EFEITOS DO TREINAMENTO RESISTIDO E COMBINADO NA GLICEMIA E RESISTÊNCIA INSULÍNICA NA GESTAÇÃO: UMA REVISÃO SISTEMÁTICA COM META-ANÁLISE

Dissertação de Mestrado

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CIP - Catalogação na Publicação

de Azevedo Frank, Paula
EFEITOS DO TREINAMENTO RESISTIDO E COMBINADO NA GLICEMIA E RESISTÊNCIA INSULÍNICA NA GESTAÇÃO: UMA REVISÃO SISTEMÁTICA COM META-ANÁLISE / Paula de Azevedo Frank. -- 2022.
46 f.
Orientador: Rodrigo Ferrari da Silva.

Dissertação (Mestrado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares, Porto Alegre, BR-RS, 2022.

1. Gestação. 2. Treinamento físico. 3. Treinamento de força. 4. Treinamento Combinado. 5. Hiperglicemia. I. Ferrari da Silva, Rodrigo, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

Programa de Pós-Graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares

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Dissertação submetida como requisito para obtenção do grau de Mestre ao Programa de Pós Graduação em Ciências da Saúde. Área de Concentração: Cardiologia e Ciências Cardiovasculares, da Universidade Federal do Rio Grande do Sul.

Porto Alegre, 2022

AGRADECIMENTOS

Ao Professor Dr. Rodrigo Ferrari, por me orientar exaustivamente ao longo deste caminho. Obrigada por possibilitar e guiar a realização deste trabalho. Obrigada por me ensinar a contornar imprevistos e a me desafiar a cada dia.

Aos membros da banca examinadora, Professor Dr. Eduardo Lusa Cadore e Professora Dra. Ana Kanitz, que gentilmente aceitaram participar e colaborar com esta dissertação. E, em especial, à Professora Dra. Sandra Costa Fuchs, que além de participar da banca examinadora, compartilhou toda estrutura do PREVER e me acolheu nesta instituição de excelência.

A todos professores e colaboradores do Programa de Pós-graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares, pelo excelente ensino que o programa oferece.

Aos meus amigos e colegas, do Grupo de Estudos em Treinamento Físico e Esportes (GET-HCPA), Leandro Carpes, Lucas Betti Domingues, Natália Jung e alunos de iniciação científica, pela amizade, ensino e pelo convívio. E, de forma especial, agradeço ao colega Vinícius Mallmann Schneider, que colaborou diretamente no desenvolvimento deste projeto.

Agradeço à minha família, ao meu esposo Gabriel e meus amigos, que sempre incentivaram meus sonhos, compreenderam minhas ausências e vibram a cada etapa conquistada.

Por fim, às minhas pacientes, que me ensinam sobre cuidado e amor todos os dias e me inspiram a buscar conhecimento para uma melhor prática.

MENSAGEM

“What can I do to make this mountain taller so people

after me can see farther?".

(Rupi Kaur)

SUMÁRIO

LISTA DE ABREVIATURAS E SIGLAS

EF = Exercício Físico

DMG = Diabetes Mellitus Gestacional

TOTG = Teste Oral de Tolerância a glicose

TC = Treinamento Combinado

TR = Treinamento Resistido

GC = Grupo Controle

RESUMO

Objetivo: O exercício físico atua na prevenção e tratamento de diversas patologias da gestação. A proposta deste estudo foi avaliar os efeitos do treinamento resistido e combinado na glicemia e resistência insulínica na gestação. **Métodos:** Incluídos ensaios clínicos randomizados, em gestantes, de intervenções contendo exercício resistido versus grupo controle sem exercício. Bases de dados MEDLINE via PubMed, Cochrane Central, EMBASE, Scielo, e LILACS foram utilizadas para busca de artigos publicados até julho de 2022. A qualidade metodológica dos estudos foi avaliada pela lista de verificação da TESTEX. Foi realizada uma meta-análise de efeitos aleatórios utilizando como medida de efeito a diferença média (MD) da alteração da glicemia de jejum (GJ), glicemia 2h pós prandial (2hPP) e índice HOMA2-IR em relação à linha de base, comparando as diferentes intervenções. Ainda, uma análise de subgrupo para avaliar a relação entre o tipo do treinamento (resistido isolado ou associado ao exercício aeróbio) e população (DMG ou não-DMG). **Resultados:** Foram incluídos 11 estudos na análise da glicemia de jejum (1426 participantes), 5 estudos na análise da glicemia 2h pós prandial (991 participantes) e 4 estudos na análise do índice HOMA2-IR (905 participantes). Nas variáveis GJ e 2hPP houve uma diminuição significativa do exercício em comparação ao controle (GJ: -0,11mmol/L, 95% IC, -0,19 a -0,03; 2hPP: -0,38mmol/L, IC 95%, -0,56 a -0,21), com heterogeneidade significativa. A análise de subgrupo da glicemia de jejum demonstrou reduções favorecendo intervenções de treinamento resistido isolado e participantes com DMG. Na variável HOMA2-IR, não houve redução significativa do grupo exercício em relação ao controle (-0,05, IC 95%, -0,22 a 0,11) **Conclusão:** O treinamento resistido é uma estratégia eficaz na redução de glicemia, especialmente em pacientes com DMG.

Palavras-chave: Atividade física; Treinamento físico; Treinamento de força; Treinamento Combinado; Hiperglicemia; Resistência Insulínica.

1. INTRODUÇÃO

Da concepção ao nascimento, o organismo materno gravídico sofre diversas alterações fisiológicas para a manutenção da gestação e crescimento fetal apropriado.[1] Entre as adaptações endócrinas, ocorrem a hiperplasia e aumento de produção de insulina pelas células pancreáticas além do aumento da resistência periférica à insulina, com objetivo de maior aporte glicêmico ao feto em crescimento. Quando o organismo materno falha no equilíbrio destas alterações, pode ocorrer o desenvolvimento e diagnóstico de diabetes mellitus gestacional (DMG).[2]

Diabetes mellitus gestacional (DMG) é definido como qualquer grau de intolerância à glicose, com início ou primeiro reconhecimento durante a gestação.[3] Previamente, definia-se DMG como diagnóstico de hiperglicemia em níveis semelhantes àqueles utilizados para diagnóstico de diabetes fora da gestação.[4] Porém, em 2008, o estudo Hiperglicemia e Resultados Adversos na Gravidez (Hyperglycemia and Adverse Pregnancy Outcomes – HAPO), estudo observacional prospectivo que incluiu aproximadamente 25.000 gestantes, demonstrou uma correlação positiva e linear entre os valores de glicemia materna e a frequência de diversos desfechos maternos e neonatais adversos, mesmo em valores de glicemia antes considerados normais.[5] Este estudo ocasionou uma mudança nos critérios diagnósticos propostos, com pontos de corte menores de glicemia e, assim, aumento significativo na prevalência de DMG.[6][7] Os fatores de risco para ocorrência de hiperglicemia na gestação são extensos e incluem: idade avançada, sobrepeso e obesidade, ganho excessivo de peso durante a gravidez, história de diabetes em parentes de 1º grau, história de abortamentos, macrossomia em gestação prévia, pré-eclâmpsia, hipertensão e gestação múltipla.[8]

