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Exercise during pregnancy in normal-weight women and risk of preterm birth: a systematic review and meta-analysis of randomized controlled trials

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Condensation

Exercise during pregnancy in normal-weight women is not associated with an increased risk of preterm birth.

Short titles

Exercise during pregnancy in normal-weight women and risk of preterm birth.

Abstract

Background: Preterm birth (PTB) is the major cause of perinatal mortality in the United States. In the past, pregnant women have been recommended against exercise because of presumed risks of PTB. Physical activity has been theoretically related to PTB as it increases the release catecholamines, especially norepinephrine, which might stimulate myometrial activity. Conversely, exercise may reduce the risk of PTB by other mechanisms such as decreased oxidative stress or improved placenta vascularization. Therefore, the safety of exercise regarding PTB and its effects on gestational age at delivery remain controversial.

Objective: To evaluate the effects of exercise during pregnancy on the risk of PTB.

Data sources: MEDLINE, EMBASE, Web of Sciences, Scopus, ClinicalTrial.gov, OVID and Cochrane Library were searched from the inception of each database to April 2016.

Methods of study selection: Selection criteria included only randomized clinical trials (RCTs) of pregnant women randomized before 23 weeks to an aerobic exercise regimen or not. Types of participants included women mainly of normal weight with uncomplicated, singleton pregnancies without any obstetric contraindication to physical activity. The summary measures were reported as relative risk (RR) or as mean difference (MD) with 95% confidence intervals (CI). The primary outcome was the incidence of PTB <37weeks.

Tabulation, integration, and results: Of the 2,059 women included in the meta-analysis, 1,022 (49.6%) were randomized to the exercise group and 1,037 (50.4%) to the control group. Aerobic exercise lasted about 35-90 minutes 3-4 times per week. Women who were randomized to aerobic exercise had a similar incidence of PTB<37 weeks (4.5% vs 4.4%; RR 1.01, 95% CI

0.68-1.50) and a similar mean gestational age at delivery (MD 0.05 week, 95% CI - 0.07 to 0.17) compared to controls. Women in the exercise group had a significantly higher incidence of vaginal delivery (73.6% vs 67.5%; RR 1.09, 95% CI 1.04-1.15) and significantly lower incidence of cesarean delivery (17.9% vs 22%; RR 0.82, 95% CI 0.69-0.97) compared to controls. The incidence of operative vaginal delivery (12.9% vs 16.5%; RR 0.78, 95% CI 0.61-1.01) was similar in both groups. Women in the exercise group had a significantly lower incidence of gestational diabetes mellitus (2.4% vs 5.9%; RR 0.41, 95% CI 0.24-0.68) and significantly lower incidence of hypertensive disorders (1.9% vs 5.1%; RR 0.36, 95% CI 0.19-0.69) compared to controls. No differences in low birth weight (5.2% vs 4.7%; RR 1.11, 95% CI 0.72-1.73) and mean birth weight (MD -10.46 grams, 95% CI -47.10 to 26.21) between exercise group and controls were found.

Conclusion: Aerobic exercise for 35-90 minutes 3-4 times per week during pregnancy can be safely performed by normal-weight women with singleton, uncomplicated gestations, as this is not associated with an increased risk of PTB or with a reduction in mean gestational age at delivery. Exercise was associated with a significantly higher incidence of vaginal delivery and a significantly lower incidence of cesarean delivery, with a significantly lower incidence of gestational diabetes mellitus and hypertensive disorders, and therefore should be encouraged.

Key words: physical activity, exercise during pregnancy, preterm birth, preterm delivery, pregnancy outcomes, obstetric outcomes.

INTRODUCTION

Preterm birth (PTB) is the major cause of perinatal mortality in the United States.[1] In the past, pregnant women have been recommended against exercise because of presumed risks of pregnancy loss and PTB, possibly due to reduced placental circulation.[2] Physical activity has been theoretically related to PTB as it increases the release of catecholamines, especially norepinephrine, which might stimulate myometrial activity.[3] Conversely, exercise may reduce the risk of PTB by other mechanisms such as decreased oxidative stress or improved placenta vascularization,[4] an adaptive response to intermittent reduction in uterine blood flow, as well as increased blood volume found in pregnant women during exercise.[5] Physical activity during pregnancy may be decreased due to lack of time, lack of energy, discomfort or pain and concern about baby's health.[6] In fact, bed rest is commonly recommended in pregnancy.[7] Therefore, the safety of exercise regarding PTB, and its effects on gestational age at delivery, remain controversial.

Objective

The aim of this systematic review and meta-analysis was to evaluate the effects of exercise during pregnancy on the risk of PTB.

METHODS

Search strategy

This meta-analysis was performed according to a protocol recommended for systematic review.[8] 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, ClinicalTrial.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" and "pregnancy" and "preterm birth" or "preterm delivery" and "randomized trial" as publication type, from the inception of each database to April 2016. Review of articles also included the abstracts of all references retrieved from the search.

