EXERCISE EFFECT ON PLACENTAL COMPONENTS: SYSTEMATIC REVIEW AND META-ANALYSIS

ABSTRACT

Physical exercise has been demonstrated a positive effect on many pregnancy outcomes. Placental components are important for exchanging oxygen and nutrients between mother and fetus. This study aimed to systematic review and meta-analysis whether physical exercise could induce a morphological adjustment on placenta components. We systematically searched PubMed database until October 30th, 2014. We included randomized and non-randomized studies with control group, which aimed to investigate the effect of the physical exercise (water, aerobic and resistance) on placental components (placental weight and volume, villous volume and vascular volume, intervillous space and stem villi). Initially, we identified 222 articles, of which 9 articles were used for full text analysis. Finally, four articles were included in the systematic review and meta-analysis. Meta-analysis demonstrated that exercise appeared to affect placental weight (95% CI, 39.73 g [4.66-74.80]), placental volume (95% CI, 47.11 cm³ [37.99-56.23]), intervillous space (95% CI, 16.76 cm³ [12.66-20.68]), villous volume (95% CI, 46.01 cm³ [40.21-51.81]), villous vascular volume (95% CI, 15.95 cm³ [7.83-24.07]) and stem villi (95% CI, 6.00 cm³ [4.25-7.75]). Apparently, physical exercise has a positive effect on placental components. However, this conclusion is based on a limited number of studies. Clearly, it stands the necessity of larger samples and better methodology quality.

Keywords: placenta, chorionic villi, physical exertion, pregnancy.

RESUMEN

El ejercicio físico ha demostrado efecto positivo en muchos resultados del embarazo. Componentes de la placenta son importantes para el intercambio de oxígeno y nutrientes entre la madre y el feto. El objetivo de este estudio fue revisar de forma sistemática y realizar un meta-análisis para comprobar si el ejercicio físico puede inducir la adaptación morfológica en los componentes de la placenta. La encuesta se realizó sistemáticamente en la base de datos PubMed hasta 30 de octubre de 2014. Se incluyeron ensayos aleatorios y no aleatorizados con grupo control, que tuvieron como objetivo investigar el efecto del ejercicio físico (agua, aeróbico y resistencia) en componentes de la placenta (peso y volumen placentario, volumen vascular y volumen viloso, espacio intervilloso y troncos vilosos). Inicialmente, identificamos 222 artículos, de los cuales nueve artículos fueron utilizados para el análisis de texto completo. Finalmente, cuatro artículos fueron incluidos en la revisión sistemática y meta-análisis. Meta-análisis demostró que el ejercicio parece afectar el peso de la placenta (95% IC, 39.73 g [4.66-74.80]), el volumen placentario (95% IC, 47.11 cm³ [37.99-56.23]), el espacio intervilloso (IC 95%, 16,76 cm³ [12,66-20,68]), el volumen viloso (IC 95%, 46,01 cm³ [40,21-51,81]), el volumen vascular viloso (IC 95%, 15,95 cm³ [7,83-24,07]) y el tronco viloso (95% IC, 6,00 cm³ [4,25-7,75]). Aparentemente, el ejercicio físico tiene efecto positivo sobre los componentes de la placenta. No entanto, esta conclusión está basada en un número limitado de estudios. Claramente, destaca-se a necessidade de amostras maiores e melhor qualidade de metodologia.

Palavras-chave: placenta, vilosidades coriônicas, esforço físico, gravidez.