O principal objetivo no tratamento da diabetes é melhorar o controle glicêmico e, assim, diminuir a ocorrência de desfechos materno fetais desfavoráveis.[9] As estratégias para manejo da glicemia incluem dieta, terapia medicamentosa e exercício físico. Atualmente, o exercício é recomendado no cuidado pré-natal habitual de todas as gestantes, mostrando-se seguro e benéfico, com respostas fisiológicas semelhantes à população em geral. [10][11] Estudos prévios demonstraram que o exercício físico é capaz de reduzir a resistência insulínica, que é o principal mecanismo fisiopatológico da DMG, além de melhorar o controle glicêmico em pacientes com DM do tipo 2.[12][13]

As principais diretrizes sobre o tema sugerem que exercícios aeróbios, especialmente quando combinados à exercícios resistidos, são a estratégia mais eficaz para pacientes com diabetes.[14][15] Já os benefícios isolados do exercício resistido ainda necessita de mais evidências para essa população. Comparado ao exercício aeróbico, o exercício resistido pode aumentar a força muscular, podendo ser mais confortável e mais bem tolerado na gestação, diminuindo desconfortos causados pelo aumento de peso, edema e mudança do centro de gravidade característicos e progressivos da gestação.[16]

O presente estudo busca responder lacunas sobre os benefícios do treinamento resistido na redução da glicemia e resistência insulínica. Tais achados poderão melhorar a qualidade da assistência prestada e disseminar o uso do treinamento resistido em gestantes saudáveis, além de possibilitar a aplicabilidade do treinamento resistido no controle glicêmico em gestantes com diabetes gestacional.

2. OBJETIVOS

2.1. Objetivo Geral

Avaliar a eficácia do treinamento resistido na redução da glicemia e resistência insulínica em gestantes.

2.2. Objetivos Específicos

Avaliar e comparar, através de abordagem meta-analítica, as mudanças na glicemia de jejum, glicemia 2 horas pós prandial e resistência insulínica após programas de treinamento resistido versus intervenção controle em gestantes.

Verificar, através de abordagem meta-analítica, a influência do tipo de treinamento (treinamento resistido isolado ou associado ao aeróbio) e características da população (gestantes com DMG ou não-DMG) na glicemia de jejum, glicemia 2 horas pós prandial e resistência insulínica.

2.3. Hipótese

A hipótese primária é que o treinamento resistido seja eficaz na redução da glicemia de jejum, glicemia 2 horas pós prandial e a resistência insulínica, quando comparado ao grupo controle de cuidados pré-natais habituais.

3. REVISÃO DE LITERATURA

3.1. Gestação e Alterações do Metabolismo da Glicose

Durante uma gestação saudável, diversas alterações no metabolismo dos carboidratos ocorrem com o objetivo de manter aporte constante de glicose ao feto em crescimento. A homeostase da glicose é regulada principalmente pela insulina, secretada pelas células beta pancreáticas em resposta à concentração de glicose sanguínea.[17]

Na gestação, há hiperplasia das células beta pancreáticas e consequente aumento da produção de insulina, enquanto na periferia ocorre aumento progressivo da resistência das células à ação da insulina. Há um aumento de até 50% na resistência insulínica, do primeiro ao terceiro trimestre, retornando a níveis normais no pós-parto imediato.[18] Estas ações, em conjunto, são responsáveis pelo característico aumento dos níveis de glicose pós prandiais em gestantes.[19]

O principal hormônio relacionado com a resistência à insulina durante a gravidez é o hormônio lactogênico placentário, um contrarregulador da insulina. Sabe-se que outros hormônios também estão envolvidos na homeostase da glicose, tais como o cortisol, estrógeno, progesterona e prolactina, de ação hiperglicemiante.[20]

A resistência insulínica pode ser avaliada através da insulina e glicose sanguíneas. Os modelos mais usados atualmente para estimar a resistência insulínica são o índice HOMA-IR e HOMA2-IR *(Homeostatic Model Assessment of Insulin Resistance)*. Valores acima dos valores de referência indicam risco de desenvolver doenças cardiovasculares, síndrome metabólica ou diabetes tipo 2. Gestantes com DMG e obesas/sobrepeso apresentam valores mais altos deste índice em relação às gestantes em geral.[21]

De maneira geral, em uma gestação saudável, o aumento da resistência insulínica é acompanhado pelo aumento da produção de insulina, otimizando o transporte de glicose para as células e mantendo a glicemia em níveis normais. Porém, nem todas as gestações respondem a esta sobrecarga de adaptações, resultando no diagnóstico de DMG. [22]

3.2. Diabetes Mellitus Gestacional

Diabetes mellitus gestacional (DMG) é definido como qualquer nível de intolerância a carboidratos, resultando em hiperglicemia de gravidade variável, com início ou diagnóstico durante a gestação, em níveis glicêmicos sanguíneos que não atingem os critérios diagnósticos para DM. Alguns fatores de estão associados com maior risco de hiperglicemia na gravidez, tais como idade materna avançada, sobrepeso e obesidade, antecedentes familiares de DM, antecedentes pessoais de alterações metabólicas ou DMG. [23]

Não é recomendado que fatores de risco sejam utilizados para fins de rastreamento de DMG. Recomenda-se o diagnóstico universal durante o pré-natal. Caso a gestante apresente, na primeira consulta de pré-natal, critérios de diagnóstico iguais àqueles predeterminados para o diagnóstico de diabetes fora da gestação, ela será considerada como portadora de DM diagnosticado na gravidez. O diagnóstico do DMG seja firmado quando a glicemia de jejum for maior ou igual a 92 mg/dL e menor ou igual a 125 mg/dL; ou ainda se pelo menos um dos valores do Teste Oral de Tolerância à gliose (TOTG) com 75 g de glicose, realizado entre 24 e 28 semanas de idade gestacional, for maior ou igual a 92 mg/dL no jejum, maior ou igual a 180 mg/dL na primeira hora ou maior ou igual a 153 mg/dL na segunda hora. O TOTG com 75 g é preconizado para todas as gestantes que não apresentaram diagnóstico de DMG ou DM diagnosticado na gravidez para o primeiro rastreio realizado no primeiro trimestre.[24]

Estes pontos de corte foram estabelecidos através do estudo Hiperglicemia e Resultados Adversos na Gravidez (*Hyperglycemia and Adverse Pregnancy Outcomes* – HAPO), que associou o aumento independente destes pontos aos seguintes desfechos neonatais adversos: peso ao nascer acima do percentil 90, porcentagem de gordura corporal neonatal acima do percentil 90 ou valor de peptídeo C no cordão umbilical acima do percentil 90.[5] Ainda, prole de mães com DMG tem mais risco de ao longo da vida desenvolverem obesidade e doenças metabólicas associadas.[25]

A gestação também é um momento decisivo para a saúde da mulher ao longo da vida. Sabe-se que o principal fator de risco para o desenvolvimento de DM do tipo 2 e de síndrome metabólica é o antecedente obstétrico de DMG. [26]

