Exercise during pregnancy and risk of gestational hypertensive disorders: a systematic review and meta-analysis

DR GABRIELE SACCONE (Orcid ID : 0000-0003-0078-2113)

DR VINCENZO BERGHELLA (Orcid ID : 0000-0001-7420-1807)

Article type : Systematic review

Exercise during pregnancy and risk of gestational hypertensive disorders: a systematic review and meta-analysis

Running title: Exercise during pregnancy for gestational hypertensive disorders

Elena Rita Magro-Malosso[1], Gabriele Saccone[2] , Mariarosaria Di Tommaso[1], Amanda Roman[3] & Vincenzo Berghella[3]

[1]Department of Health Science, Division of Pediatrics Obstetrics and Gynecology, Careggi Hospital University of Florence, Florence, [2]Department of Neuroscience Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy [3]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA

Correspondence

Vincenzo Berghella

Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Thomas Jefferson University, 833 Chestnut, Philadelphia, PA 19107, USA.

E-mail: vincenzo.berghella@jefferson.edu

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/aogs.13151

Disclosure: The authors report no conflict of interest

Abstract

Introduction: Gestational hypertensive disorders, including gestational hypertension and preeclampsia, are one of the leading causes of maternal morbidity and mortality. The aim of our study was to evaluate the effect of exercise during pregnancy on the risk of gestational hypertensive disorders. *Material and methods:* Electronic databases were searched from their inception to February 2017. Selection criteria included only randomized controlled trials of uncomplicated pregnant women assigned before 23 weeks to an aerobic exercise regimen or not. The summary measures were reported as relative risk (RR) with 95% confidence intervals (CI). The primary outcome was the incidence of gestational hypertensive disorders, defined as either gestational hypertension or preeclampsia. *Results:* Seventeen trials, including 5,075 pregnant women, were analyzed. Of them, seven contributed data to quantitative meta-analysis for the primary outcome. Women who were randomized in early pregnancy to aerobic exercise for about 30-60 minutes 2-7 times per week had a significant lower incidence of gestational hypertensive disorders (5.9% vs 8.5%; RR 0.70, 95% CI 0.53 to 0.83; 7 studies, 2,517 participants), specifically a lower incidence of gestational hypertension (2.5% vs 4.6%; RR 0.54, 95% CI 0.40 to 0.74; 16 studies, 4,641 participants) compared to controls. The incidence of preeclampsia (2.3% vs 2.8%; RR 0.79, 95% CI 0.45 to 1.38; 6 studies, 2,230 participants) was similar in both groups. The incidence of cesarean delivery was decreased by 16% in the exercise group. *Conclusions:* Aerobic exercise for about 30-60 minutes 2-7 times per week during pregnancy, as compared to being more sedentary, is associated with a significantly reduced risk of gestational hypertensive disorders overall, gestational hypertension, and cesarean delivery.

Key words

physical activity, exercise in pregnancy, preterm birth, hypertension, obesity

Abbreviations:

RCT randomized controlled trial

RR relative risk

CI confidence interval

Key message

Exercise during pregnancy reduces the risk of gestational hypertensive disorders.

Introduction

Gestational hypertensive disorders, including gestational hypertension and preeclampsia, are one of the leading causes of maternal morbidity and mortality (1). Hypertensive disorders may result in fetal complications such as growth restriction, oligohydramnios, placental abruption, preterm birth and perinatal death (2).

Risk factors associated with hypertensive disorders include, among others, a previous history of preeclampsia, nulliparity, obesity or excessive weight gain in pregnancy, diabetes mellitus, inherited or acquired thrombophilia, and advanced maternal age (3,4). Although the etiology of preeclampsia is not completely known, several studies suggest that the endothelial dysfunction is involved in the development of this disease (2, 5). Exercise in pregnancy, reducing oxidative stress, may improve endothelial function and could theoretically reduce the risk of preclampsia (5).

Few studies have evaluated the impact of exercise in pregnancy on gestational hypertensive disorders as primary outcome. A recent randomized controlled trial (RCT) showed that maternal exercise may be a preventative tool for hypertension (6). However, there is limited evidence on the possible association between the effect of exercise during pregnancy and the risk of gestational hypertension and preeclampsia.

The aim of this systematic review and meta-analysis was to evaluate the effect of exercise during pregnancy on the risk of gestational hypertensive disorders as a primary outcome.

Material and methods

This meta-analysis was performed according to a protocol recommended for systematic review (7). The review protocol was designed a priori defining methods for collecting, extracting and analyzing data. The research was conducted using MEDLINE, EMBASE, Web of Sciences, Scopus, ClinicalTrials.gov, OVID and Cochrane Library as electronic databases. The trials were identified with the use of a combination of the following text words: "exercise" or "physical activity" or "high risk pregnancy" or "hypertensive disorders" or "gestational hypertension" or "preeclampsia," with "randomized trial" as publication type, from the inception of each database to February 2017. Review of articles also included the abstracts of all references retrieved from the search. No language restriction was applied.

Study selection

Selection criteria included only (RCTs of pregnant women randomized to an exercise regimen or not. We included only RCTs on singleton pregnancies without any obstetric contraindication to physical activity reporting data on gestational hypertensive disorders. All women who developed gestational hypertension or preeclampsia were included in the meta-analysis, even if at times they might have been excluded from the main analysis in the original RCT. Therefore, all women randomized were included as denominator in the meta-analysis, even if they were excluded in some analyses of certain RCTs during follow-up. In all the trials, the intervention group participated in planned aerobic exercise. In the control group, women did not participate in exercise sessions and attended regular scheduled obstetric visits. RCTs including only diet, exercise counseling, or weight monitoring, those assessing reduction in exercise and those only in at-risk populations (e.g. all women were smokers) were excluded. Quasi-randomized trials (i.e. trials in which allocation was done on the basis of a pseudo-random sequence, e.g. odd/even hospital number or date of birth, alternation) were also excluded.