Study selection

Selection criteria included only randomized clinical trials (RCTs) of pregnant women randomized to an exercise regimen or not. We included only RCTs reporting PTB as an outcome. Types of participants included women with uncomplicated, singleton pregnancies without any obstetric contraindication to physical activity. In all the trials, the intervention group participated in planned aerobic exercise. In the control group, women did not participate in exercise sessions and only attended regular scheduled obstetric visits. When possible, data only on women with normal body mass index (BMI) (18.5-24.9) were selected. RCTs including only underweight (BMI≤18.5) or only overweight or obese (BMI ≥25) women, those including diet, counseling, and/or weight monitoring, and those assessing reduction in exercise, 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.

Data extraction and risk of bias assessment

The risk of bias in each included study was assessed by using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*.[8] 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.[8]

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 PTB <37weeks. Secondary outcomes were gestational age at delivery, spontaneous vaginal delivery, operative vaginal delivery, cesarean delivery, gestational diabetes, hypertensive disorders (defined as gestational hypertension or preeclampsia) and neonatal outcomes including birth weight and low birth weight (i.e. birth weight <2500 grams).

We assessed the primary outcome (i.e. incidence of PTB <37weeks) in a sensitivity analysis according to the risk of bias of the included trials;[8] and in subgroup analysis according to the type and length of exercise.

Data analysis

Data analysis was completed using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Center, Cochrane Collaboration, 2014).[8] Statistical heterogeneity between studies was assessed using the Higgins I^2 statistics. In case of statistical significant heterogeneity ($I^2 \geq 0$), 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 ($I^2=0$), a fixed effect model was used.[8] The summary measures were reported as relative risk (RR) or as mean difference (MD) with 95% confidence intervals (CI). Potential publication biases were assessed graphically by using

the funnel plot and statistically by using Begg's and Egger's tests. 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.[9] Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42016037841).

Three authors (DDM, EMM, GS) independently assessed inclusion criteria, risk of bias, data extraction and data analysis. Disagreements were resolved by discussion with a fourth reviewer (VB). Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. Differences were reviewed, and further resolved by common review of the entire process. Data not presented in the original publications were requested from the principal investigators.

Results

Study selection and study characteristics

Figure 1 shows the flow diagram (PRISMA template) of information derived from review of potentially relevant articles. Nine RCTs, including 2,059 sedentary women with an uncomplicated, singleton pregnancy were included in the meta-analysis.[10-18] One study was published in abstract form only.[10]

The quality of RCTs included in our meta-analysis was assessed by the Cochrane Collaboration's tool.[8] All the included studies, except one,[10] used a computer-generated table of random numbers and had low risk of bias in "incomplete outcome data." No method of blinding

as to the group allocation was reported (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=0.48 and 0.51, respectively). Unpublished data was kindly provided by an author[10] who was contacted by email.

Table 1 shows the characteristics of the included trials. In five trials,[12,15-18] women were randomized during the first trimester; in four studies,[10,11,13,14] women were randomized during the early second trimester (≤22 weeks). Table 2 shows inclusion and exclusion criteria of these trials. Characteristics of the women included were reported in Table 3. All studies randomized only sedentary, pregnant women with uncomplicated, singleton gestations. Women were excluded if any obstetric contraindications, mostly as recommended by ACOG (Table 2).[19] In all nine trials, the intervention group participated in aerobic exercise. Seven trials[10,12,14-18] were toning, resistance and flexibility exercise, together with joint mobilization activities, mostly according to ACOG recommendations.[19] Two trials[11,13] were water aerobics. The mean time of every session was 57 minutes, three times a week in eight trials,[11-18] four times a week in one trial.[10] In the control group, women did not participate in any exercise sessions and attended only regularly scheduled obstetric visits.

Synthesis of results

Of the 2,059 women included in the meta-analysis, 1,022 (49.6%) were randomized to the exercise group and 1,037 (50.4%) to the control group. The statistical heterogeneity within the studies was low with no inconsistency (I^2=0) for the risk estimates for the primary outcome. Table 4 shows the pooled data of primary and secondary outcomes of the meta-analysis. Pregnant women who were randomized before 23 weeks to 35-90 minutes of aerobic exercise 3-

4 times per week for 10 weeks or up to delivery had a similar incidence of PTB<37 weeks (4.5% vs 4.4%; RR 1.01, 95% CI 0.68-1.50) and a similar mean gestational age at delivery (MD 0.05 week, 95% CI -0.07 to 0.17) compared to controls. Women in the exercise group had a significantly higher incidence of vaginal delivery (73.6% vs 67.5%; RR 1.09, 95% CI 1.04-1.15) and significantly lower incidence of cesarean delivery (17.9% vs 22%; RR 0.82, 95% CI 0.69-0.97) compared to controls. The incidence of operative vaginal delivery (12.9% vs 16.5%; RR 0.78, 95% CI 0.61-1.01) was similar in both groups. Women in the exercise group had a significantly lower incidence of gestational diabetes mellitus (2.4% vs 5.9%; RR 0.41, 95% CI 0.24-0.68) and significantly lower incidence of hypertensive disorders (1.9% vs 5.1%; RR 0.36, 95% CI 0.19-0.69) compared to controls. No differences in low birth weight (5.2% vs 4.7%; RR 1.11, 95% CI 0.72-1.73) and mean birth weight (MD -10.46 grams, 95% CI -47.10 to 26.21) between exercise group and controls were found. Sensitivity analysis, excluding studies judged at high risk of bias,[10,15,16,18] concur with the overall analysis (RR 0.82, 95% CI 0.42-1.60). Pooled data from subgroup analyses according to the type of exercise, including trials on water aerobic exercise (RR 1.25, 95% CI 0.34-4.58);[11,13] and according to the length of exercise, including trials had length of ≥60minutes (RR 0.88, 95% CI 0.44-1.74),[10,11,14,16,17] showed no difference in the primary outcome.