Nesse contexto, a hiperglicemia durante o ciclo gravídico-puerperal constitui um relevante problema da atualidade, não só pelo risco de piores desfechos perinatais e de desenvolvimento de doenças futuras, como também pelo aumento de sua prevalência, seguindo a epidemia de obesidade que tem sido observada em vários países.[27]

3.3. Exercício Físico e Diabetes

Alterações na dieta, exercício e ganho de peso gestacional adequado são encorajados pelas diferentes sociedades de obstetrícia, fazendo parte das orientações habituais do pré-natal. [28] No manejo de gestantes com diabetes gestacional ou risco desta patologia, modalidades de tratamento com o objetivo de melhorar a sensibilidade insulínica podem ser úteis. O exercício pode oferecer benefícios que o tratamento com insulina não atinge, como a melhora da resistência insulínica, principal mecanismo fisiopatológico da DMG.[29] Em pacientes com diabetes mellitus da população em geral, o EF demonstrou melhorar a sensibilidade insulínica e controle glicêmico.[30] Uma revisão sistemática com metanálise realizada em 2019 também demonstrou que o exercício estruturado é eficaz para melhora da resistência insulínica em pacientes com diabetes mellitus.[31]

Estudos demonstraram evidência que o exercício aeróbico pode diminuir os níveis glicêmicos em gestantes com DMG, reduzindo a necessidade de insulina.[32][33] Em relação a resistência insulínica e glicose sanguínea, uma revisão demonstrou que modalidades aeróbicas e combinadas podem ser úteis para redução da glicemia e índices de resistência insulínica, porém, sem achados consistentes entre os estudos analisados.[34]

As recomendações gerais incluem a realização de ambos os exercícios aeróbicos e resistidos aproximadamente 30 minutos ao dia, totalizando 150 minutos de atividades físicas na semana em intensidade moderada. Exercícios aeróbicos, como caminhada, bicicleta, natação e yoga são considerados seguros e aplicáveis na gestação. Intervenções aeróbicas combinadas a elementos de força também estão sendo desenvolvidas, utilizando faixas elásticas, peso leves ou peso corporal. [35]

O treinamento resistido é uma forma de exercício caracterizada pela repetição e contração muscular voluntária contra alguma resistência externa (gravidade, halteres, faixas elásticas) e sua prática tem ganhado popularidade na população em geral. Evidências sobre a segurança desta modalidade progressivamente têm refutado crenças de que a prática de elementos de força seja contraindicada em gestantes.[36]

Entretanto, não estão claros e individualizados os benefícios do treinamento resistido na gestação. Dois estudos mostraram diminuição na necessidade de uso de insulina e melhora do controle glicêmico domiciliar através de intervenção com treinamento resistido em gestantes com diabetes gestacional.[37][38] Porém, existem poucos estudos com intervenções de treinamento resistido isolado e variáveis de treinamento como frequência, volume, duração e intensidade não são frequentemente avaliados, limitando a prescrição e uso do TR na prática clínica. Ainda, os ensaios clínicos conduzidos apresentam resultados e intervenções distintas, tornando necessária a síntese destas informações para a prática clínica.

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5. ARTIGO CIENTÍFICO

Effects of resistance and combined training on blood glucose and insulin resistance in pregnancy:

a systematic review with meta-analysis

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ABSTRACT

Aim: Exercise have been shown several benefits on high-risk pregnancies. The purpose of this systematic review with meta-analysis was to evaluate the effects of resistance and combined training on blood glucose and insulin resistance during pregnancy. **Methods:** Randomized clinical trials in pregnant women using interventions with resistance exercise versus a control group without exercise were included. MEDLINE databases via PubMed, Cochrane Central, EMBASE, Scielo, and LILACS were used to search for articles published until July 2022. The methodological quality of the studies was evaluated using the TESTEX checklist. A random effects meta-analysis was performed using the mean difference (MD) of the change in fasting glucose (FG), 2h postprandial glucose (2hPP) and HOMA2-IR index compared to baseline as a measure of effect comparing exercise versus control. A subgroup analysis was performed to assess the relationship between the type of training (resistance or combined) and population (gestational diabetes or non-gestational diabetes). **Results:** 11 studies were included in the analysis of FG (1426 participants), 5 studies in the analysis of 2hPP (991 participants) and 4 studies in the analysis of the HOMA2-IR index (905 participants). In the variables FG and 2hPP there was a significant decrease in exercise compared to control (FG -0.11mmol/L, 95% CI, -0.19 to -0.03) (2hPP -0.38mmol/ L, 95% CI, -0.56 to -0.21), with significant heterogeneity. In the HOMA2-IR, there was no significant reduction after exercise compared to control (-0.05, 95% CI, -0.22 to 0.11). FG subgroup analysis of these variables demonstrated reductions favoring resistance training alone and women with gestational diabetes. **Conclusion:** Resistance training is an efficacy strategy to reduce glycemia, especially in pregnant women with gestational diabetes.

Keywords: Exercise; Pregnancy; Resistance Exercise; Blood Glucose; Hyperglycemia; Insulin Resistance.

INTRODUCTION

From conception to birth, the maternal body undergoes several physiological changes to nurture the developing fetus and prepare the mother for labor and delivery. [1] In health pregnancy occurs a state of hyperinsulinism from hyperplasia of pancreatic cells along with a state of peripheral insulin resistance. The onset of maternal insulin resistance prompts the maternal pancreas to upregulate insulin production and secretion, so that plasma glucose values remain normal or even decreases. When maternal organism fails to respond to these adaptive changes, it can lead to the development and diagnosis of gestational diabetes mellitus. [2] The cornerstone management to prevent and treat this condition is promoting a lifestyle that includes a healthy diet and regular physical activity. [3]

In particular, regular physical exercises can induce positive physiological and metabolic adaptations, helping to prevent and treat hyperglycemia, enhancing the activity of insulin transport of blood glucose, thereby reducing gestational insulin resistance. [4] Most of studies on pregnancy have suggested aerobic exercises such as walking and jogging as safe and feasible strategies during pregnancy, providing evidence that aerobic training reduces blood glucose levels in women with gestational diabetes. [5, 6]

Pregnancy and increasing body weight may limit the practice of some traditional aerobic activities. Compared with aerobic exercise, resistance exercise is relatively stable, and avoids the discomfort caused by the forward shift of the center of gravity in the late pregnancy. [7] This exercise regimen can be more comfortable and easier to tolerate. [8] The additional benefits of regular resistance exercise include improvements in muscular strength, improvement of balance and risk of falls. [9]

Despite being a commonly reported activity overall, resistance training is not a common performed activity in pregnancy.[10] That fact could be explained by misconceptions about safety and the lack of rigorous research regarding the impact of resistance training during pregnancy, especially pregnancies with any pathology. [11, 12] There are few studies with exercise on abnormal glucose pregnancies, with contradicted results and variety of trianing. Therefore, it is not entirely clear the benefits of exercise training on maternal and offspring outcomes, and the synthesis os theses results became relevant. [13]

The aim of this systematic review is to update the evidence on interventions with training (resistance or combined) on on blood glucose and insulin resistance during pregnancy.

2. METHODS

Eligibility Criteria

Types of studies

Randomized controlled trials comparing resistance or combined (i.e., aerobic + resistance) training interventions with a habitual pre-natal care control treatment (recommendations of exercise) were eligible for this study. Training interventions are considered eligible if the intervention was partially or fully supervised. Interventions with only exercise advice were excluded.

