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

EFEITO DO EXERCÍCIO NOS COMPONENTES PLACENTÁRIOS: REVISÃO SISTEMÁTICA E META-ANÁLISE

EFECTO DEL EJERCICIO EN COMPONENTES PLACENTARIOS: REVISIÓN SISTEMÁTICA Y META-ANÁLISIS

Systematic Review Article
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Walter Krause Neto[1]
(Educador Físico)
Eliane Florencio Gama[1]
(Fisioterapeuta)

1. Universidade São Judas Tadeu, Departamento de Educação Física, Laboratório de Estudos Morfoquantitativos e Imunohistoquímica, São Paulo, SP, Brasil.

Correspondência:
Rua Taquari, 546, Mooca, São Paulo, SP, Brasil. 03166-000.
wild_krause@hotmail.com

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, 39.73g [4.66-74.80]), placental volume (95% CI, 47.11 cm^3 [37.99-56.23]), intervillous space (95% CI, 16.76 cm^3 [12.66-20.68]), villous volume (95% CI, 46.01 cm^3 [40.21-51.81]), villous vascular volume (95% CI, 15.95 cm^3 [7.83-24.07]) and stem villi (95% CI, 6.00 cm^3 [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.

RESUMO

O exercício físico tem demonstrado efeito positivo nos muitos desfechos da gravidez. Componentes da placenta são importantes para a troca de oxigênio e nutrientes entre mãe e feto. O objetivo deste estudo foi revisar de forma sistemática e realizar uma meta-análise para verificar se o exercício físico pode induzir um ajuste morfológico nos componentes da placenta. A pesquisa foi feita sistematicamente no banco de dados PubMed até 30 de outubro de 2014. Foram incluídos estudos randomizados e não-randomizados com grupo controle, que tiveram como objetivo investigar o efeito do exercício físico (água, aeróbico e resistência) em componentes da placenta (peso e volume placentário, volume vascular e volume viloso, espaço interviloso e troncos vilosos). Inicialmente, identificamos 222 artigos, dos quais nove artigos foram utilizados para a análise de texto completo. Por último, quatro artigos foram incluídos na revisão sistemática e meta-análise. A meta-análise demostrou que o exercício parece afetar o peso da placenta (95% IC, 39,73g [4,66-74,80]), o volume placentário (IC 95%, 47,11 cm^3 [37,99-56,23]), o espaço interviloso (IC 95%, 16,76 cm^3 [12,66-20,68]), o volume viloso (IC 95%, 46,01 cm^3 [40,21-51,81]), o volume vascular viloso (95% IC, 15,95 cm^3 [7,83-24,07]) e o tronco viloso (95% IC, 6,00 cm^3 [4,25-7,75]). Aparentemente, o exercício físico tem efeito positivo sobre os componentes da placenta. No entanto, esta conclusão é baseada em um número limitado de estudos. Claramente, destaca-se a necessidade de amostras maiores e melhor qualidade de metodologia.

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

RESUMEN

El ejercicio físico ha demostrado efecto positivo en los 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 de resistencia) en los componentes de la placenta (peso y volumen de la placenta, el volumen vascular y volumen velloso, espacio intervelloso y troncos vellosos). 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 cm^3 [37,99-56,23]), el espacio intervelloso (IC del 95%, 16,76 cm^3 [12,66-20,68]), el volumen velloso (IC del 95%, 46,01 cm^3 [40,21-51,81]), el volumen vascular velloso (95 IC%, 15,95 cm^3 [7,83-24,07]) y el tronco velloso (IC 95%, 6,00 cm^3 [4,25-7,75]). Aparentemente, el ejercicio físico tiene un efecto positivo sobre los componentes de la placenta. Sin embargo, esta conclusión se basa en un número limitado de estudios. Claramente, hay una necesidad para mayores tamaños de muestra y una mejor calidad de la metodología.