Comment

Main findings

This pooled meta-analysis of nine RCTs including 2,059 women with uncomplicated, singleton pregnancies showed that exercise during pregnancy in mostly normal-weight women is not associated with an increased risk of PTB. Exercise during pregnancy is associated with a

significantly increased incidence of vaginal delivery and significantly decreased incidence of cesarean delivery, while there is no difference with operative vaginal delivery, compared to controls. Exercise during pregnancy is also associated with a significantly lower incidence of gestational diabetes mellitus and hypertensive disorders.

Comparison with existing literature

A 2006 Cochrane review showed that increasing exercise in sedentary pregnant women was associated with a statistically non-significant increase in the risk of PTB and with a clinically irrelevant shortening of gestational age at delivery.[20] No significant effects on mean birth weight and on risk of cesarean delivery were found.[20] However, only three trials were included. In 2012 another meta-analysis of 44 RCTs including 7,278 pregnant women evaluated diet, exercise and a mixed approach of these two interventions.[21] They found an overall trend towards reduction in PTB with diet, exercise and/or mixed approach compared to controls.[21] The subgroup analysis on exercise included only 5 RCTs with PTB outcome and no effect was found.[21] A 2015 Cochrane review, evaluating diet or exercise or both during pregnancy showed no difference in PTB between the intervention and standard care groups.[22] The subgroup analysis on exercise included only 3 RCTs with PTB outcome and also no effect was found.[22] A 2015 systematic review of RCTs demonstrated that structured prenatal exercise did not adversely affect birth weight compared to standard prenatal care alone.[23]

Strengths and limitations

Our study has several strengths. This meta-analysis included all RCTs - nine - published so far on the topic. These studies in general are of high quality and with a low risk of bias according to the Cochrane risk of bias tools. To our knowledge, no prior meta-analysis with PTB as a primary outcome on the issue of exercise during pregnancy is as large, up-to-date or comprehensive. The statistical heterogeneity within the studies was low. The number of the included women - 2,059 - was high. In addition, publication bias was not apparent by statistical analysis. These are key elements that are needed to evaluate the reliability of a meta-analysis.[8]

Limitations of our study include that the trimester in which exercise was performed, the adherence to exercise sessions, and the variation in maternal nutritional intake, could all have influenced outcomes. In only one study,[15] outcomes are stratified by pre-pregnancy BMI categories; while in one study,[18] only PTB and low birth weight are stratified by pre-pregnancy BMI categories. Therefore, while mean BMIs for included women in all randomized studies were always in the normal range (Table 3), some studies included a minority of underweight, overweight and obese women, which could not be excluded as their outcomes were not reported separately. In four studies,[12,16-18] 27 women already randomized to exercise or not (11 in the exercise group and 16 in the control group) were excluded from further analyses because they had preterm labor. Another limitation of this study is that the individual trials differ somewhat in how they define aerobic exercise, intensity of exercise and time of exercise. Spontaneous PTB was not reported separately in the trials, except in one trial,[17] where iatrogenic PTB was excluded as an outcome.

Conclusions and implications

Aerobic exercise for 35-90 minutes 3-4 times per week during pregnancy can be safely performed by normal-weight women with singleton, uncomplicated gestations, as this is not associated with an increased risk of PTB or with a reduction in mean gestational age at delivery. As supported by recent literature,[24] exercise was associated with a significantly higher incidence of vaginal delivery, and significantly lower incidences of cesarean delivery, gestational diabetes, and hypertensive disorders, and therefore should be encouraged.

Our findings support the ACOG recommendations about exercise during uncomplicated pregnancies,[19] and the U.S. Department of Health and Human Services guidelines for healthy pregnant and postpartum women that recommend at least 150 minutes of moderate-intensity activity per week.[25]

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341 **Table 1**. Characteristics of the included trials