The risk of bias in each included study was assessed by using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (7). Seven domains related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with biased estimates of treatment effect: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting; and 7) other bias. Review authors' judgments were categorized as "low risk," "high risk" or "unclear risk" of bias (7).

Data extraction and outcomes

All analyses were done using an intention-to-treat approach, evaluating women according to the treatment group to which they were randomly allocated in the original trials. The primary outcome was the incidence of gestational hypertensive disorders, defined as either gestational hypertension or preeclampsia. Secondary outcomes were incidence of gestational hypertension, and preeclampsia.

We also assessed the following posthoc secondary outcomes: cesarean delivery, gestational age at delivery, and neonatal outcomes including birth weight, and APGAR score at 1 and at 5 minutes.

We planned to calculate the primary outcome (i.e. gestational hypertensive disorders) in subgroup analyses including trials with only aerobic exercise as intervention. This subgroup analysis therefore included trials in which no dietary measures were included.

Statistical analyses

Data analysis was completed using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Center, Cochrane Collaboration, 2014). Statistical heterogeneity between studies was assessed using the Higgins I^2 statistics. In case of statistical significant heterogeneity ($I^2 \geq 50\%$), the random effects model of DerSimonian and Laird was used to obtain the pooled risk ratio estimate; otherwise, in case of no inconsistency in risk estimates ($I^2 < 50\%$), a fixed effect models was used (7). The summary measures were reported as relative risk (RR) or as mean difference with 95% confidence intervals (CI). Potential publication biases were assessed graphically by using the funnel plot of the primary outcome, and statistically by using Begg's and Egger's tests. A p value < 0.05 was considered statistically significant.

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement (8). Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42016041926).

Two authors (EMM, GS) independently assessed inclusion criteria, risk of bias, data extraction and data analysis. Disagreement was resolved by discussion with a third reviewer (VB). Data not presented in the original publications were requested from the principal investigators.

Results

Seventeen RCTs, including 5,075 women with singleton pregnancy were included in the meta-analysis (Figure 1) (6,9-24).

All the included studies used had low risk of bias in "random sequence generation" and "incomplete outcome data." High risk of reporting bias was not found in any of the included trials (Figure 2).

Figure 3 shows the funnel plot for the primary outcome for assessing publication bias; the symmetric plot suggests no publication bias. Publication bias, assessed using Begg's and Egger's tests, was not significant (p=0.21 and 0.33, respectively).

Six trials (9, 10, 13, 14, 19, 20) reported randomized women who could not continue the study for different reasons, including gestational hypertension disorders; we did include these cases in our meta-analysis (Table 1). Gestational age at randomization was for all studies on the first trimester except in three trials in which women were randomized also or only during second trimester (11, 17, 23). The intervention program included aerobic exercise and dietary counseling in five RCTs (12,16-18,24), aerobic exercise and dietary intervention by a dietitian in one study (22) and only aerobic exercise in ten studies (6,9-11, 13-15, 19-21). One trial (23), randomized pregnant women in 3 groups: physical activity and dietary intervention (group 1); physical activity intervention (group 2); standard care (group 3) (Supporting Information Table S1). We included both physical activity groups, with and without dietary intervention, in the exercise group. One trial (15) randomized women in 3 groups: exercise initiated at 13 weeks (group 1); exercise initiated at 20 weeks (group 2); no supervised exercise (group 3). We included both groups, exercise initiated at 13 weeks and at 20 weeks, in the intervention group (Table S1).

The definition of preeclampsia was different among the trials. Eight trials defined preeclampsia as gestational hypertension plus proteinuria within 7 days of each other, HELLP syndrome, or eclampsia. Seven trials did not define preeclampsia. One defined preeclampsia as blood pressure of 140/90 mm Hg or higher for the first time during pregnancy with proteinuria, and one defined it as proteinuria and persistently elevated blood pressure greater than 140/90mm Hg on more than one occasion (Table 1).

All studies included only uncomplicated singleton pregnancies randomized <23 weeks to an aerobic exercise regimen or not. Women were excluded at randomization in case of any obstetric contraindications to exercise, mostly as recommended by the American Congress of Obstetricians and Gynecologists (ACOG) (25) (Supporting Information Table S2). Women in the intervention group participated in aerobic exercise consisting of walking session, light-intensity to moderate-intensity exercise or aquatic exercise (Table S1). The mean time of every session was around 45 minutes (30-60 minutes) while in two trials (12,23) physical activity was recommended daily with duration not specified, and in one trial (15) the initial duration of physical activity was 15 minutes, gradually increasing over the study period according with the previous fitness level of the woman. In the control group, women did not participate in exercise sessions and only attended regular scheduled obstetric visits

Characteristics of the women included in the trials were reported in Supporting Information Table S3.