Palabras clave: *placenta, vellosidades coriónicas, esfuerzo físico, embarazo.*

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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, steam villi and total peripheral villi increase among women who continued moderate exercise training through pregnancy. Others also showed interesting placental 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 doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[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 prospectiv*[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 effort physical OR efforts physical OR physical efforts OR resistance training OR training resistance OR strength training OR training, strength OR weight lifting strengthening programs 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 placentome OR placentomes OR placentome, normal OR normal placenta OR normal placentas OR placentomes, normal OR 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, uteroplacental 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 scales[8-10].

Data synthesis and analysis

Review manager software 5.2 was used to calculate heterogeneity by the I^2, Chi^2 and Tau^2 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 studied 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), and stem villi (cm^3).

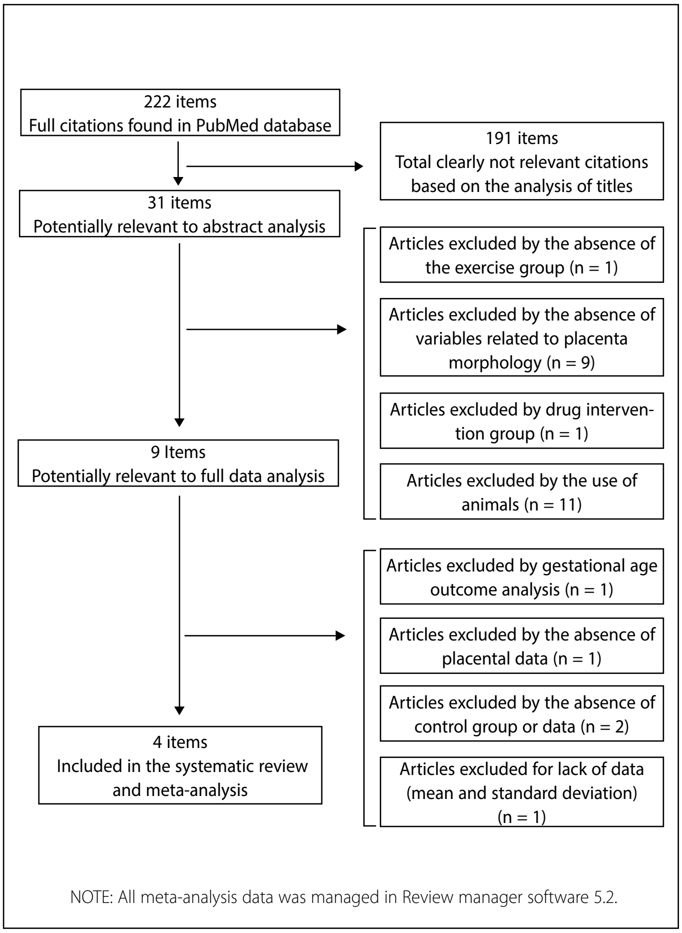


Figure 1. Flux gram of the articles selection process and exclusion criteria.

Data Synthesis

Placenta weight: Data are presented by the analysis of three articles and 124 patients studied. Forest plot demonstrated homogeneity (p=0.69, I^2= 0%) between studies and exercise appeared to affect placental weight by increasing it (95% CI, 39.73g [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, I^2=0%) between studies and exercise increased placental volume by 47.11 cm^3 (95% CI, 37.99-56.23). Table 4 presented data and forest plot.

Intervillous space

A total of 108 patients were evaluated from three studies. Exercise demonstrated to affect intervillous space. The forest plot showed a low heterogeneity level (p= 0.34, I^2= 8%). Effect estimated was 16.67 cm^3 (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.

Villous volume

Forest plot demonstrated that exercise induced increase in villous volume. This analysis showed a high level of homogeneity (p= 0.97, I^2=0%). Placenta from 68 patients were evaluated. Data is presented are table 6.

Villous vascular volume

Exercise effective altered villous vascular volume. However, it showed a high level of heterogeneity (p= 0.04, I^2=75%). Effect estimated was 15.95 cm^3 (95% IC, 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, I^2= 0%). Effect estimated was 6.00 cm^3 (95% IC, 4.25-7.75) Data are presented in table 8.