Participants

Pregnant women. Studies with participants with severe obstetric complications and contraindications to exercise were excluded.

Exercise training interventions

The resistance training interventions included any exercise with a dynamic training with an external resistance (e.g., gravity during body weight exercises, free weights, elastic bands). The combined training interventions included the combination of any aerobic exercise (i.e., cycling, walking, or running) with any dynamic resistance training performed at the same week (i.e., at the same session or on separate days), with a minimum duration of 4 weeks.

Exercise training was considered in which the participants performed partially or fully intervention training with supervision by an exercise training specialist. Interventions with only exercise advice (lifestyle counseling), yoga, stretching or breathing exercises were excluded.

Non-exercising control interventions

As a comparator intervention, a group of the participants who did not perform any type of regular exercise training was included. Considering the characteristics of habitual prenatal care, participants who received diet interventions, exercise advice or were not excluded.

Outcomes assessment

The outcomes of interest were measurements of changes in fasting glucose, 2-hour post meal glucose and HOMA2-IR index that could be assessed by different measurement methods (i.e., blood or capillary samples, made by study evaluators or patients at home). The HOMA2-IR index was performed accessing fasting glucose and insulin blood results, by author's own calculation using the software “HOMA Calculator V2 2.2”. [14] Units were standardized to mmol/L for glycemia and μUI/ml for insulin.

The outcomes of interest used on analysis were outcomes performed any time before the intervention and the last measurements performed during pregnancy intervention or capillary glucose measures means performed during the intervention. Glycated hemoglobin was initially intended to be analyzed, however, only one of the 11 studies included HbA1c as an outcome.

Search strategy

We systematically searched in PubMed, Cochrane Central, Embase, Scielo, and LILACS databases until July 2022. In the search strategy, we used the terms “Pregnancy”, “Exercise”

“Resistance Training”, "Combined training" and "Randomized clinical trials”, complementing with the addition of keywords (synonyms) and MeSH/ DeCS terms through boolean operators (AND/OR). The complete search strategy that was used in all databases is detailed in the supplementary table S1.

Previous systematic reviews of related topics were also searched for relevant studies and references of identified potentially relevant studies were manually searched for inclusion of additional studies. [15-17] In addition, to search the gray literature (unpublished studies) we used Google Scholar website (URL: https://scholar.google.com) to identify possible studies eligible for inclusion in the review. There was no language or year of study limitation in our search, however we found only studies published in English or Portuguese that met the eligibility criteria. All searches were conducted by the same author (P.A.F.), the search results were collated using EndNote software (Thomson Reuters, New York), and duplicates were removed.

Selection and Data collection process

The screening was carried out independently, following the exclusion of duplicate articles by two reviewers blind (P.A.F. and V.M.S.). Initially, these authors screened titles and abstracts to identify potentially relevant articles according to the eligibility criteria described above. Any study selected for the next step of the evaluation was analyzed in full text and considered if, after the randomization, reported pre-post intervention glucose changes after an exercise training intervention versus a control group. Studies with some populations of interest (gestational diabetes participants) or that mentioned this outcome on title or abstract were included for full text reading.

Disagreements regarding the eligibility of the studies were resolved by consensus and, eventually, by a third reviewer (R.F.). The study selection process followed the PRISMA flowchart in figure 1.

The authors (P.A.F. and V.M.S.) independently performed data extraction using a standardized form in Microsoft Excel (2020). Data regarding the characterization of the sample (number of participants included in the analysis, comorbidities, age, gestational age, athletic category, BMI, baseline outcomes of interest values) were extracted, protocol adherence (session attendance [%]), sample loss rate (participants dropout [%]), variables of the training interventions (frequency, volume, frequency, follow-up, intensity, and type) and method of outcomes assessment used in each study were also collected. Data of glucose expressed on mg/dL were standardized for mmol/L and insulin (for HOMA2-IR calculation) were standardized for µUI/ml. Data were extracted and measures of dispersion (standard deviation, standard error, confidence interval) or the mean difference before and after the training period for glycemia results of interventions (i.e., exercise training and control groups). If there was not enough information, the authors of these studies (n=1) were contacted via e-mail. If authors didn't responde, data showed on previous reviews were used.

Methodological quality

The methodological quality of the included studies was assessed using the "Tool for the assEssment of Study qualiTy and reporting in EXercise" (TESTEX) checklist, two reviewers (P.A.F. and V.M.S.) evaluated each study and they worked independently. [18] The checklist has two sections that refer to study quality (items 1–5) and study reporting (items 6–12). Each item on the TESTEX checklist is answered with a "yes" if the criteria are satisfied or with a "no" if the criteria are not satisfied (only the answer "yes" is associated with a point). Items 6 and 8 have three and two questions, respectively. The answer "yes" to each of these subquestions is also associated with a point. Therefore, the maximum number of possible points on the checklist is 15. Based on the summary scores, we classified studies from 0 to 5 points as a low-quality study, from 16 to 10 points as a medium quality study, and from 11 to 15 points as a high-quality study.

Data synthesis and statistical analysis

Effect sizes were calculated based on the change score (mean difference, MD) with a 95% confidence interval (95% CI) between baseline and follow-up (at the end of intervention during pregnancy or mean values performed during intervention) measures to demonstrate the clinical impact of combined and resistance training. Random effects models were used because great heterogeneity was expected due to the different methodological and population characteristics variations of the studies. Primarily, a pooled analysis of exercise training versus the control group on the effects on fasting glucose, 2 hour post meal glucose and HOMA2-IR index were conducted. P values ≤0.05 were considered statistically significant. Heterogeneity was assessed using the Cochran Q (chi2) test, with P ≤0.05 indicating statistically significant heterogeneity between treatment effects. The extent of heterogeneity was quantified using the inconsistency index (I2), and values >50% were considered to represent substantial heterogeneity. [19] Subgroup analyses were performed to investigate possible factors that promoted statistical heterogeneity in our analysis. We assumed that different characteristics of population, use of hypoglycemic agents, gestational age, different baseline glucose values, assessment methods and assessment of glucose values as the primary or secondary outcomes may have influenced heterogeneity. Publication bias was assessed by visually examining the asymmetry of the funnel plot of the fasting glucose analysis variable. The Egger's test was used on fasting glycemia to verify the funnel asymmetry, being considered significant when P ≤ 0.05. [20] Statistical analysis and the forest plots were performed in OpenMeta Analyst Software version 10.1030.

RESULTS

Study characteristics

A total of 4969 records were retrieved from database searches, of which 1744 records were duplicates. A further 2941 records were eliminated after the screening of titles and abstracts. Ten potentially relevant articles were identified from the screening of systematic review and gray literature reference lists. After screening the full text of 294 articles (284 via databases and 10 other methods), 11 randomized clinical trials were included in this review. The flowchart of study selection is shown in figure 1.

Exercise training effect on fasting glucose

The fasting glucose (n=11 interventions) results are presented in figure 2. When compared to the control, exercise training reduced fasting glucose (MD: -0.11 mmol/L, 95% CI: -0.19 to -0.03, $P < 0.01$). There was significant heterogeneity between studies ($I2 = 87.61\%$, P for heterogeneity <0.01). Figure 2 shows the forest plots for fasting glucose.