Of the 5,075 women included in the meta-analysis, 2,646 (52%) were randomized to the exercise group, and 2,429 (48%) to the control group. The statistical heterogeneity within the studies was low. Pregnant women who were randomized in early pregnancy to approximately 30-60 minutes of aerobic exercise 2-7 times per week until at least week 35 or up to delivery had a significant lower incidence of gestational hypertensive disorders, defined as gestational hypertension or preeclam

psia, (5.9% vs 8.5%; RR 0.70, 95% CI 0.53 to 0.83; 7 studies, 2,517 participants; Figure 4) and a lower incidence of gestational hypertension (2.5% vs 4.6%; RR 0.54, 95% CI 0.40 to 0.74; 16 studies, 4,641 participants) compared to controls. The incidence of preeclampsia (2.3% vs 2.8%; RR 0.79, 95% CI 0.45 to 1.38; 6 studies, 2,230 participants) was similar in both groups (Table 2).

Subgroup analyses including trials with only aerobic exercise versus no such exercise showed a significant decrease in gestational hypertensive disorders (RR 0.39, 95% CI 0.20 to 0.73) and gestational hypertension (RR 0.54, 95% CI 0.32 to 0.91) and a similar incidence of preeclampsia (RR 0.37, 95% CI 0.12 to 1.15).

Posthoc secondary outcomes, including cesarean delivery, gestational age at delivery and neonatal outcomes are reported in Table 3. Women in the exercise group had a significantly lower rate of cesarean delivery compared to women in the control group (RR 0.84, 95% CI 0.73 to 0.98).

Discussion

This pooled meta-analysis of seventeen RCTs including 5,075 women showed that aerobic exercise in singleton pregnancies is associated with a significant reduced risk of gestational hypertensive disorders overall and with a significantly reduced risk of gestational hypertension specifically. There was no difference in the incidence of preeclampsia between exercise group and controls, but the meta-analysis was underpowered to detect difference in this secondary outcome. We observed that with an α of 0.05 and 80% power, a sample size of 1,803 patients in each group is required to detect a 21% reduction in preeclampsia from a baseline risk of 2.3%.

The incidence of cesarean delivery was decreased by 16% in the exercise group. The subgroup analysis for aerobic exercise only, in which no dietary measures were included, confirmed a significant 61% decrease in gestational hypertensive disorders.

A recent Cochrane Review evaluated the effect of exercise during pregnancy on the risk of hypertensive disorders; it supports our findings (26). The authors found a reduction of maternal hypertension (not a pre-specified outcome) in women receiving diet or exercise, or both interventions, compared with the control group; they found no difference with regard to preeclampsia between the two groups. Another prior meta-analysis also found that exercise in pregnancy is associated with a significant decrease in gestational diabetes mellitus (27). A review by Wolf et al. including eleven studies evaluated leisure time physical activity and the risk of preeclampsia, but no RCTs were included (28). They found that high intensity leisure time physical activity before or during pregnancy or more than 4 hour per week of leisure time physical activity may reduce the risk of preeclampsia (28). Di Mascio et al. in a recent

meta-analysis of 9 studies, including 2,059 women, showed that in low risk uncomplicated normal-weight singleton gestations aerobic exercise can be safely performed, as this is not associated with an increased risk of preterm birth or with a reduction in mean gestational age at delivery, but is associated with higher chance of vaginal delivery and lower rate of caesarean delivery as well as lower incidence of gestational diabetes mellitus (29). Another meta-analysis by Magro-Malosso et al. found that overweight or obese women with singleton pregnancy who were randomized to 30-60 minutes 3-7 times per week during pregnancy had a reduced risk of preterm birth (30).

Our study has several strengths. This meta-analysis included all RCTs - seventeen- published so far on this topic. The studies in general were at low risk of bias according to the Cochrane risk of bias tools. The number of the included women - 5,075 - was high. The statistical heterogeneity within the studies was low. In addition, publication bias was not apparent by statistical analysis. These are key elements needed to evaluate the reliability of a meta-analysis.

The main limitation of our study was that dietary counseling was provided as additional intervention in some trials (Table 1), but subgroup analysis evaluating aerobic exercise only confirmed a statistically significant decrease in the incidence of gestational hypertensive disorders and gestational hypertension. The majority of the included studies did not properly define gestational hypertension of preeclampsia. We also acknowledge that the analysis of preeclampsia, with 2,230 women included, was underpowered statistically. Preeclampsia was indeed an uncommon outcome, with an overall rate <3%. Another limitation of our study is that seven out of the 17 studies came from the same author over a period of only a few years. He assured us that these were indeed separate studies (personal communication). Performing an analysis for an exercise dose effect was not feasible, given the lack of individual level patient data. This analysis would have added important information on the likelihood of a cause and effect relationship. The studies varied in type, duration, frequency and length of exercise programs, and whether dietary counseling was included in the study (Table 1, Table S1). The studies also varied in terms of prevalence of smoking, parity, type of employments (in terms of associated exercise activity) and BMI (Table S3). Therefore, there were many individual covariates that might have been associated with risk of hypertensive disorders that could not be controlled for. Although 17 studies were identified as relevant and included in the meta-analysis, only seven contributed data to quantitative meta-analysis for the primary outcome. Indeed, only seven trials reported data on both gestational hypertension

and preeclampsia. Information on intervention compliance was not available. While the exercise interventions were provided only to the intervention group, it may be worth noting that women randomized in the control group may have participated in self-initiated physical activity.

In summary, women without a contraindication to exercise (25), can be counseled that aerobic exercise for about 30-60 minutes 2-7 times per week during pregnancy is associated with a reduced incidence of gestational hypertensive disorders overall, gestational hypertension, gestational diabetes mellitus, and cesarean delivery. During pregnancy aerobic exercise is beneficial, and should therefore be encouraged.

Acknowledgments

The authors thank Dr. Bradley B. Price and R. Barakat for providing additional unpublished data from their trials.