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

Study	Patients (number)	Randomization	Age (years)	Gestational age during Study Recruitment	Physical Activity prior protocol	Gestational Age that Stopped Intervention	Exercise protocol	Control	Results
Price et al.[12]	62	Yes	Exercise group: 30.5±5 Control group: 27.6±7.3	12-14 weeks	No	36 week gestation or delivery	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 eliptical trainers or stationary bicycles, alternated with weight training that included upper, lower and core exercises]; Day 4: walking)	Every day tasks	Placenta weight did not significant differ between groups (Exercise: 691±178g/ Control: 625±103g)
Bergmann et al.[11]	22	No	Ranged between 29 and 35	Not mensioned	Yes	Delivery	Running ≥4x/week, 40-60 minutes duration, intensity fixed at 55-65% maximal aerobic capacity	Stopped running through gestation and did every day tasks	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.
Clapp 3rd et al.[5]	46	Yes	31±1	8 weeks	No	Delivery	20 minutes of aerobic exercise (treadmill, step aerobics or stair stepper), 3-5x/week and intensity fixed about 55-60% of the maximal aerobic capacity	Every day tasks	Midtrimester placenta growth rate, volume, functional and nonfunctional volume, villous volume and terminal villi were statistically increased in exercise group
Jackson et al.[3]	40	Yes	Ranged between 21 and 40	6 months prior pregnancy	Yes	Delivery	30 minutes of aerobic exercise, ≥3x/week, ≥50% maximal capacity	Every day tasks	Placenta weight did not diferred significantly between groups (Exercise: 499±96g/ Control: 472±62g) Placenta and Villous composition were increased in exercising group

Table 2. Description of data quality assessment.

Study	Quality assessment	Jadad (0-5)	Quality assessment	Oxford (0-7)	Quality assessment	Delphi (0-10)
Price et al.[12]	1a. Yes, 1b. Yes, 2a. No, 2b. No, 3. Yes	3	Described and adequated, no, no, described and adequated	4	1a. Yes, 1b. No, 2. Yes, 3. Yes, 4. Yes, 5. No, 6. No, 7. Yes, 8. Yes, 9. Yes	7
Bergmann et al.[11]	1a. No, 1b. No, 2a. No, 2b. No, 3. No	0	No, no, no, no	0	1a. Not described, 1b. Not described, 2. Yes, 3. No, 4. Not described, 5. Not described, 6. Not described, 7. Yes, 8. Yes, 9. Not described	3
Clapp 3rd et al.[5]	1a. Yes, 1b. Yes, 2a. No, 2b. No, 3. Yes	3	Described, no, no, described and adequated	3	1a. Yes, 1b. No, 2. Yes, 3. Yes, 4. No, 5. Not described, 6. No, 7. Yes, 8. Yes, 9. Yes	6
Jackson et al.[3]	1a. Yes, 1b. No, 2a. No, 2b. No, 3. No	1	Described, no, no, described however incomplete	2	1a. Yes, 1b. Not described, 2. Yes, 3. Not described, 4. Not described, 5. Not described, 6. Not described, 7. Yes, 8. Yes, 9. Not described	4

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

	Exercise			Control			Mean difference		Mean difference
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Bergmann et al.[11]	440	80	11	400	80	11	27.5%	40.00 (-26.86, 106.86)	
Jackson et al.[3]	499	96	20	472	62	20	49.0%	27.00 (-23.08, 77.08)	
Price et al.[12]	691	178	31	625	103	31	23.5%	66.00 (-6.39, 138.39)	
Total (95% CI)			62			62	100.0%	39.73 (4.66, 74.80)	
Heterogeneity: Chi^2 = 0.75, df = 2 (p = 0.69): I^2 = 0%									
Test for overall effect: Z = 2.22 (p = 0.03)									

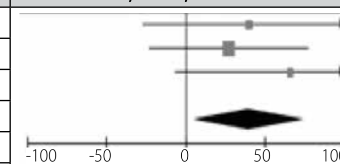


Table 4. Forest plot presented information about aerobic exercise effect on placenta volume (cm^3).