	Carpenter, 1990[10]	**Prevedel, 2003[11]**	**Barakat, 2008[12]**	**Cavalcante, 2009[13]**	**Haakstad, 2011[14]**	**Ruiz, 2013[15]**	**Barakat, 2014[16]**	**Barakat, 2014[17]**	**Barakat, 2016[18]**
Study Location	USA	Brazil	Spain	Brazil	Norway	Spain	Spain	Spain	Spain
Sample size*	14 (7 vs 7)	41 (22 vs 19)	142 (72 vs 70)	71 (34 vs 37)	105 (52 vs 53)	687 (335 vs 352)	200 (107 vs 93)	290 (138 vs 152)	513 (257 vs 256)
GA (weeks) at randomization **Mean±SD or WR**	20 to 22	16 to 20	12 to 13	16 to 20	17.3±4.1 vs 18.0±4.3	5 to 6	6 to 7**	8 to 10	9 to 11
Type of exercise	30 min physical training preceded and followed by 30 min cycle ergometry at 60% VO_2 max.	Hydrotherapy exercises: stretching; resistance, targeted, respiratory exercises in an indoor swimming pool with water at 28-32°C.	Stretching; toning and joint mobilization exercises; resistance exercises.	Water aerobics in an indoor swimming pool with water at 28-30°C.	Aerobic dance, followed by abdominal, pelvic floor and back muscle training, stretching, relaxation and body awareness exercises.	Aerobic, resistance and stretching exercises.	Walking and stretching, followed by toning and joint mobilization exercises, aerobic dance and specific exercises for leg, buttocks and abdomen.	Toning, joint mobilization, resistance exercises preceded and followed by walking and light stretching.	Aerobic exercise, aerobic dance, muscular strength and flexibility exercises preceded by walking and light stretching and followed by relaxation and pelvic floor exercise.

Duration of a single session (min)	90	60	35	50	60	50-55	55-60	55-60	50-55
Times per week (# days)	4	3	3	3	3	3	3	3	3
Intensity of exercise (HR)	NR	NR	<80% of their age-predicted max HR.	<70% of their age-predicted max HR.	NR	<60% of their age-predicted max HR.	<60% of their age-predicted max HR.	<60-75% of their age-predicted max HR.	<70% of their age-predicted max HR.
Self-reported intensity of exercise (Borg scale*)**	NR	NR	NR	NR	12-14	10-12	12-13	NR	12-14
Control group	10 weeks of non-exercise.	No hydrotherapy program.	No exercise, except those activities necessary for daily living.	No regular physical activity during the entire pregnancy.	Women were not encouraged neither discouraged from exercising.	Regular scheduled visits, every 4 to 5 weeks until the 35th week of GA then weekly until delivery. Women received general nutrition and physical activity counseling	No exercise during pregnancy.	NR	General advice from their health care provider about positive effects of physical activity; regular scheduled visits; women not discouraged from exercising on

						and were not discouraged from exercising.			their own and asked by telephone about their exercise once each trimester.
Primary outcome	Change in resting heart rate; exercise stroke volume; exercise VO_2; O_2 pulse.	Maternal outcomes: body composition and cardiovascular capacity; Perinatal outcomes: weight and prematurity.	Healthy gravidae and GA at delivery.	Evolution of pregnancy (GA at delivery, preterm birth), maternal body composition (weight gain, BMI, proportion of fat mass) and perinatal outcomes (Apgar score, weight at birth and birth weight adequate for GA).	Infant birth weight.	Maternal weight gain.	Maternal (GA, preterm birth, blood pressure, weight gain, type of delivery, GDM) and fetal (birth weight, head circumference, birth size, Apgar score, pH of umbilical cord, gender) outcomes.	GA at delivery.	Gestational hypertension.
Other comments	Physical training	---	---	---	In addition to joining	Sample size refers to	---	---	Sample size refers to only

	only 10 weeks in mid-pregnancy.				the scheduled exercise sessions, all women in the exercise group were asked to include 30 minutes of moderate self-imposed physical activity on the remaining week-days.	only normal-weight women included in the original trial.			normal-weight women included in the original trial.

342 HR, hearth rate; GA, gestational age; BMI, body mass Index; GDM, gestational diabetes mellitus, ACOG, American Congress of Obstetricians
343 and Gynecologists; NR, not reported

344 *Data are presented as total number (number in the intervention group vs number in the control group).

345 **Pregnant women who underwent their first ultrasound examination at 10 to 12 weeks were offered the opportunity to participate, following a
346 randomization process.

347 ***Borg Scale is a 15 category scale (from 6 to 20) to measure the level of perceived exertion. Light exercise is about 6-11; 13 somewhat hard; 15
348 hard; 19 extremely hard.

349 **Table 2.** Inclusion and exclusion criteria of the women included in the trials.

	Inclusion criteria	Exclusion criteria
Carpenter, 1990[10]	Sedentary, pregnant women.	Not Reported.
Prevedel, 2003[11]	Nulliparous with singleton, uncomplicated gestations.	Any medical or obstetrical contraindication.
Barakat, 2008[12]	Women with singleton, uncomplicated gestations, not at high risk of preterm delivery.	Any obstetric contraindication to exercise suggested by ACOG; not planning to give birth in the same obstetrics hospital department; not to be under medical follow-up throughout the entire pregnancy; any serious medical condition.
Cavalcante, 2009[13]	Low-risk, sedentary pregnant women with uncomplicated, singleton gestations.	History of two or more cesarean sections; medical conditions contraindicating the practice of physical exercise and/or practical impediments.
Haakstad, 2011[14]	Nulliparous women with uncomplicated, singleton gestations whose pre-pregnancy exercise levels did not include participation in a structured exercise program; ability to read, understand and speak Norwegian; to be within the first 24 weeks of pregnancy.	History of more than 2 miscarriages, severe heart disease and persistent bleeding after 12 weeks of gestation; multiple pregnancy; poorly controlled thyroid disease; gestational hypertension or preeclampsia; diabetes or gestational diabetes.
Ruiz, 2013[15]	Sedentary women with singleton, uncomplicated gestations, not at high risk of preterm delivery and not participating in any other trial.	Any obstetric contraindication to exercise suggested by ACOG.