Exercise training effect on 2-hour post meal glucose

The 2-hour post meal glucose (n=5 interventions) results are presented in figure 3. When compared to the control, exercise training reduced 2-hour post meal glucose (MD: -0.38 mmol/L, 95% CI: -0.56 to -0.21, $P < 0.01$). There was significant heterogeneity between studies ($I2 = 89.19\%$, P for heterogeneity <0.01). Figure 3 shows the forest plots for 2-hour post meal glucose.

Exercise training effect on HOMA2-IR index

The HOMA2-IR index (n=4 interventions) results are presented in figure 4. When compared to the control, exercise training didn’t significantly reduce HOMA2-IR index (MD: -0.05, 95% CI: -0.22 to 0.11, $P = 0.52$). There was significant heterogeneity between studies ($I2 = 98.09\%$, P for heterogeneity <0.01). Figure 4 shows the forest plots for fasting glucose HOMA2-IR index.

Quality assessment (Risk of bias) and publication bias

Supplementary Material Figure S1 presents the results of the quality assessment. The average score on the checklist was 6 points (range 4-14 points). Based on the qualitative classification, 10 studies presented low methodological quality, and 1 medium methodological qualities. Egger's regression test showed publication bias for exercise training in the analysis of fasting glucose (see Figure S2 and S3 in Supplementary material). Egger’s regression test wasn’t performed on 2-hour post meal glucose and HOMA2-IR index because of the low number of studies.

Subgroup analysis

Table 1 displays the results of the subgroup analysis, we found that the population and type of training can influence the magnitude of glucose reduction after exercise training. Regarding population, gestational diabetes participants had greater fasting glucose reduction. Considering training analysis, resistance training has greater fasting and 2-hour post meal glucose reductions. Only 1 study with non-gestational diabetes mellitus participants had values of 2-hour post meal glucose, so subgroup analyses of 2-hour post meal regarding population (gestational diabetes or non-gestational diabetes) wasn’t performed.

DISCUSSION

The purpose of our study was to evaluate the efficacy of resistance or combined training on reduction of glucose and insulin resistance in pregnancy. We found a reduction in fasting glucose of -0.11 mmol/dL and in 2-hour post meal glucose of -0.38 mmol/dL, favoring the exercise training versus a control group without exercise. The findings in the present review could be clinically important, considering consistent associations with increased fasting glucose and 2-hour post meal glucose and pregnancy and neonatal outcomes. The HAPO (Hyperglycemia and Adverse Pregnancy Outcomes), a cohort study with 25.000 pregnant women, showed that small increases (0,4mmol-L) of glycemia have significant effects on pregnancy and neonatal outcomes. [21] Another substantial cohort with 97.032 participants confirmed that lower levels of maternal glycemia (compared to population in general) were associated with adverse outcomes, showing association with increased fasting glucose alone to twofold increased risk of larger for gestational age fetus. [22] Postprandial plasma glucose excursions have been suggested as an important variable for pregnant women, directly correlated with HbA1c. Considering the limited time frame of pregnancy, and the clinical interpretation of HbA1c (an estimation of 8-12 past glucose control weeks) in pregancy scenario, this may be a more relevant marker than HbA1c, highlighting the importance of our findings.[23] The clearly clinical significance of our results in pregnancy remains unknown on literature. [13]

Exercise is an effective method for prevention of gestational diabetes and reduces the chances of developing diabetes mellitus type 2 in the long term, and gestational diabetes management has gradually become the focus of different studies. [13] Approximately 39% of gestational diabetes patients fails on diet treatment alone, requiring insulin for control of glycemia, so adding exercise as a co treatment can be effective and delay or even avoid the necessity for insulin. [24]

Aerobic exercise has been shown to have positive effects in pregnancy glycemia. Exercises with aerobic interventions (i.e., walking, cycling) performed three times a week with moderate intensity showed that the fasting glucose and insulin levels were reduced in the intervention group. [5][6] Therefore, considering exercise benefits, it is important to achieve the recommended level of international gestational exercise, what could become a challenge in pregnancy, due to the gestational weight gain, shift of the center of gravity and discomfort associated with unstable movements. [25] Resistance training emerges as an option, as it is an effective strategy to improve overall metabolic health and reduce metabolic risk factors and enhances expression of muscle proteins involved on insulin sensitivity and glucose uptake on larger muscles in diabetic patients. [26] The findings of this study on reduction of fasting glycemia and 2-hour post meal glucose confirmed previous reviews. [15-17].

The results of the analyses showed significant heterogeneity. By subgroups analyses, the heterogeneity was explained by the characteristics of the population (gestatioanl diabetes or non-gestational diabetes participants) and by different types of exercise training (resistance training performed alone or combined to aerobic exercise) on fasting glucose and 2-hour post meal glucose.

In contrast to our working hypotesis and in accordance with previous studies on patients with diabetes no reduction on HOMA2-IR index after exercise compared to control was found. [27][28] We speculate that the lack of trials and diversity of training interventions could partially help to explain it. The sensitivity of measures and the heterogeneity of baseline measures between studies could also help to justify this result.

Limitations of these study included lack of evidence, diversified population (gestational diabetes, obese and overweigh participants), diversified gestational age at recruitment, outcome measures and interventions. Fasting glucose measures were performed by diversified methods (blood sample, capillary sample) and at diversified times of intervention. Two studies performed fasting glucose measures were as a median of home monitored blood glucose values, while in other studies blood samples were assessed pre and post intervention. [8, 29] Although adherence is considered necessary to achieve the potential benefits of the exercise interventions, only few studies evaluated adherence and four trials contained interventions that weren't supervised, although had some type of control of home exercises (phone calls and text reminders).

It is important to highlight that actual exercise in pregnancy recommendations on available guidelines are based in evidence of clinical trials, so the quality of trials enhance guideline execise recommendations. The trials eligible on our study presented quality of the evidence analyzed by TESTEX between 'low' and 'medium'. The present study suggests that these findings could be used to design randomized clinical trials to evaluate the effects of resistance exercise with different intensity, duration, and other variables of training. It may improve guidelines for resistance training and popularize its application in glucose management in pregancy. Moreover, few studies have evaluated the effect of exercise on pregnancy outcomes, which further restricts our understanding of the real role of exercise training.

CONCLUSION

Our findings suggest that the resistance training alone is an effective intervention to reduce fasting glucose and postprandial glucose during pregnancy, especially in women with gestational diabetes.

Acknowledgements

None declared.

Conflict of interest

None declared.

