pregnant women is associated with increased sympathoadrenal and neurohumoral activity. We hypothesized that these biochemical changes may interfere with the control of prostaglandins and nitric oxide within the ductal tissue.

Prior to pregnancy, exercise improves oxygenation in muscle and skin but oxygen delivery to most viscera falls because of a decrease in blood flow. During pregnancy the exercise effect on visceral flow persists but oxygen delivery to and utilization by the feto-placental unit is maintained by several mechanisms which include maternal hemoconcentration, and improved perfusion–perfusion balance at the placental interphase. Even though oxygen uptake is maintained, the fall in placental bed blood flow shifts oxygen delivery to a lower point on the oxyhemoglobin dissociation curve. This lowers fetal pO2 which, in the human, initiates a sympathetic response which produces an increase fetal heart rate. However, the experimental evidence indicates that tissue perfusion and oxygenation must be maintained at normal levels because no increased levels of erythropoietin in either cord blood or amniotic fluid have been shown.

The ductus arteriosus is widely patent in fetal life. The factors contributing to the maintaining ductal patency in the fetus, include exposure to low partial pressure of oxygen, prostaglandins, and local nitric oxide production. Oxygen has been shown to constrict the ductus arteriosus in vitro and in vivo[10].

In addition, Fetal Ejection Fraction in exercising pregnant women has not yet been investigated. This present randomized controlled trial represents the first time that fetal cardiac function has been studied in relation to exercise during pregnancy. Functional echocardiography has been demonstrated to select high-risk population and to be associated with outcome in several fetal conditions. However, it has not yet been incorporated into clinical practice. It is well known that cardiovascular diseases in adulthood undergo a long subclinical phase over time, which may start in childhood and also in fetal life. Fetal programming of adult cardiovascular diseases occurs when a stimulis or an insult in the in utero environment during a sensitive period of cardiovascular development permanently alters cardiovascular structure and function.

Strengths and limitations

There are no studies published so far, on which fetal cardiac function parameters have been studied in relation to the practice of a supervised program of exercise during pregnancy in a randomized controlled trial, and this is the one of the strengths of the present research.

Although the sample size was calculated in order to demonstrate a reduction of maternal weight gain in the exercise group, it has proved differences in the ductus arteriosus and ejection fraction in both groups studied. The limitation of the present study in the size difference between groups, can be explained by the simple randomization method used.

Other limitations of the study are that includes a higher nulliparous population compared to the general low risk pregnant population followed in Hospital de Torrejón (76,6% vs. 54,9%) and this could represents a selection bias. Also, the study could have improved if a special nutritional counselling and follow-up would have been assessed, and a questionnaire to assess the physical activity performed in both groups was given during the pregnancy.

Conclusions

In summary, the performance of moderate physical exercise throughout pregnancy increases weight loss after delivery, and may induce a beneficial fetal cardiovascular development; however, it is still unknown the long term impact. More large prospective studies are needed to add knowledge about this fact.

Table 1. Characteristics of the study participants

Table 2. Pregnancy and Perinatal outcomes according to allocation group

Table 3. Cardiac function parameters (MPI, TAPSE, MAPSE, Tricuspid E/A ratio, Mitral E/A ratio), Aortic and Pulmonary Velocities and DA and Aortic Arch Pulsatility Indexes and Ejection Fraction, according to allocation group.

Figure 1. Trial profile

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