Barakat, 2014[16]	Women with uncomplicated, singleton gestations.	Any obstetric contraindication to exercise suggested by ACOG; not planning to give birth in the obstetrics department of the study; not receiving medical follow-up throughout pregnancy; participating in another physical program or having a high level of pre-gestational physical exercise.
Barakat, 2014[17]	Women with uncomplicated, singleton gestations.	Any obstetric contraindication to exercise suggested by ACOG; not planning to give birth in the obstetrics department of the study; not receiving medical follow-up throughout pregnancy; participating in another physical program or having a high level of pre-gestational physical exercise.
Barakat, 2016[18]	Women with uncomplicated, singleton gestations.	Any obstetric contraindication to exercise suggested by ACOG; not planning to give birth in the obstetrics department of the study; not receiving medical follow-up throughout pregnancy; history of risk of preterm birth.

350 BMI, Body Mass Index; ACOG, American Congress of Obstetricians and Gynecologists

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356 **Table 3.** Characteristics of the women included in the trials

		Carpenter, 1990[10]	Prevedel, 2003[11]	Barakat, 2008[12]	Cavalcante, 2009[13]	Haakstad, 2011[14]	Ruiz, 2013[15]	Barakat, 2014[16]	Barakat, 2014[17]	Barakat, 2016[18]
Maternal age (y) Mean±SD		NR	20	30.4±2.9 vs 29.5±3.7	25.8±4.6 vs 24.4±5.8	31.2±3.7 vs 30.3±4.4	31.6±4 vs 31.9±4	31.57±3.87 vs 31.51±3.92	31.4±3.2 vs 31.7±4.5	31.6±4.2 vs 31.8±4.5
Parity	**0**	NR	NR	72.2% vs 57.1%	47.1%* vs 62.2%*	NR	NR	60.7% vs 53.9%	60.9% vs 54.6%	67.8% vs 59.8%
	1	NR	NR	22.2% vs 35.7%	NR	NR	NR	34.6% vs 40.4	33.3% vs 39.5%	26.2% vs 33.2%
	>1	NR	NR	5.6% vs 7.2%	NR	NR	NR	4.7% vs 5.6%	2.9% vs 5.9%	6% vs 7.1%
	Sedentary	NR	NR	26/72 (36.1%) vs 21/70 (30%)	NR	37/52 (71.2%) vs 36/53 (67.9%)	195/476 (41%) vs 184/477 (38.6%)	NR	58/138 (42%) vs 68/152 (44.7%)	171/382 (44.8%) vs 148/383 (38.6%)

Occupation	**Housewife**	NR	NR	31/72 (43.1%) vs 30/70 (42.9%)	NR	NR	126/476 (26.5%) vs 118/477 (24.7%)	NR	25/138 (18.1%) vs 33/152 (21.7%)	72/382 (18.8%) vs 93/383 (24.3%)
	Active	NR	NR	15/72 (20.8%) vs 19/70 (27.1%)	NR	NR	155/476 (32.5%) vs 175/477 (36.7%)	NR	55/138 (39.9%) vs 51/152 (33.6%)	139/382 (36.4%) vs 142/383 (37.1%)
Daily smokers (%)		NR	10% (overall smoking index)	16/72 (22.2%) vs 20/70 (28.6%)	NR	2/52 (3.8%) vs 1/53 (1.9%)	NR	11/107 (10.3%) vs 12/89 (13.5%)	18/138 (13%) vs 29/152 (19.1%)	40/382 (10%) vs 54/383 (14.1%)
Pre-pregnancy BMI Mean±SD		NR	NR	24.3±0.5 vs 23.4±0.5	24.1±4.5 vs 23.4±3.8	23.8±3.8 vs 23.9±4.7	23.7±3.9 vs 23.5±4.2	23.8±4.4 vs 24.1±4.3	24.0±4.3 vs 23.6±4	23.6±3.8 vs 23.4±4.2
Pre-pregnancy BMI (%)		NR	NR	NR	NR	NR	**<18.5** 11/480 (2.3%) vs 24/482	**<18** 1/106 (0.9%) vs 2/90	NR	**<18.5** 10/382 (2.6%) vs 20/383