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Tables

Table 1. Subgroup analysis of change in fasting glucose and 2-hour post meal glucose

Subgroup	Number of interventions	Number of participants ET	CG	Mean difference [95% CI]	P values	Heterogeneity
Fasting glucose						
Population						
GDM	6	184	191	-0.14 [-0.20 to -0.08]	**<0,001**	I² = 0%, P = 0.71
No-GDM	5	539	512	-0.06 [-0.18 to 0.06]	0.322	I² = 93.81%, P < 0.001
Training						
Resistance	3	87	90	-0.13 [-0.20 to -0.05]	**<0,001**	I² = 0%, P = 0.39
Combined	8	636	633	-0.09 [-0.19 to 0.01]	0.080	I² = 90.14%, P < 0.001
2h post meal glucose						
Training						
Resistance	3	87	90	-0.20 [-0.29 to -0.11]	**<0,001**	I² = 0%, P = 0.41
Combined	8	636	633	-0.51 [-0.97 to -0.05]	0.028	I² = 94.4%, P < 0.001

GDM - Gestational Diabetes Mellitus ET - Exercise Training CG - Control Group

Table 2. The general characteristics of the studies

Author year	Sample Size	Health	IG (weeks)	Components of exercise interventions						Main Findings
				Type	**Duration (min)**	**Totally Supervised by Instructor**	**Frequency n/week**	**Intensity**	**Total period (weeks)**	
Allman et al. (2021)	80 (EC=40 GC=40)	Obesity	12	**CT** walking, cycling, elliptical **RT**: circuit; major muscle groups	30-45	Yes	3	Moderate	~12	FG and HOMA2-IR means didn't change
Brankston et al. (2004)	24 (EC=16 GC=16)	GDM + Obesity	26-32	**RT:** circuit; rubber tubing	not described	No (3 inicial sessions supervised)	3	Moderate	Recruitment untill birth	Less rate of insulin injection and insulin dosage in EG
Daly et al. (2017)	76 (EC=42 GC=34)	Obesity	13	**CT** aerobic **RT**: weights	50-60	Yes	3	Moderate	~12	FG means didn't change; less GWG in EG
de Barros et al. (2010)	64 (EC=32 GC=32)	GDM	24-34	**RT:** circuit; elastic bands	30-40	No (1x/week supervised)	3	Moderate	Recruitment untill birth	FG, 2hPPG and rate of insulin injection decreased in EG
Fernández-Buhigas et al. (2020)	92 (EC=41 GC=51)	None specified	<16	**CT** aerobic **RT**: light weights	35	Yes	3	Moderate	Recruitment untill birth	FG means didn't change
Huifen et al. (2022)	89 (EC=43 GC=46)	GDM	24-31	**RT:** major muscles; light weights	50-60	Yes	3	Moderate	Minimum of 6 weeks	Glucose control means and use of insulin decreased in EG

CT = Combined Training RT = Resistance Training RPE = Rating of Perceived Exertion GDM: Gestational Diabetes IG = Gestational Age at recruitment
FG = Fasting Glucose 2hPPG = 2-hour post meal glucose BCAA = branched-chain amino acid GWG = Gestational Weight Gain

cont Table 2. The general characteristics of the studies

Author year	Sample Size	Health	IG (weeks)	Components of exercise interventions						Main Findings
				Type	Duration (min)	Totally Supervised by Instructor	Frequency n/week	Intensity	Total period (weeks)	
Kasemi et al. (2017)	22 (EC=11 GC=11)	GDM	24	**CT (water)** aerobic **RT**: circuit elastic bands	25-40	Yes	3	Moderate	6	FG decreased and HOMA b increased
Kokic et al. (2018)	38 (EC=18 GC=20)	GDM	not described	**CT** treadmill **RT**: light weights, elastic bands	50-55	Yes	2	Moderate	Minimum of 6 weeks	2hPPG decreased and FG didn't change
Oostdam et al. (2012)	101 (EC=49 GC=52)	Obesity	14-20	**CT** walking, cycling **RT**: strenght of major muscle groups	60	Yes	2	Moderate	Recruitment untill birth	FG and HOMA2-IR means didn't change
Stafne et al. (2012	702 (EC=375 GC=327)	None specified	20	**CT** group aerobic class **RT**: body weight	60	No	1	Moderate	12	Rates of GDM and HOMA index didn't change
Wu et al. (2021)	138 (EC=68 GC=70)	GDM	24-28	**CT** aerobic + **RT**: light weights	not described	No	7	Moderate	4	FG and 2hPPG decreased in IG

CT = Combined Training   RT = Resistance Training RPE = Rating of Perceived Exertion GDM: Gestational Diabetes   IG = Gestational Age at recruitment
FG = Fasting Glucose 2hPPG = 2-hour post meal glucose BCAA = branched-chain amino acid   GWG = Gestational Weight Gain

Figures

Figure 1. PRISMA flow diagram

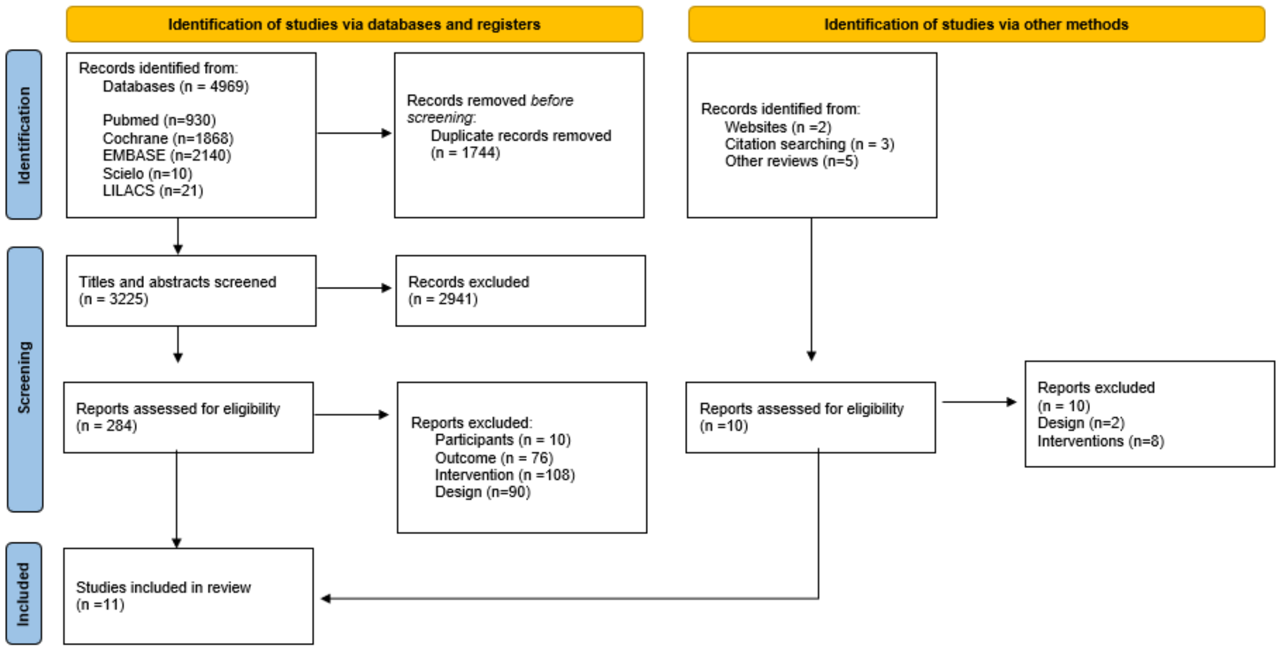


Figure 2. Random-effects meta-analysis of the effects of exercise training versus control group in the reduction of fasting glucose.