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El ejercicio físico ha demostrado efecto positivo en muchos resultados del embarazo. Los componentes de la placenta son importantes para el intercambio de oxígeno y nutrientes entre la madre y el feto. El objetivo de este estudio fue revisar de forma sistemática y realizar un meta-análisis para comprobar si el ejercicio físico puede inducir la adaptación morfológica en los componentes de la placenta. La encuesta se realizó sistemáticamente en la base de datos PubMed hasta 30 de octubre de 2014. Se incluyeron ensayos aleatorios y no aleatorizados con grupo control, que tenían como objetivo investigar el efecto del ejercicio físico (agua, aeróbico y resistencia) en componentes de la placenta (peso y volumen placentario, volumen vascular y volumen viloso, espacio intervilloso y troncos vilosos). Inicialmente, se identificaron 222 artículos, de los cuales nueve artículos fueron utilizados para el análisis de texto completo. Finalmente, cuatro artículos fueron incluidos en la revisión sistemática y meta-análisis. El meta-análisis mostró que el ejercicio parece afectar el peso de la placenta (IC del 95%, 39.73g [4.66-74.80]), el volumen de la placenta (IC del 95%, 47.11 cm³ [37.99-56.23]), el espacio intervilloso (IC del 95%, 16,76 cm³ [12,66-20,68]), el volumen viloso (IC del 95%, 46,01 cm³ [40,21-51,81]), el volumen vascular viloso (IC del 95%, 15,95 cm³ [7,83-24,07]) y el tronco viloso (IC del 95%, 6,00 cm³ [4,25-7,75]). Aparentemente, el ejercicio físico tiene efecto positivo sobre los componentes de la placenta. No entanto, esta conclusión está basada en un número limitado de estudios. Claramente, destaca-se a necessidade de amostras maiores e melhor qualidade de metodologia.

Palavras-chave: placenta, vilosidades coriônicas, esforço físico, gravidez.
INTRODUCTION

Placenta serves as a selective barrier tissue between mother and child. During physical exertion, cardiac output is driven away from splenic organs and might lead to decrease oxygen and nutrients delivery. By means, maternal metabolism might adapt and activate several cellular and/or molecular mechanisms to counterbalance this gas rate reduction\(^1,2\). Many data have been published regarding placenta morphological adaptation during maternal physical training. Jackson and colleagues\(^3\) showed villi, stem villi and total peripheral villi increase among women who continued moderate exercise training through pregnancy. Others also showed interesting placential morphology adjustments both trained and sedentary pregnant women\(^4-6\). However, many methodological issues such as few patients’ number, gestational age at beginning and others might influence outcomes.

Therefore, the aim of this systematic review with meta-analysis was to determine whether physical exercise could induce a morphological adjustment on placenta components.

METHODS

This systematic review was developed based on the PRISMA guideline (preferred reporting items for systematic reviews and meta-analysis)\(^7\). On October 30th, 2014, we did a systematic review search in the Pubmed database, using the following Mesh and Entry terms: (((Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (“clinical trial”[tw] OR (singl*[tw] OR double*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (“latin square”[tw] OR placebo[mh]) OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospective*[tw] OR volunteer*[tw] OR non-randomized clinical trials OR non-randomized trials OR non random OR non randomized clinical trials OR non randomized trials)) AND (exercises OR exercise physical OR exercises physical OR physical exercise OR physical exercises OR exercise isometric OR exercises isometric OR isometric exercises OR isometric exercise OR exercise aerobic OR aerobic exercises OR exercises aerobic OR aerobic exercise OR exertion OR physical fitness OR exercise therapy OR physical endurance OR physical exertion OR exertion physical OR exertions physical OR physical exertion OR physical effort OR exertion physical OR efforts physical OR physical efforts OR resistance training OR training resistance OR strength training OR training, strength OR weight lifting strengthening programs OR strengthening program, weight-lifting OR strengthening programs, weight-lifting OR weight lifting strengthening program OR weight-lifting strengthening programs OR weight-lifting exercise program OR exercise program, weight-lifting OR exercise programs, weight-lifting OR weight lifting exercise program OR weight-lifting exercise programs OR weight-bearing strengthening program OR strengthening program, weight-bearing OR strengthening programs, weight-bearing OR weight bearing strengthening program OR weight-bearing strengthening programs OR weight-bearing exercise program OR exercise program, weight-bearing OR exercise programs, weight-bearing OR weight bearing exercise program OR weight bearing exercise programs OR running or jogging or swimming or walking)) AND (placenta OR placentas OR placenta OR placentomes OR placenta, normal OR normal placenta OR normal placentas OR placentomes, normal OR normal maternal-fetal exchange OR exchange, maternal-fetal OR maternal fetal exchange OR transplacental exposure OR exposure, transplacental OR placental circulation OR circulation, placental OR uteroplacental circulation OR circulation, utero-placental OR fetoplacental circulation OR circulations, fetoplacental OR fetoplacental circulations OR circulation, fetoplacental OR fetal-placental circulation OR circulation, fetal-placental OR circulations, fetal-placental OR fetal placental circulation OR fetal-placental circulations OR chorionic villi OR chorionic villus OR villi, chorionic OR villus, chorionic OR placental villi OR placental villus OR villi, placental OR villus, placental OR decidua OR deciduas OR deciduous OR deciduoma OR trophoblasts OR trophoblast OR cytotrophoblasts OR cytotrophoblast OR syncytiotrophoblasts OR syncytiotrophoblast). Studies Selection