						(5%) **18.5-24.9** 323/480 (67.3%) vs 329/482 (68.2%) **25-29.9** 111/480 (23.1%) vs 92/482 (19.1%) **>30** 35/480 (7.3%) vs 37/482 (7.7%)	(2.2%) **18-24.9** 73/106 (68.9%) vs 58/90 (64.5%) **25-29.9** 25/106 (23.6%) vs 21/90 (23.3%) **>30** 7/106 (6.6%) vs 9/90 (10%)		(5.2%) **18.5-24.9** 258/382 (67.5%) vs 259/383 (67.6%) **25-29.9** 89/382 (23.3%) vs 75/383 (19.6%) **>30** 25/382 (6.5%) vs 29/383 (7.6%)
Prior PTB	NR	NR	2.8% vs 4.3%	NR	NR	0% vs 0%	NR	5.8% VS 3.9%	0% vs 0%

357 GA, Gestational Age; BMI, Body Mass Index; SD, Standard Deviation; WR, Week Range; NR, Not Reported.

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359 Data are presented always in the same order: intervention group vs control group.

360 * These data are taken from reference[26] of the same authors on the very same pregnant women population.

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371 **Table 4**. Primary and secondary outcomes

	Carpenter, 1990[10]	Prevedel, 2003[11]	Barakat, 2008[12]	Cavalcante, 2009[13]	Haakstand, 2011[14]	Ruiz, 2013[15]	Barakat, 2014[16]	Barakat, 2014[17]	Barakat, 2016[18]	Total	RR or MD (95% CI)
PTB <37weeks	0/7 (0%) vs 0/7 (0%)	3/22 (13.6%) vs 1/19 (5.3%)	2/72 (2.8%) vs 3/70 (4.3%)	2/33** (6.1%) vs 3/37 (8.1%)	2/52 (3.8%) vs 1/53 (1.9%)	8/335 (2.3%) vs 2/352 (0.6%)	4/106 (3.8%) vs 4/91 (4.4%)	6/138 (4.3%) vs 11/152 (7.2%)	19/257 (7.4%)[§§] vs 21/256 (8.2%)[§§]	46/1022 (4.5%) vs 46/1037 (4.4%)	1.01 [0.68, 1.50]
GA at delivery (weeks) Mean ± SD	NR	NR	39.57±1.1 vs 39.71±1.4	39.2±2.2 *** vs 39.1±1.6 ***	39.9±1.2 vs 39.6±1.2	39.6±1.5 vs 39.6±1.3	39.46±1.9 vs 39.2±2.2	39.6±1.1 vs 39.7±1.3	39.6 ±1.74 vs 39.4 ±1.86	---	0.05 [-0.07, 0.17]
Spontaneous vaginal delivery	NR	NR	51/72 (70.8%)* vs 50/70 (71.4%)*	21/33 (63.6%) vs 20/37 (54,1%)	NR	280/335 (83.6%) vs 286/352 (81.3%)	72/105 (68.6%) vs 52/91 (57.1%)	100/138 (72.5%)[§§] vs 88/152 (57.9%)[§§]	260/382 (68.1%) vs 236/383 (61.6%)	784/1065 (73.6%) vs 732/1085 (67.5%)	**1.09 [1.04, 1.15]**
Operative vaginal	NR	NR	10/72 (13.9%)*	NR	NR	NR	15/105 (14.3%)	16/138 (11.6%)[§]	49/382 (12.8%)	90/697 (12.9%)	0.78 [0.61, 1.01]

delivery			vs 9/70 (12.9%)*				vs 13/91 (14.3%)	vs 29/152 (19.1%)§	vs 64/383 (16.7%)	vs 115/696 (16.5%)	
Cesarean delivery	NR	NR	11/72 (15.3%)* vs 11/70 (15.7%)*	12/33 (36.4%) vs 17/37 (45.9%)	NR	55/335 (16.4%) vs 66/352 (18.7%)	18/105 (17.1%) vs 26/91 (28.6%)	22/138 (15.9%)§ vs 35/152 (23%) §	73/382 (19.1%) vs 83/383 (21.7%)	191/1065 (17.9%) vs 238/1085 (22%)	**0.82 [0.69, 0.97]**
GDM	NR	NR	NR	NR	NR	7/335 (2.1%) vs 18/352 (5.1%)	5/106 (4.7%) vs 5/90 (5.6%)	6/138 (4.3%) vs 12/152 (7.9%)	2/257 (0.8%) vs 15/256 (5.9%)	20/836 (2.4%) vs 50/850 (5.9%)	**0.41 [0.24, 0.68]**
Hypertensive disorders	NR	NR	NR	NR	1/52 (1.9%) vs 1/53 (1.9%)	5/335 (1.5%) vs 20/352 (5.7%)	NR	NR	6/257 (2.3%) vs 13/256 (5.1%)	12/644 (1.9%) vs 34/661 (5.1%)	**0.36 [0.19, 0.69]**
Birth weight (g) **Mean ± SD**	NR	3110 vs 3175	3165±411 vs 3307±477	3222.2±562.7 vs 3312.7±656.1	3477±424 vs 3542±464	3219±433 vs 3215±419	3186.6±440.76 vs 3261.18±466.59	3203±461 vs 3232±448	3252±438 vs 3218±453	---	-10.46 [-47.1 to 26,21]

LBW	NR	NR	4/72 (5.6%) vs 4/70 (5.7%)	3/33 (9.1%) vs 2/37 (5.4%)	1/52 (1.9%) vs 1/53 (1.9%)	19/335 (5.7%) vs 15/352 (4.3%)	NR	NR	12/257 (4.7%)[§§] vs 14/256 (5.5%)[§§]	39/749 (5.2%) vs 36/768 (4.7%)	1.11 [0.72, 1.73]

372 GA, gestational age; LBW, low birth weight; PTB, preterm birth; GDM, gestational diabetes mellitus; Hypertensive disorders include gestational

373 hypertension and preeclampsia

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

375 * These data are taken from reference[27] of the same authors on the very same pregnant women population.