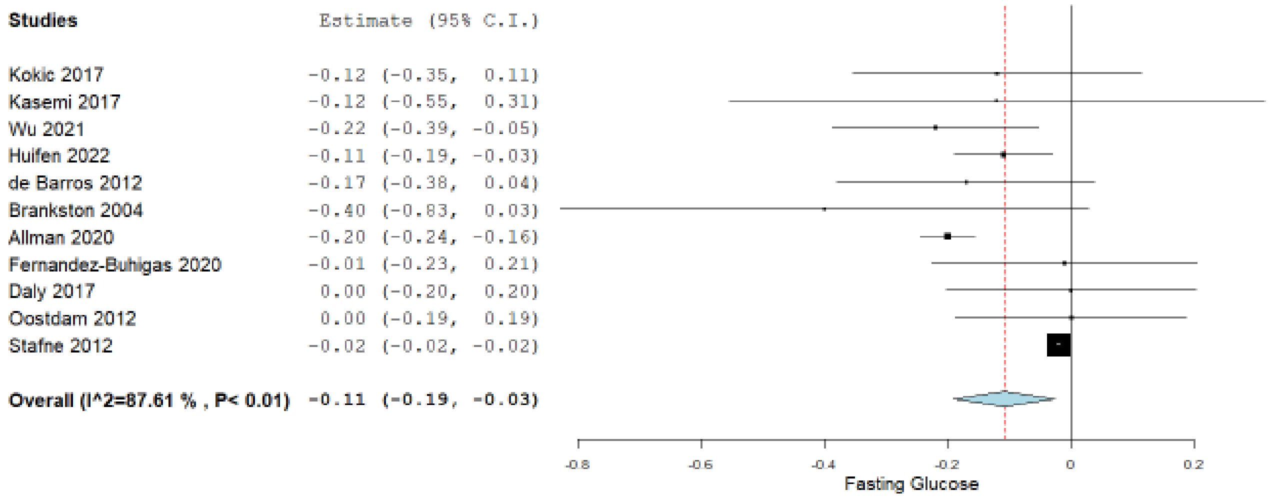


Figure 3. Random-effects meta-analysis of the effects of exercise training versus control group in the reduction of 2-hour post meal glucose.

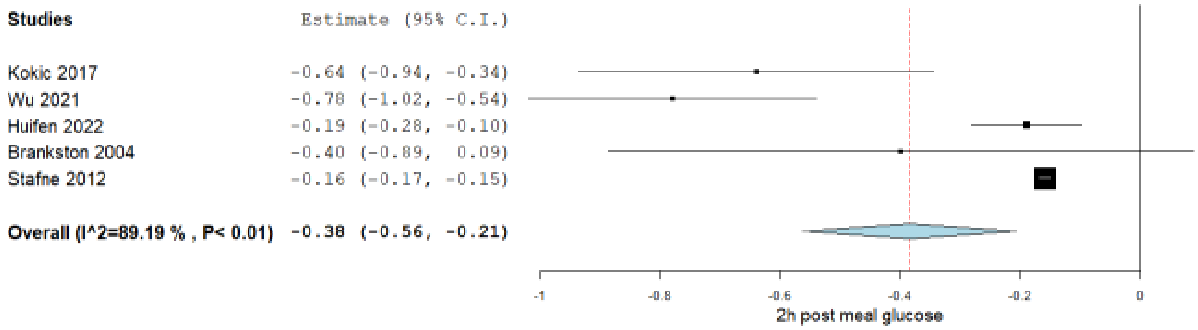
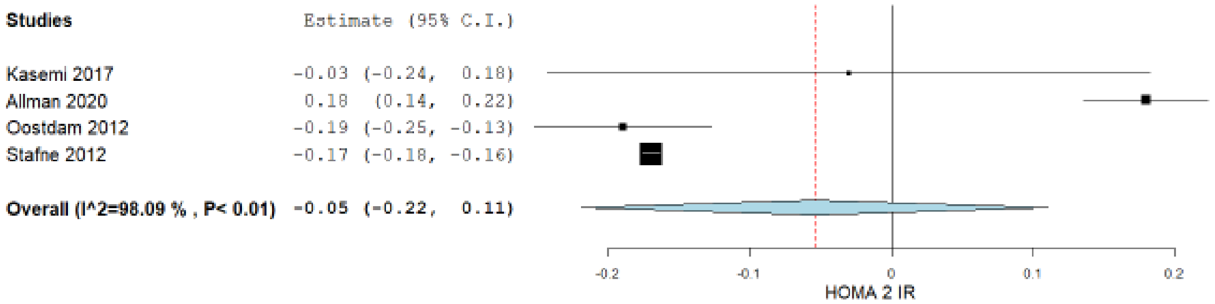


Figure 4. Random-effects meta-analysis of the effects of exercise training versus control group in the reduction of HOMA2-IR index.



Material Suplementar do Artigo

Supplementary Material Table S1. Literature search strategy used for all databases

PubMed

("pregnancy"[MeSH Terms] OR ("gestate"[All Fields] OR "gestated"[All Fields] OR "gestates"[All Fields] OR "gestating"[All Fields] OR "gestational"[All Fields] OR "gestations"[All Fields] OR "pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "gestation"[All Fields]) OR ("gestate"[All Fields] OR "gestated"[All Fields] OR "gestates"[All Fields] OR "gestating"[All Fields] OR "gestational"[All Fields] OR "gestations"[All Fields] OR "pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "gestation"[All Fields]) OR "pregnant women"[All Fields] OR ("gravidity"[MeSH Terms] OR "gravidity"[All Fields] OR "pregnant"[All Fields] OR "pregnants"[All Fields])) AND ("resistance training"[MeSH Terms] OR "resistance exercise"[All Fields] OR "Strength Training"[All Fields] OR "body-weight exercise"[All Fields] OR "combined exercise"[All Fields] OR "combined training"[All Fields] OR "concurrent training"[All Fields] OR "circuit based exercise"[MeSH Terms] OR "exercise"[MeSH Terms] OR "exercise therapy"[MeSH Terms]) AND ("clinical trials as topic"[MeSH Terms] OR "randomized controlled trials as topic"[MeSH Terms] OR "random allocation"[MeSH Terms] OR "clinical trials as topic"[MeSH Terms] OR "controlled clinical trials as topic"[MeSH Terms] OR "randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "clinical trial"[Title/Abstract] OR "random"[Title/Abstract])

EMBASE

('pregnancy' OR 'gestation period' OR 'pregnant woman') AND ('resistance training' OR 'exercise' OR 'strength training' OR 'body-weight exercise' OR 'combined exercise' OR 'combined training' OR 'concurrent training' OR 'circuit based exercise' OR 'exercise therapy')

AND ('clinical trial' OR 'controlled clinical trial' OR 'randomized controlled trial' OR 'clinical trial (topic)' OR 'trial')

Cochrane

#1 (pregnancy OR gestate OR gestational OR "pregnant women" OR pregnant) 83686

#2 ("resistance training" OR "resistance exercise" OR "Strength Training" OR "body-weight exercise" OR "combined exercise" OR "combined training" OR "concurrent training" OR "circuit based exercise" OR exercise OR "exercise therapy") 117603