First, we searched for randomized controlled trials. However, very few evidence appeared. Therefore, we decided to include randomized and non-randomized control trials, which aimed to investigate the effect of physical exercise (water, aerobic and resistance) on placenta components at delivery day.

The primary outcome was placenta weight and volume. The secondary outcomes analyzed were intervillous space, villous volume and vascular volume, and stem villi.

We extracted total patients number, randomization, age, gestational age during study recruitment, physical activity level prior protocol intervention, final gestational age prior to birth time, exercise and control protocols and research primary results. After complete data extraction, authors independently assessed the methodological quality of each article using the Jadad, Oxford and Delphi quality scale\(^8-10\).

Data synthesis and analysis

Review manager software 5.2 was used to calculate heterogeneity by the \(I^2\), \(Chiz\) and Tau\(z\) values. We used \(I^2\) to assess heterogeneity between trials, using fixed effect models where there was high heterogeneity. We also used inverse variance method and 95% total confidence interval.

This study is an analysis of published data, which did not require ethics committee approval.

RESULTS

The initial search identified 222 articles titles, of which 31 articles were used for initial abstract analysis. From this, nine articles were included for full text analysis, leaving four papers to systematic review and meta-analysis\(^3,5,11,12\). The selection process is shown in figure 1.

Participants

A total of 170 patients were included in the systematic review analysis (84 and 86 patients in exercising and control group, respectively). Table 1 described the information extracted from each selected trial.

Exercise Interventions

At all interventions considered, predominantly, aerobic exercise training was applied \(^3,5,11\). Only one study used a multiple exercise type intervention\(^12\).

We applied Jadad, Oxford and Delphi quality scale as tools to verify the quality assessment of randomized and non-randomized trials. These scales were developed with the objective to help the researchers to rapidly identify if these studies contain enough internal and statistical information, and further quality. Our results demonstrated Jadad scores that ranged from 0 to 3, which did not demonstrated enough internal and statistical information presented by the trials. Oxford scale showed a wider score (ranged from 0 to 4),Delphi list scored from 3 to 7 (table 2).

Meta-analysis

Meta-analysis was applied for placenta weight (g) and volume (cm\(^3\)), intervillous space (cm\(^3\)), villous volume (cm\(^3\)) and vascular volume (cm\(^3\)).
Data Synthesis

Placenta weight: Data are presented by the analysis of three articles and 124 patients studied. Forest plot demonstrated homogeneity (p=0.69, I²=0%) between studies and exercise appeared to affect placental weight by increasing it (95% CI, 39.73[4.66-74.80]). Table 3 presented data and forest plot.

Placenta Volume: Data are presented by the analysis of 108 patients from three articles. Meta-analysis showed also homogeneity (p= 0.69, I²=0%) between studies and exercise increased placental volume by 47.11 cm³ (95% CI, 37.99-56.23). Table 4 presented data and forest plot.

Interval space

A total of 108 patients were evaluated from three studies. Exercise demonstrated to affect interval space. The forest plot showed a low heterogeneity level (p=0.34; I²=8%). Effect estimated was 16.67 cm³ (95% CI, 12.66-20.68). In addition, physical training demonstrated a significant overall effect (Z=8.14 [p<0.00001]). Table 5 presented data and forest plot.