Financial Support: No financial support was received for this study

References

(1) Lo JO, Mission JF, Caughey AB. Hypertensive disease of pregnancy and maternal mortality. Curr Opin Obstet Gynecol. 2013; 25:124-32.
(2) Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet. 2005;365:785-99.
(3) Wong TY, Groen H, Faas MM, van Pampus MG. Clinical risk factors for gestational hypertensive disorders in pregnant women at high risk for developing preeclampsia. Pregnancy Hypertens. 2013;3:248-53
(4) Saccone G, Berghella V, Maruotti GM, Ghi T, Rizzo G, Simonazzi G et al. Antiphospholipid antibody profile based obstetric outcomes of primary antiphospholipid syndrome: the PREGNANTS study. Am J Obstet Gynecol. 2017 Jan 30. pii: S0002-9378(17)30148-5. doi: 10.1016/j.ajog.2017.01.026. [Epub ahead of print].

(5) Genest DS, Falcao S, Gutkowska J, Lavoie JL. Impact of exercise training on preeclampsia: potential preventive mechanisms. Hypertension. 2012;60:1104-9.

(6) Barakat R, Pelaez M, Cordero Y, Perales M, Lopez C, Coteron J et al. Exercise during pregnancy protects against hypertension and macrosomia: randomized clinical trial. Am J Obstet Gynecol 2016; 214: 649.e1-8.

(7) Higgins JPT, Altman DG, Sterne JAC. Cochrane handbook for systematic reviews of interventions, version 5.1.0 (update March 2011). The Cochrane Collaboration, 2001. Available at: http://training.cochrane.org/handbook (Accessed on 20 December 2016).

(8) Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol, 2009; 62:1006-12.

(9) Barakat R, Ruiz JR, Stirling JR, Zakynthinaki M, Lucia A. Type of delivery is not affected by light resistance and toning exercise training during pregnancy: a randomized controlled trial. Am J Obstet Gynecol. 2009;201:590.e1-6.

(10) Barakat R, Pelaez M, Montejo R, Luaces M, Zakynthinaki M. Exercise during pregnancy improves maternal health perception: a randomized controlled trial. Am J Obstet Gynecol. 2011; 204:402.e1-7.

(11) Haakstad LAH, Bo K. Exercise in pregnant women and birth weight: a randomized controlled trial. BMC Pregnancy Childbirth, 2011; 30:11:66.

(12) Vinter CA, Jensen DM, Ovesen P, Beck-Nielsen H, Jørgensen JS. The LiP (Lifestyle in Pregnancy) study: a randomized controlled trial of lifestyle intervention in 360 obese pregnant women. Diabetes Care. 2011;34(12):2502-7.

(13) Barakat R, Pelaez M, Lopez C, Montejo R, Coteron J. Exercise during pregnancy reduces the rate of cesarean and instrumental deliveries: results of a randomized controlled trial. J Matern Fetal Neonatal Med. 2012; 25:2372-6.

(14) Barakat R, Cordero Y, Coteron J, Luaces M, Montejo R. Exercise during pregnancy improves maternal glucose screen at 24-28 weeks: a randomised controlled trial. Br J Sports Med. 2012;46(9):656-61.

(15) de Oliveria Melo AS, Silva JL, Tavares JS, Barros VO, Leite DF, Amorim MM. Effect of a physical exercise program during pregnancy on uteroplacental and fetal blood flow and fetal growth: a randomized controlled trial. Obstet Gynecol. 2012;120:302-10.

(16) Price B, Amini SB, Kappler K. Exercise in pregnancy: effect of fitness and obstetric outcomes – a randomized controlled trial. Med Sci Sports Exerc, 2012; 44:2263-9.

(17) Stafne SN, Salvesen KÅ, Romundstad PR, Eggebø TM, Carlsen SM, Mørkved S. Regular exercise during pregnancy to prevent gestational diabetes: a randomized controlled trial. Obstet Gynecol. 2012;119:29-36.

(18) Ruiz JR, Perales M, Pelaez M, Lopez C, Lucia A, Barakat R. Supervised exercise-based intervention to prevent gestational weight gain: a randomized controlled trial. Mayo Clin Proc, 2013; 88:1388-1397.

(19) Barakat R, Perales M, Bacchi M, Coteron J, Refoyo I. A program of exercise throughout pregnancy. Is it safe to mother and newborn? Am J Health Promot, 2014; 29:2-8.

(20) Barakat R, Pelaez M, Montejo R, Refoyo I, Coteron J. Exercise throughout pregnancy does not cause preterm delivery: a randomized, controlled trial. J Phys Act Health, 2014; 11:1012-7.

(21) Kong KL, Campbell CG, Foster RC, Peterson AD, Lanningham-Foster L. A pilot walking program promotes moderate-intensity physical activity during pregnancy. Med Sci Sports Exerc. 2014;46:462-71

(22) Petrella E, Malavolti M, Bertarini V, Pignatti L, Neri I, Battistini NC et al. Gestational weight gain in overweight and obese women enrolled in a healthy lifestyle and eating habits program. J Matern Fetal Neonatal Med. 2014;27:1348-52.

(23) Renault KM, Nørgaard K, Nilas L, Carlsen EM, Cortes D, Pryds O et al. The Treatment of Obese Pregnant Women (TOP) study: a randomized controlled trial of the effect of physical activity intervention assessed by pedometer with or without dietary intervention in obese pregnant women. Am J Obstet Gynecol. 2014;210:134.e1-9.