#3 ("clinical trials as topic" OR "randomized controlled trials" OR "random allocation" OR "clinical trials" OR "controlled clinical trials as topic" OR "randomized controlled trial" OR "controlled clinical trial" OR "clinical trial") 1349810

#4 #1 AND #2 AND #3 2360

Scielo

(pregnancy OR gestate OR gestational OR "pregnant women" OR pregnant) AND ("resistance training" OR "resistance exercise" OR "Strength Training" OR "body-weight exercise" OR "combined exercise" OR "combined training" OR "concurrent training" OR "circuit based exercise" OR exercise OR "exercise therapy") AND ("clinical trials as topic" OR "randomized controlled trials" OR "random allocation" OR "clinical trials" OR "controlled clinical trials as topic" OR "randomized controlled trial" OR "controlled clinical trial" OR "clinical trial" OR trial OR random)

LILACS

pregnancy OR gestate OR gestational OR "pregnant women" OR pregnant [Palavras] and "resistance training" OR "resistance exercise" OR "Strength Training" OR "body-weight exercise" OR "combined exercise" OR "combined training" OR "concurrent training" OR "circuit based exercise" OR exercise OR "exercise therapy" OR "atividade física" [Palavras] and "clinical trials as topic" OR "randomized controlled trials" OR "random allocation" OR "clinical trials" OR "controlled clinical trials as topic" OR "randomized controlled trial" OR "controlled clinical trial" OR "clinical trial" OR trial OR random

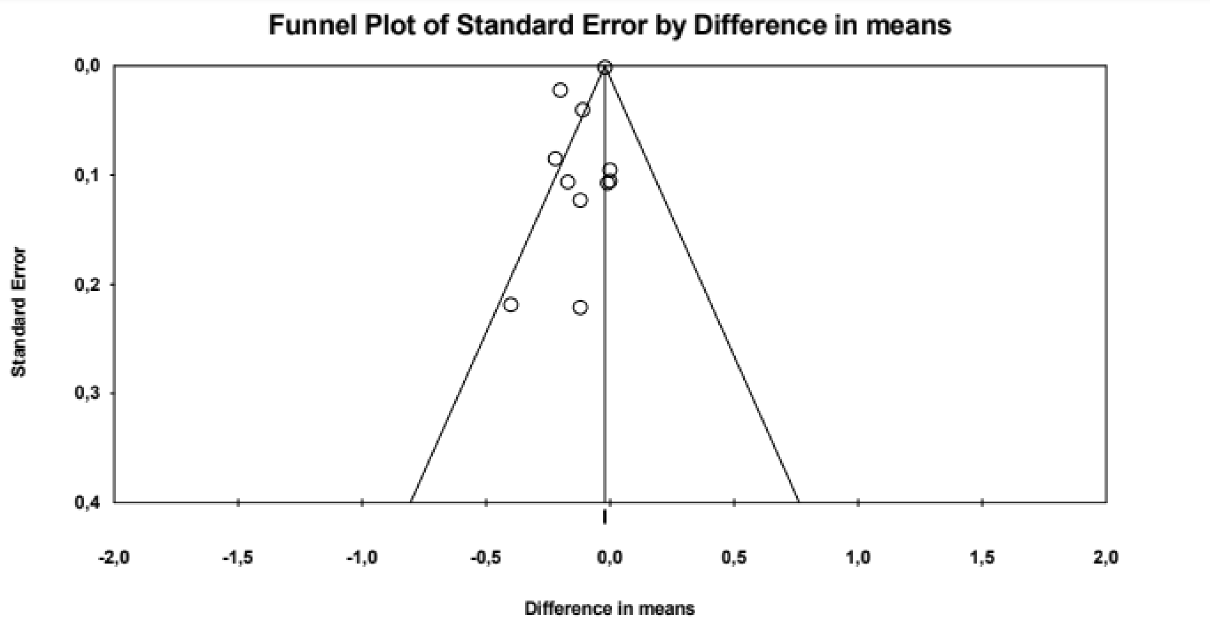
Supplementary Material Figure S1. The methodological quality of studies included in the meta-analysis.

Reference	Year	Study Quality					Score (0-5)	Study Reporting												Score (0-10)	Total Score (0-15)
		1	2	3	4	5		6a	6b	6c	7	8a	8b	9	10	11	12		
Allman	2020	+	+	-	+	-	3	-	+	-	+	+	+	+	+	-	+	7	10
Brankston	2008	+	+	+	-	-	3	-	-	+	-	+	+	+	-	-	-	4	7
Daly	2008	+	+	-	+	-	3	-	+	+	+	+	+	+	-	-	-	6	9
de Barros	2016	+	+	-	+	-	3	-	-	-	-	+	+	-	-	+	-	3	6
Fernandez	2013	+	-	-	+	-	2	-	-	+	-	+	+	-	-	-	-	3	5
Huifen	2010	+	-	-	+	-	2	-	+	-	-	+	+	-	-	-	-	3	5
Kasemi	2020	-	+	-	+	-	2	-	-	-	+	+	+	-	-	-	-	3	5
Kokic	2012	-	+	-	+	+	3	-	-	-	+	+	-	-	-	+	-	3	6
Oostdam	2020	+	+	-	+	+	4	-	-	-	-	+	+	+	-	-	-	3	7
Stafne	2020	-	-	-	+	-	1	-	-	+	-	+	+	-	-	-	-	3	4
Wu	2012	+	+	-	+	-	3	-	+	-	-	+	+	+	-	-	+	4	7

Study quality: 1 = Eligibility criteria specified; 2 = Randomization specified; 3 = Allocation concealment; 4 = Groups similar at baseline; 5 = Blinding of assessor (for at least one key outcome)

Study reporting: 6 = Outcome measures assessed in 85% of participants (6a = 1 point if completion rate is [85%; 6b = 1 point if adverse events are reported; 6c = 1 point if exercise attendance is reported); 7 = Intention-to-treat analysis; 8 = Between-group statistical comparisons reported (8a = 1 point if between-group statistical comparisons are reported for the primary outcome measure of interest; 8b = 1 point if between-group statistical comparisons are reported for at least one secondary outcome measure); 9 = Point measures and measures of variability for all reported outcome measures; 10 = Activity monitoring in control groups; 11 = Relative exercise intensity remained constant; 12 = Exercise volume and energy expenditure

+ meet the criteria; - do not meet the criteria



Supplementary Material Figure S2. Funnel plot of the effect of exercise training versus control group for blood fasting glucose. The solid line represents the pooled effect estimate expressed as the mean difference (MD) for each analysis. Dashed lines present pseudo-95% confidence intervals and the circles represent effect estimates for each included study.

Supplementary Material Figure S2.

Regression test for Funnel plot asymmetry ("Egger's test")

	z	**p**
sei	-1,64	0,03500

6. CONSIDERAÇÕES FINAIS

A hiperglicemia na gestação possui considerável morbidade materna e fetal associadas e elevada prevalência. Mudanças no estilo de vida através de exercícios físicos são essenciais para o controle glicêmico em gestantes. Os resultados desta dissertação confirmam a eficácia do treinamento resistido na redução da glicemia de gestantes, especialmente naquelas sob maior risco de hiperglicemia.