Villos volume

Forest plot demonstrated that exercise induced increase in villous volume. This analysis showed a high level of homogeneity (p=0.97, I²=0%). Placenta from 68 patients were evaluated. Data is presented in table 6.

Villous vascular volume

Exercise effective altered villous vascular volume. However, it showed a high level of heterogeneity (p=0.04, I²=75%). Effect estimated was 15.95 cm³ (95% CI, 7.83-24.07) from 62 patients. Data are presented in table 7.

Stem villi

Exercise altered stem villi. This analysis showed high homogeneity level between studies (p= 1.00, I²=0%). Effect estimated was 6.00 cm³ (95% CI, 4.25-7.75) Data are presented in table 8.

Table 1. Information description of sample characteristics, training protocol and primary results.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (num- ber)</th>
<th>Random- ization</th>
<th>Age (years)</th>
<th>Gestational age during Study Recruitment</th>
<th>Physical Activity prior protocol</th>
<th>Gestational Age that Stopped Intervention</th>
<th>Exercise protocol</th>
<th>Control</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Price et al.12</td>
<td>62</td>
<td>Yes</td>
<td>Exercise group: 30±5</td>
<td>12-14 weeks</td>
<td>No</td>
<td>36 week gestation or delivery</td>
<td>45-60 minutes duration, 4x/week, 12-14 Borg scale intensity (Day 1: step aerobics; Day 2: walking over adjacent hilly terrain; Day 3: circuit resistance training [1-10 minutes aerobics on treadmill or elliptical trainers or stationary bicycles, alternated with weight training that included upper, lower and core exercises]; Day 4: walking)</td>
<td>Every day tasks</td>
<td>Placenta weight did not significant differ between groups (Exercise: 691±178g/ Control: 625±103g)</td>
</tr>
<tr>
<td>Bergmann et al.13</td>
<td>22</td>
<td>No</td>
<td>Ranged between 29 and 35</td>
<td>Not mentioned</td>
<td>Yes</td>
<td>Delivery</td>
<td>Running ≥4x/week, 40-60 minutes duration, intensity fixed at 55-65% maximal aerobic capacity</td>
<td>Stopped running through gestation and did every day tasks</td>
<td>Placenta weight did not significant differ between groups (Exercise: 440±80g/ Control: 400±80g) Villous vascular volume and indices of cell proliferation were increased significantly in Exercise group compared to control.</td>
</tr>
<tr>
<td>Clapp 3rd et al.1</td>
<td>46</td>
<td>Yes</td>
<td>31±1</td>
<td>8 weeks</td>
<td>No</td>
<td>Delivery</td>
<td>20 minutes of aerobic exercise (treadmill), step aerobics or stair steppes), 3x/week and intensity fixed about 55-65% of the maximal aerobic capacity</td>
<td>Every day tasks</td>
<td>Mid trimester placenta growth rate, volume, functional and nonfunctional volume, villous volume and terminal villi were statistically increased in exercise group</td>
</tr>
<tr>
<td>Jackson et al.1</td>
<td>40</td>
<td>Yes</td>
<td>Ranged between 21 and 40</td>
<td>6 months prior pregnancy</td>
<td>Yes</td>
<td>Delivery</td>
<td>30 minutes of aerobic exercise, ≥3x/week, ≥50% maximal capacity</td>
<td>Every day tasks</td>
<td>Placenta weight did not differ significantly between groups (Exercise: 499±96g/ Control: 472±62g) Placenta and Villous composition were increased in exercising group</td>
</tr>
</tbody>
</table>

Figure 1. Flux gram of the articles selection process and exclusion criteria.
DISCUSSION

This systematic review with meta-analysis analyzed four studies of varying designs evaluating, predominantly, aerobic exercise training as a stimulus to increase placental components. Thus, low number of articles and patients included in this meta-analysis, we could indicate that aerobic training might increase placenta weight and volume, villous volume and vascular volume, intervillous space and stem villi. However, it is clear the necessity of better quality studies and higher number of participants (as showed in table 2). In addition, it’s necessary apply for future research several training parameters that might interfere in the results, such as: total training volume, total training loading and load evolution graphics by gestational age, time under tension, higher vs low time exertion, and others.