(24) Perales M, Santos-Lozano A, Sanchis-Gomar F, Luaces M, Pareja-Galeano H, Garatachea N et al. Maternal cardiac adaptations to a physical exercise program during pregnancy. Med Sci Sports Exerc. 2016;48:896-906.

(25) American College of Obstetricians and Gynecologists (ACOG). Physical activity and exercise during pregnancy and the postpartum period. Committee Opinion 650.

(26) Muktabhant B, Lawrie TA, Lumbiganon P, Laopaiboon M. Diet or exercise, or both, for preventing excessive weight gain in pregnancy. Cochrane Database Syst Rev. 2015;(6):CD007145.

(27) Russo LM, Nobles C, Ertel KA, Chasan-Taber L, Whitcomb BW. Physical activity interventions in pregnancy and risk of gestational diabetes mellitus: a systematic review and meta-analysis. Obstet Gynecol. 2015;125:576-82.

(28) Wolf HT, Owe KM, Juhl M, Hegaard HK. Leisure time physical activity and the risk of pre-eclampsia: a systematic review. Matern Child Health J. 2014;18:899-910.

(29) Di Mascio D, Magro-Malosso ER, Saccone G, Marhefka GD, Berghella V. Exercise during pregnancy in normal-weight women and risk of preterm birth: a systematic review and meta-analysis of randomized controlled trials. Am J Obstet Gynecol, 2016; 215:561-571.

(30) Magro-Malosso ER, Saccone G, Di Mascio D, Di Tommaso M, Berghella V. Exercise during pregnancy and risk of preterm birth in overweight and obese women: a systematic review and meta-analysis of randomized controlled trials. Acta Obstet Gynecol Scand, 2017; 96(3):263-273.

Supporting Information legends

Table S1. Type of intervention and primary outcome of the included trials.

Table S2. Inclusion and exclusion criteria of the women included in the trials.

Table S3. Characteristics of the women included in the trials.

Figures

Figure 1. Flow diagram of studies identified in the systematic review. (Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses]).

Figure 2. Assessment of risk of bias. (A) Summary of risk of bias for each trial; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

Figure 3. Funnel plot for assessing publication bias in the primary outcome. RR, relative risk.

Figure 4. Forest plot for the risk of gestational hypertensive disorders, defined as either gestational hypertension or preeclampsia. CI, confidence interval; M-H, Mantel-Haenszel; df, degrees of freedom.

Table 1. Characteristics of the included trials.

Study, year (Ref)	**Study location**	**Sample size[a]**	**Diet intervention in exercise group**	**GA at randomization (weeks)**	**End of exercise program (weeks)**	**Gestational hypertension definition**	**Pre-eclampsia definition**
Barakat, 2009 (9)	Spain	160 (80 vs 80)	NR	12 to 13	38-39	Diastolic BP of ≥ 90 mm Hg and a systolic BP ≥ 140 mm Hg, based on the average of at least 2 measurements, using the same arm and recorded in the medical file.	Gestational hypertension plus proteinuria within 7 days of each other, HELLP syndrome, or eclampsia.
Barakat, 2011 (10)	Spain	80 (40 vs 40)	NR	6 to 9	38-39	Diastolic BP of ≥ 90 mm Hg and a systolic BP ≥ 140 mm Hg, based on the average of at least 2 measurements, using the same arm and recorded in the medical file.	Gestational hypertension plus proteinuria within 7 days of each other, HELLP syndrome, or eclampsia.
Haakstad, 2011 (11)	Norway	105 (52 vs 53)	NR	17.3±4.1 vs 18.0±4	36.5 ±4.2	NR	NR

				.3			
Vinter, 2011 (12)	Den mark	304 (150 vs 154)	Dietary counseli ng	10 to 14	Until delivery	NR	NR
Barakat, 2012 (13[j])	Spain	320 (160 vs 160)	NR	6 to 9	38-39	Diastolic BP of ≥ 90 mm Hg and a systolic BP ≥ 140 mm Hg, based on the average of at least 2 measurements, using the same arm and recorded in the medical file.	Gestational hypertension plus proteinuria within 7 days of each other, HELLP syndrome, or eclampsia.
Barakat, 2012 (14)	Spain	100 (50 vs 50)	NR	6 to 9	38-39	Diastolic BP of ≥ 90 mm Hg and a systolic BP ≥ 140 mm Hg, based on the average of at least 2 measurements, using the same arm and recorded in the medical file.	Gestational hypertension plus proteinuria within 7 days of each other, HELLP syndrome, or eclampsia.
de Oliveria Melo, 2012 (15)	Brazi l	171 (54 vs 60 vs 57)[b]	NR	13	38	Systolic BP 140 mm Hg or more or diastolic BP 90 mm Hg or more, or both.	NR
Price, 2012 (16)	USA	62 (31 vs 31)	Dietary counseli ng	12 to 14	36	BP of 140/90 or higher for the first time during pregnancy without proteinuria.	BP of 140/90 mmHG or higher for the first time during pregnancy with proteinuria.
Stafne, 2012 (17)	Norw ay	855 (429 vs 426)	Dietary counseli ng	18 to 22	36	Systolic BP more than 140, diastolic BP more than 90, or both.	NR
Ruiz, 2013 (18)	Spain	962 (481 vs 481)	Dietary counseli ng	5 to 6[d]	38-39	NR	NR
Barakat, 2014 (19)	Spain	242 (128 vs 114)	NR	9 to 13	39-40	Diastolic BP of ≥ 90 mm Hg and a systolic BP ≥ 140 mm Hg, based on the average of at least 2 measurements, using the same arm and recorded in the medical file.	Gestational hypertension plus proteinuria within 7 days of each other, HELLP syndrome, or eclampsia.
Barakat, 2014 (20)	Spain	320 (160 vs	NR	8 to 10	38-39	Diastolic BP of ≥ 90 mm Hg and a systolic BP ≥ 140 mm	Gestational hypertension plus