	Exercise			Control			Mean difference		Mean difference
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Bergmann et al.[11]	431	76	11	391	80	11	2.0%	40.00 (-25.21, 105.21)	
Clapp 3rd et al.[5]	462	18	22	414	14	24	94.6%	48.00 (38.62, 57.38)	
Jackson et al.[3]	481	94	20	454	60	20	3.5%	27.00 (-21.87, 75.87)	
Total (95% CI)			53			55	100.0%	47.11 (37.99, 56.23)	
Heterogeneity: Chi^2 = 0.73, df = 2 (p = 0.69): I^2 = 0%									
Test for overall effect: Z = 10.13 (P < 0.00001)									

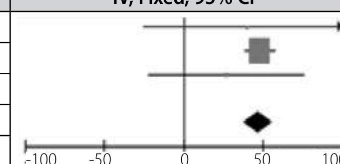


Table 5. Forest plot presented information about aerobic exercise effect on intervillous space (cm^3).

	Exercise			Control			Mean difference		Mean difference
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Bergmann et al.[11]	136	26	11	136	31	11	2.8%	0.00 (-23.91, 23.91)	
Clapp 3rd et al.[5]	166	8	22	149	6	24	95.0%	17.00 (12.88, 21.12)	
Jackson et al.[3]	188	53	20	164	33	20	2.1%	24.00 (-3.36, 51.36)	
Total (95% CI)			53			55	100.0%	16.67 (12.66, 20.68)	
Heterogeneity: Chi^2 = 2.17, df = 2 (P = 0.34): I^2 = 8%									
Test for overall effect: Z = 8.14 (P < 0.00001)									

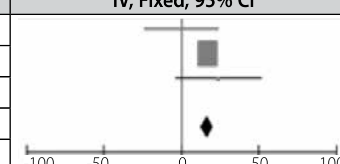
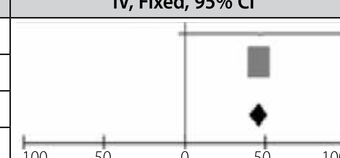


Table 6. Forest plot presented information about aerobic exercise effect on villous volume (cm^3).

	Exercise			Control			Mean difference		Mean difference
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Bergmann et al.[11]	284	65	11	237	56	11	1.3%	47.00 (-3.70, 97.70)	
Clapp 3rd et al.[5]	268	11	22	222	9	24	98.7%	46.00 (40.16, 51.84)	
Total (95% CI)			33			35	100.0%	46.01 (40.21, 51.81)	
Heterogeneity: Chi^2 = 0.00, df = 1 (p = 0.97): I^2 = 0%									
Test for overall effect: Z = 15.55 (p < 0.00001)									



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 steam 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.[11] 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 7. Forest plot presented information about aerobic exercise effect on villous vascular volume (cm^3).

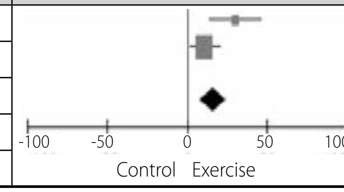
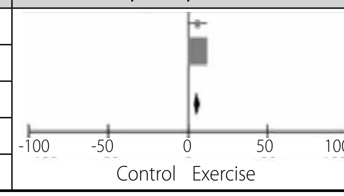
	Exercise			Control			Mean difference		Mean difference
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Bergmann et al.[11]	77	20	11	47	18	11	26.1%	30.00 (14.10, 45.90)	
Clapp 3rd et al.[5]	62	20	20	51	8	20	73.9%	11.00 (1.56, 20.44)	
Total (95% CI)			31			31	100.0%	15.95 (7.83, 24.07)	
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).

	Exercise			Control			Mean difference		Mean difference
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Jackson et al.[3]	20	11	20	14	5	20	10.9%	6.00 (0.70, 11.30)	
Clapp 3rd et al.[5]	29	4	22	23	2	24	89.1%	6.00 (4.15, 7.85)	
Total (95% CI)			42			44	100.0%	6.00 (4.25, 7.75)	
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[5,6]. 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[6]. 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 through 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.

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