376 **Authors report that a woman in the exercise group was lost to follow up: data on her delivery and on the newborn infant are not available.

377 ***These data are taken from reference[26] of the same authors on the very same pregnant women population.

378 [§] These data are taken from reference[28] of the same authors on the very same pregnant women population.

379 [§§]Data from only normal BMI women subgroup.

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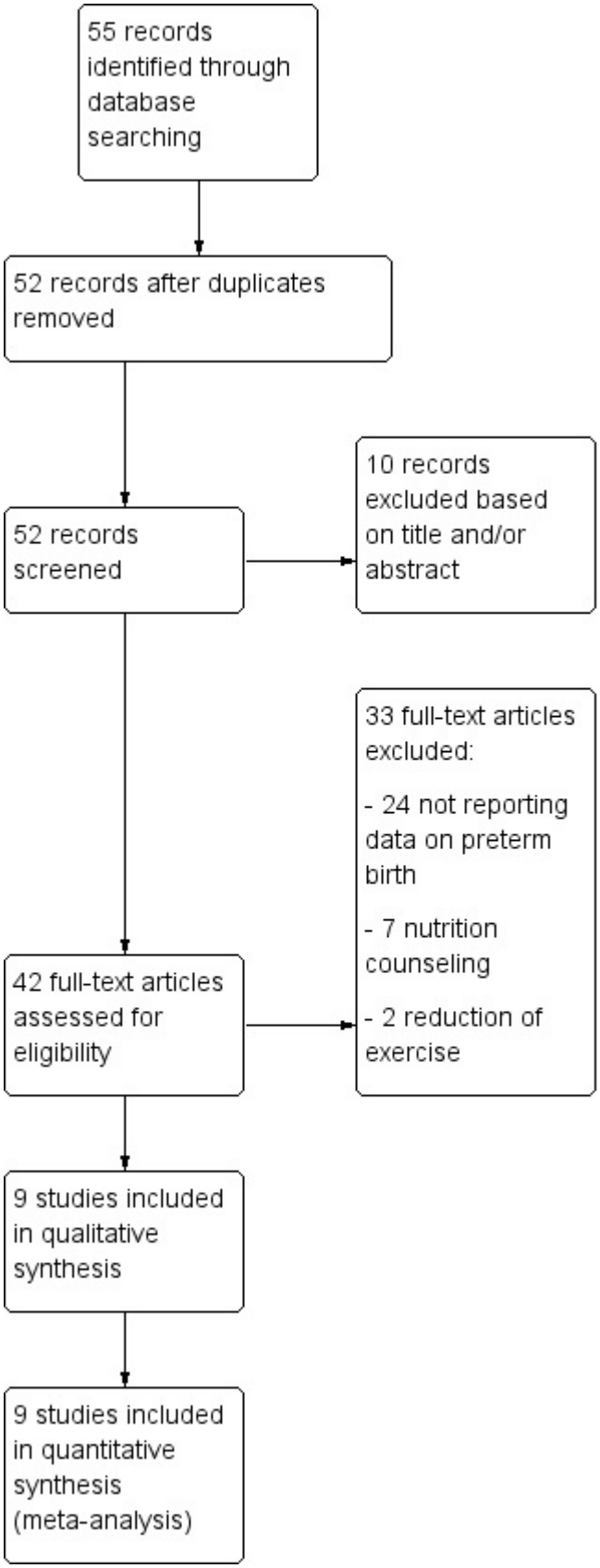
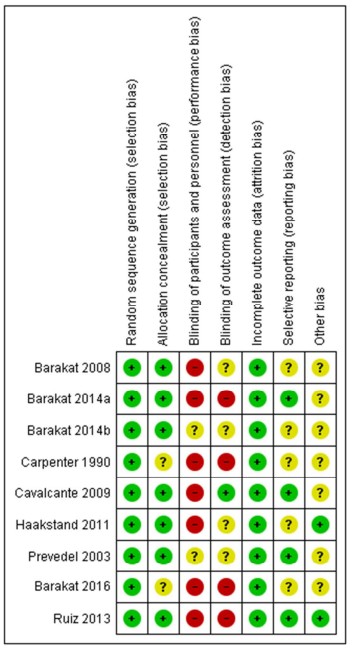
Figure 1. Flow diagram of studies identified in the systematic review. (Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses])

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 (i.e. incidence of preterm birth). RR, relative risk

Figure 4. Forest plot for the risk of the primary outcome (i.e. incidence of preterm birth). CI, confidence interval; M-H, Mantel-Haenszel; df, degrees of freedom.