		160)				Hg, based on the average of at least 2 measurements, using the same arm and recorded in the medical file.	proteinuria within 7 days of each other, HELLP syndrome, or eclampsia.
Kong, 2014 (21)	USA	37 (18 vs 19)	NR	12 to 14	until at least week 35	NR	NR
Petrella, 2014 (22)	Italy	61 (33vs 28)	Dietary intervention	12	Until at least week 36	NR	NR
Renault, 2014 (23)	Den mark	389 (130 vs 125 vs 134)[c]	Dietary intervention or dietary counseling	<16	36-37	Persistently elevated BP greater than 140/90 mm Hg on more than 1 occasion.	Proteinuria (Dipstick, greater than 1) and persistently elevated BP greater than 140/90 mm Hg on more than 1 occasion.
Barakat, 2016 (6)	Spain	765 (382 vs 383)	NR	9 to 11	38-39	Diastolic BP of ≥ 90 mm Hg and a systolic BP ≥ 140 mm Hg, based on the average of at least 2 measurements, using the same arm and recorded in the medical file.	Gestational hypertension plus proteinuria within 7 days of each other, HELLP syndrome, or eclampsia.
Perales, 2016 (24)	Spain	142 (83 vs 59)	Dietary counseling	9 to 11	38-39	Diastolic BP of ≥ 90 mm Hg and a systolic BP ≥ 140 mm Hg, based on the average of at least 2 measurements, using the same arm and recorded in the medical file.	Gestational hypertension plus proteinuria within 7 days of each other, HELLP syndrome, or eclampsia.

[a]Data are presented as total number (number in the intervention group vs number in the control group).

[b]Group1/group2/group3. Group 1 = exercise initiated at 13 weeks; group 2 = exercise initiated at 20 weeks; group 3 = control group. All women were randomized in week 13 of pregnancy.

[c]Group1/group2/group3. Group 1 = physical activity and dietary intervention; group 2 = physical activity intervention and dietary counseling; group 3 = standard care including dietary counseling.

[d]Exercise intervention program started from 9 weeks.

GA, gestational age; HR, hearth rate; BP, blood pressure; HELLP, hemolysis, elevated liver enzymes, and low platelet count; NR, not reported.

Table 2. Outcomes in the overall analysis.

	Gestational hypertensive disorders	**Gestational hypertension**	**Preeclampsia**
Barakat, 2009 (9)	NR	1/80 (1.25%) vs 2/80 (2.5%)	NR
Barakat, 2011 (10)	NR	1/40 (2.5%) vs 2/40 (5.0%)	NR
Haakstad, 2011 (11)	1/52 (1.9%) vs 1/53 (1.9%)	1/52 (1.9%) vs 0/53 (0.0%)	0/52 (0.0%) vs 1/53 (1.9%)
Vinter, 2011 (12)	23/150 (15.4%) vs 28/154 (18.2%)	NR	NR
Barakat, 2012 (13)	NR	2/160 (1.25%) vs 2/160 (1.25%)	NR
Barakat, 2012 (14)	NR	0/50 (0.0%) vs 1/50 (2.0%)	NR
De Oliveria Melo, 2012 (15)	NR	9/114 (7.9%) vs 5/57 (8.8%)	NR
Price, 2012 (16)	0/31(0.0%) vs 3/31 (9.7%)	0/31(0.0%) vs 2/31(6.5%)	0/31(0.0%) vs 1/31(3.2%)
Stafne, 2012 (17)	27/429 (6.3%) vs 27/426 (6.3%)	11/385 (2.9%) vs 11/340 (3.2%)[b]	16/426 (3.8%) vs 16/426 (3.8%)
Ruiz, 2013 (18)	NR	13/481 (2.7%) vs 30/481(6.2%)	NR
Barakat, 2014 (19)	NR	1/128 (0.8%) vs 2/114 (1.7%)	NR
Barakat, 2014 (20)	NR	2/160 (1.3%) vs 2/160 (1.3%)	NR
Kong, 2014 (21)	1/18 (5.5%) vs 0/19 (0.0%)	0/18 (0.0%) vs 0/19 (0.0%)	1/18 (5.5%) vs 0/19 (0.0%)
Petrella, 2014 (22)	NR	1/33 (3.0%) vs 7/28 (25.0%)	NR
Renault, 2014 (23)	16/255 (6.3%) vs 12/134 (9.0%)	9/255 (3.5%) vs 9/134 (6.7%)	7/255 (2.7%) vs 3/154 (1.9%)

Barakat, 2016 (6)	10/382 (2.6%) vs 31/383 (8.1%)	8/382 (2.1%) vs 22/383 (5.7%)	2/382 (0.5%) vs 9/383 (2.3%)
Perales, 2016[a] (24)	NR	2/83 (2.4%) vs 3/59 (5.1%)	NR
Total	78/1,317 (5.9%) vs 102/1,200 (8.5%)	61/2,452 (2.5%) vs 100/2,189 (4.6%)	26/1,164 (2.3%) vs 30/1,066 (2.8%)
I^2	34%	10%	0%
RR or MD (95% CI)	**0.70 (0.53 to 0.93)**	**0.54 (0.40 to 0.74)**	0.79 (0.45 to 1.38)

NR, not reported; MD, mean difference.

Data are presented as number in the intervention group vs number in the control group with percentage.