Several mechanisms could explain these findings. Bergmann et al. published the first paper to show that exercise training can increase cell proliferation indexes. Increased and decreased oxygen delivery during physical effort might stimulate cell proliferation. This acute change leads to a Hypoxia Induced Growth Factor (HIF) action. Following, Vascular

Table 2. Description of data quality assessment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Jadad (0-5)</th>
<th>Oxford (0-7)</th>
<th>Delphi (0-10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Price et al.</td>
<td>1a. Yes, 1b. Yes, 2a. No, 2b. No, 3. Yes</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Bergmann et al.</td>
<td>1a. No, 1b. No, 2a. No, 2b. No, 3. No</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Jackson et al.</td>
<td>1a. Yes, 1b. No, 2a. No, 2b. No, 3. No</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3. Forest plot presented information about aerobic exercise effect on placenta weight (g).

Table 4. Forest plot presented information about overall aerobic exercise effect on placenta volume (cm³).

Table 5. Forest plot presented information about aerobic exercise effect on intervillous space (cm³).

Table 6. Forest plot presented information about aerobic exercise effect on villous volume (cm³).
Table 7. Forest plot presented information about aerobic exercise effect on villous vascular volume (cm$^3$).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Exercise</th>
<th>Control</th>
<th>Mean difference</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Clapp 3rd et al$^5$</td>
<td>77</td>
<td>20</td>
<td>11</td>
<td>26.1%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>62</td>
<td>20</td>
<td>20</td>
<td>73.9%</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td></td>
<td>31</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi$^2$ = 4.06, df = 1 (p = 0.04); I$^2$ = 75%

Test for overall effect: Z = 3.85 (p = 0.0001)

Table 8. Forest plot presented information about aerobic exercise effect on stem villi (cm$^3$).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Exercise</th>
<th>Control</th>
<th>Mean difference</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Jackson et al$^3$</td>
<td>20</td>
<td>11</td>
<td>20</td>
<td>10.9%</td>
</tr>
<tr>
<td>Clapp 3rd et al$^5$</td>
<td>29</td>
<td>4</td>
<td>22</td>
<td>89.1%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>42</td>
<td></td>
<td>44</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi$^2$ = 0.00, df = 1 (p = 1.00); I$^2$ = 0%

Test for overall effect: Z = 6.72 (p < 0.00001)

**Endothelial Growth Factor (VEGF)** induces a cascade downstream, stimulating the formation of new blood vessels. This cellular cascade might explain the increased villous vascular volume. Others growth factors such as **Insulin Growth factor** (IGFs), **Placental growth factor** (PGF) and **Pregnancy-associated plasma protein-A** (PAPP-A) might also be involved in placenta adaptation to training stimulus$^{13-15}$.

Gestational age might influence morphological adaptation to exercise$^{16}$. Beginning exercise prior the half of the first trimester could induce a significant increase in placental function in previous sedentary women$^5$. However, reducing training volume during the first trimester might be detrimental for placental adaptation induced by physical training$^6$.

Finally, exercise type is known to induce several different physiological adaptations. Perhaps, time under exertion is a factor to contribute for placental adaptation$^8$. However, it is necessary to study the differences of resistance training and endurance training on placental components adaptation. Price et al$^{12}$ combined endurance and resistance training throughout 36 weeks of gestation. The results showed improved aerobic fitness, muscular strength, fewer cesarean delivery rates and recovered faster postpartum. However, placental weights did not differ between groups. These result was computed in our meta-analysis and overall effect was significant (p=0.03) which indicate a positive effect on larger placental weights over training stimulus. Clearly, it is needed more high quality studies for a more precise result.

**FINAL CONSIDERATIONS**

This study revealed a clear positive effect of exercise training on placental components. However, number of patients and studies identified were low and the study quality analysis showed a necessity of higher quality studies with a more well conducted methodology.

All authors have declared there is not any potential conflict of interests concerning this article.