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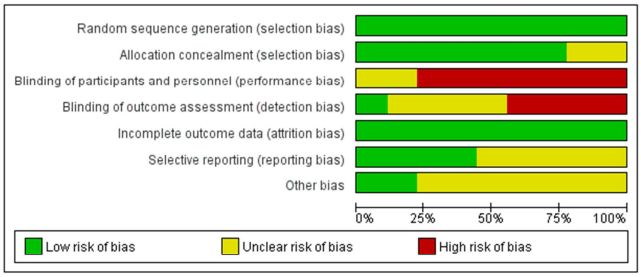

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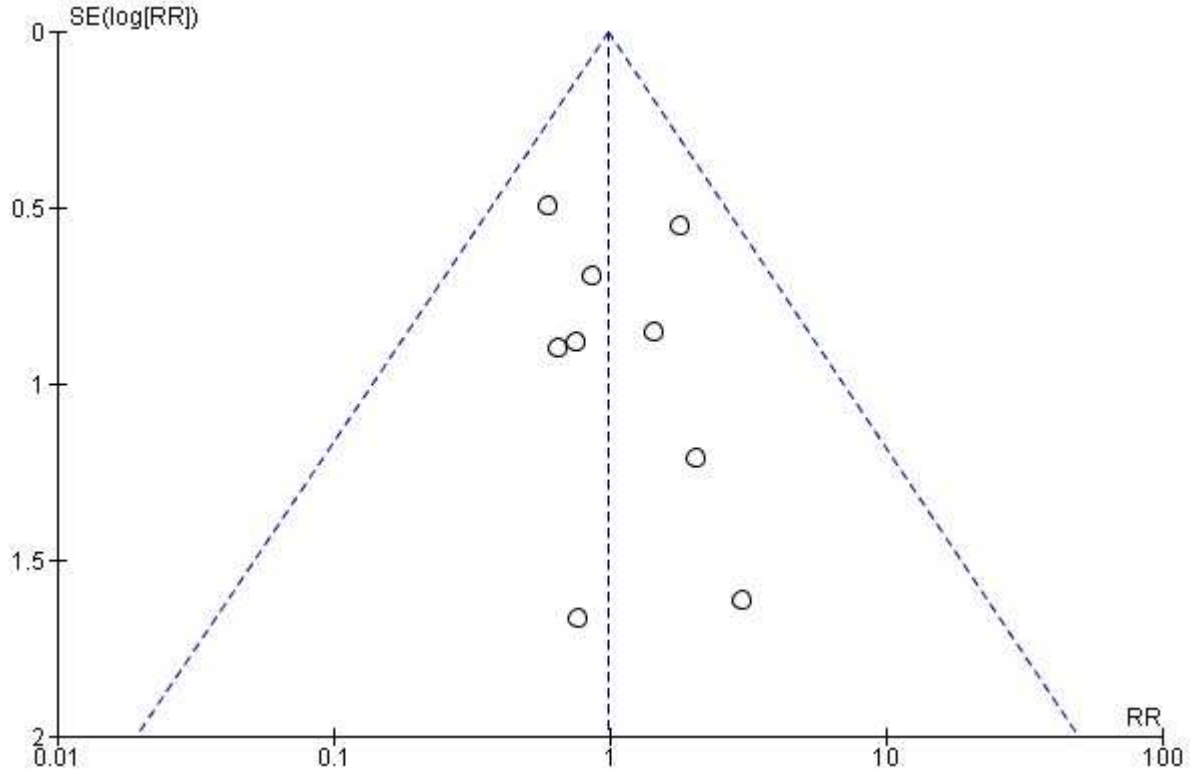

Study or Subgroup	Exercise Events	Exercise Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Carpenter 1990	0	7	0	7		Not estimable	1990
Prevedel 2003	3	22	1	19	2.3%	2.59 [0.29, 22.88]	2003
Barakat 2008	2	72	3	70	6.7%	0.65 [0.11, 3.76]	2008
Cavalcante 2009	2	33	3	37	6.2%	0.75 [0.13, 4.20]	2009
Haakstand 2011	2	52	1	53	2.2%	2.04 [0.19, 21.80]	2011
Ruiz 2013	8	335	2	352	4.3%	4.20 [0.90, 19.65]	2013
Barakat 2014a	4	106	4	91	9.4%	0.86 [0.22, 3.34]	2014
Barakat 2014b	6	138	11	152	22.9%	0.60 [0.23, 1.58]	2015
Barakat 2016	19	257	21	256	46.0%	0.90 [0.50, 1.64]	2016
Total (95% CI)		**1022**		**1037**	**100.0%**	**1.01 [0.68, 1.50]**	
Total events	46		46				

Heterogeneity: $Chi^2 = 6.00$, $df = 7$ ($P = 0.54$); $I^2 = 0\%$

Test for overall effect: $Z = 0.04$ ($P = 0.97$)