[a]prevalence of hypertension determined at 34 weeks.

[b]Data were missing for 15.2% of cases.

Boldface data: statistically significant.

Table 3. Posthoc secondary outcomes.

	Cesarean delivery	**GA at delivery (weeks)**	**Birth weight (grams)**	**Apgar score at 1 min**	**Apgar score at 5 min**
Barakat, 2009 (9)	11/72 (15.3%) vs 11/70 (15.7%)	39.4±1.2 vs 39.5±1.2	3165±411 vs 3307±477	8.9±1.1 vs 8.8±1.2	9.9±0.2 vs 9.9±0.3
Barakat, 2011 (10)	7/34 (20.6%) vs 10/33 (30.3%)	39.7±1.7 vs 39.9±1.6	3250±493 vs 3402±328	8.9±1.1 vs 8.8±1.2	9.9±0.2 vs 9.9±0.3
Haakstad, 2011 (11)	NR	39.9±1.2 vs 39.6±1.2	3477±424 vs 3542±464	8.8±0.8 vs 8.6±1.2	9.6±0.6 vs 9.4±0.8
Vinter, 2011 (12)	40/150 (26.7%) vs 39/154 (25.3%)	40.4 (39-41.4) vs 40.4 (39.2-41.3)	3742 (3464-4070) vs 3593 (3335-3930)	NR	NR
Barakat, 2012 (13)	22/138 (15.9%) vs 35/152 (23.0%)	39.8±1.4 vs 39.7±1.5	3203±461 vs 3232±448	8.7±1.4 vs 8.6±1.3	9.7±0.6 vs 9.8±0.8
Barakat, 2012 (14)	12/40 (30.0%) vs 6/43 (14.1%)	39.6±1.3 vs 39.7±1.1	3404±465 vs 3465±411	8.7±1.1 vs 8.7±0.8	9.9±0.9 vs 9.9±0.7
De Oliveria Melo, 2012 (15)	NR	39.6 vs 39.4	3282±465 vs 3378±593	NR	NR

Price, 2012 (16)	4/31 (12.9%) vs 12/31 (38.7%)	39.2 vs 39.4	3329±519 vs 3308±103	8.2±1.9 vs 8.1±0.9	9.0±0.5 vs 8.7±0.5
Stafne, 2012 (17)	45/426 (10.6%) vs 50/425 (11.8%)	40.0±1.9 vs 40.2±3.2	3515±534 vs 3523±546	NR	NR
Ruiz, 2013 (18)	93/481 (19.3%) vs 94/481 (19.6%)	39.6±1.7 vs 39.6±1.3	3234±453 vs 3239±433	8.8±1.2 vs 8.7±1.1	9.8±0.5 vs 9.8±0.5
Barakat, 2014 (19)	18/107 (17.1%) vs 26/93 (28.6%)	39.5±1.9 vs 39.2±2.2	3187±441 vs 3261±467	8.8±1.2 vs 8.8±1.6	9.8±0.5 vs 9.8±0.6
Barakat,2014 (20)	NR	39.6±1.1 vs 39.7±1.3	3203±461 vs 3232±448	8.7±1.4 vs 8.6±1.3	9.7±0.6 vs 9.8±0.8
Kong, 2014 (21)	5/18 (27.8%) vs 9/19 (47.4%)	39.4±0.9 vs 39.5±1.2	3650±475 vs 3765±470	8.0±0.8 vs 7.7±1.4	8.8±0.7 vs 8.5±1.4
Petrella, 2014 (22)	11/33 (33.3%) vs 9/28 (32.1%)	39.8±0.8 vs 37.3±3.2	3498±342 vs 3010±715	NR	NR
Renault, 2014 (23)	83/255 (32.5%) vs 50/134 (37.3%)	39.7±1.8 vs 39.7±1.7	3605 (1945-5450), 3695 (805-4910) vs 3641 (1223-5280)	NR	NR
Barakat, 2016 (6)	73/382 (19.1%) vs 83/383 (21.7%)	39.6±1.7 vs 39.4±1.8	3252±438 vs 3218±453	NR	NR
Perales, 2016[a] (24)	11/57 (19.3%) vs 24/82 (29.3%)	NR	3166±428 vs 3212±421	8.8±1.3 vs 8.9±0.7	9.8±0.5 vs 9.9±0.3
Total	435/2,224 (19.6%) vs 458/2,128 (21.5%)	-			
I^2	14%	50%	30%	0%	0%
RR or MD (95% CI)	**0.84 (0.73 to 0.98)**	0.03 week (-0.06 to 0.13)	-57.23 grams (-117.45 to 26.14)	0.01 (-0.15 to 0.17)	0.01 (-0.05 to 0.07)

Data are presented as number in the intervention group vs number in the control group with percentage; or as mean ± standard deviation; or as median (range).

NR, not reported; GA, gestational age; RR, relative risk; MD, mean difference; CI, confidence interval.

Boldface data, statistically significant.

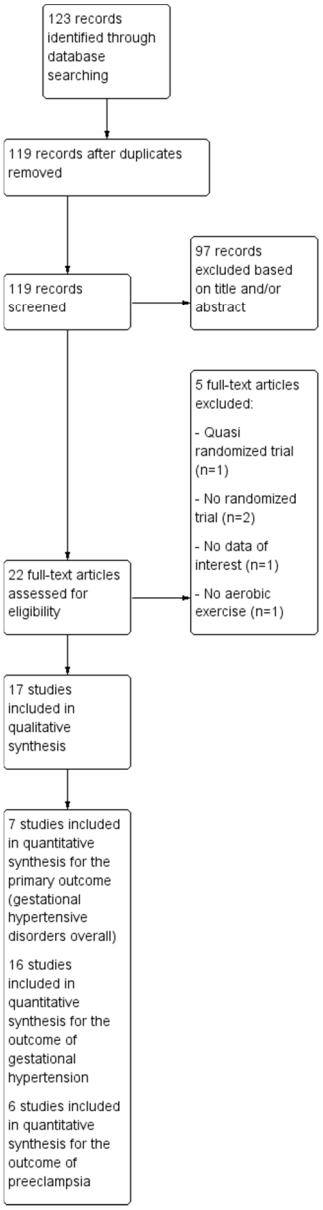

Figure 1

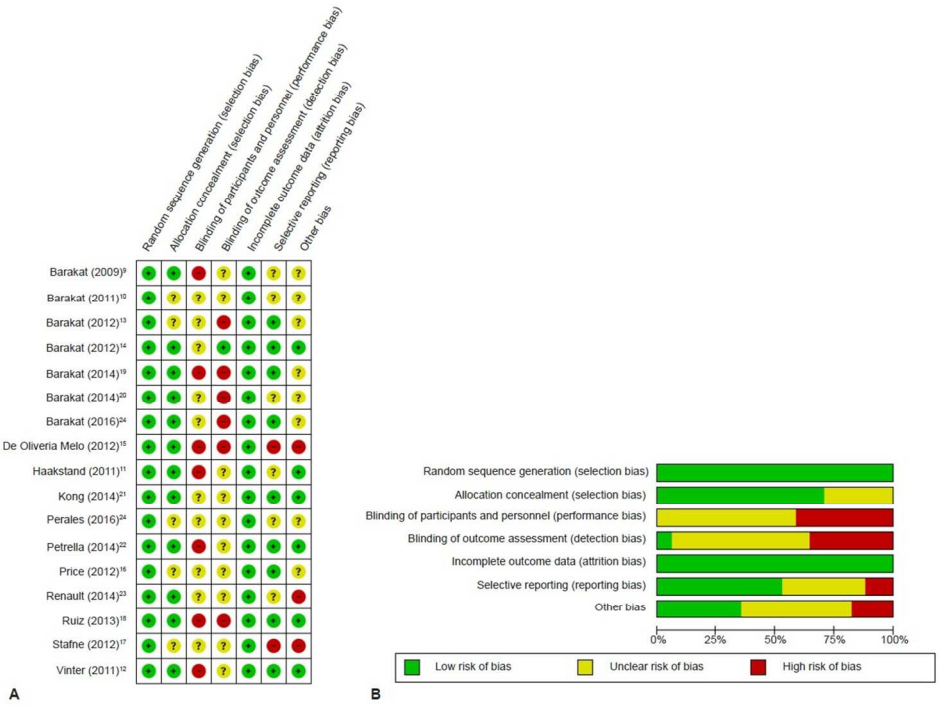

Figure 2

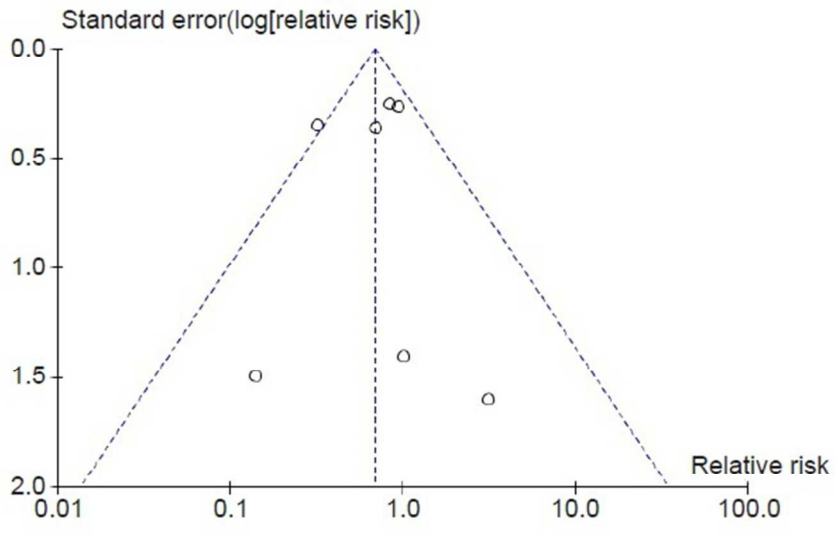

Figure 3

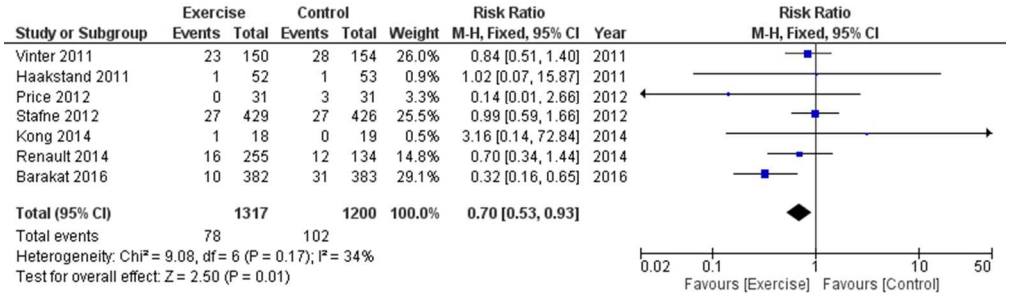

Figure4