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Effects of physical exercise during pregnancy on mothers' and neonates' health: a protocol for an umbrella review of systematic reviews and meta-analysis of randomised controlled trials

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ABSTRACT

Introduction A growing interest has emerged on the effects of exercise during gestation. Several systematic reviews and meta-analyses have shown that prenatal exercise could reduce the mothers' risk for some disorders. Despite this, evidence regarding the risk of caesarean section, birth weight or Apgar score at delivery is still controversial. Furthermore, practitioners are reluctant to recommend exercise to pregnant women suffering from some disorders, such as hypertension, pre-eclampsia or pregnant women with obesity. Moreover, the scarcity of studies addressing the risks and benefits of exercise at higher intensity prevent practitioners from recommending it at higher dosages. Umbrella reviews represent an appropriate design to elucidate the reasons behind the contradictory findings of previous systematic reviews.

Methods This protocol was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols and the Cochrane Collaboration Handbook. Medline, EMBASE, Web of Science, Cochrane database of systematic reviews, Epistemonikos, Prospero register and SPORTDiscuss databases will be searched to identify systematic reviews, meta-analyses and randomised controlled trials that examine the effect of exercise on pregnancy outcomes from inception to August 2019. Searches will be conducted from September to November 2019.

Statistical analysis Methodological quality will be evaluated using the AMSTAR 2 tool. The certainty of evidence and strength of recommendations for meta-analyses will be assessed by the Grading of Recommendations Assessment, Development and Evaluation framework. The summary effect sizes will be calculated through the use of random-effects and fixed-effects models. Heterogeneity among studies will be assessed using the I^2 statistic, and evidence of excess significance bias and evidence of small study effects will also be evaluated.

Ethics and dissemination Ethical approval will not be needed for this review protocol. The results will be disseminated to academic audiences by peer-reviewed publications. Furthermore, results will be disseminated to clinical audiences through professionals' associations and social networks, and may influence guidelines developers in order to improve outcomes in mothers and offspring.

PROSPERO registration number CRD42019123410.

Strengths and limitations of this study

- ► This protocol aims to overcome the inconclusive evidence about the effect of exercise on overweight pregnant women and pregnant women with obesity.
- ► We aim to elucidate the safety and benefits of physical activity at intensity levels significantly higher than the moderate-intensity usually recommended.
- ► This umbrella review will provide a definitive support to the evidence to recommend exercise during pregnancy in some prevalent disorders, such as hypertension, pre-eclampsia or gestational diabetes.
- ► The main anticipated limitations include the low-medium quality level of some studies.
- ► Heterogeneity among the included studies could lead to bias in the results; therefore, a random-effects model will be considered for medium-high heterogeneity reviews.

BACKGROUND

The need for this work

Regular physical exercise (PE) is associated with physical, psychological and social benefits in the general population.[1] In recent years, a growing interest has emerged on the beneficial effects of PE during gestation.[2–4] In fact, professional associations of obstetricians and gynaecologists[5] and, more recently, international guidelines for physical activity[1 6] endorse PE throughout the gestational period recommending pregnant women to accumulate at least 150 min of moderate-intensity aerobic activity per week, distributed over at least 3 days a week. However, being active every day is the most beneficial for maternal health.[5 7]

This evidence comes from several systematic reviews and meta-analyses supporting that prenatal exercise, besides benefiting newborn infants, could reduce the mothers' risk for some disorders, such as gestational diabetes mellitus, excessive maternal weight gain, pre-eclampsia and hypertensive disorders of pregnancy, incontinence urinary or postpartum depression.[3 4 8 9] Furthermore, maternal PE reduces caesarean delivery rates in healthy pregnant women.[10] Despite this, <15% of pregnant women follow the physical activity recommendations.[11 12]

Moreover, although numerous systematic reviews and meta-analyses have addressed the effects of PE on maternal health, evidence regarding the risk of caesarean section, birth weight or Apgar score at delivery is still controversial. In this sense, a recent systematic review and meta-analysis[13] did not find a significant association between prenatal exercise and the risk of caesarean section, while two meta-analyses indicated a decrease in the risk of caesarean delivery among pregnant women who exercised.[10 14] Likewise, another meta-analysis concluded that prenatal PE was not associated with birth weight or Apgar score at delivery,[15] whereas two previous meta-analyses supported that newborns of mothers who were active during pregnancy had a lower weight within the normal range and higher Apgar scores than their counterparts.[16 17] However, despite these inconclusive findings, because the effects of exercise in women with excess of weight continue to be an unresolved question for both clinicians and pregnant women, it is worthwhile to conduct other broader research approaches, such as an umbrella review, which increases the likelihood of providing more consistent evidence on this issue.

If this happens when dealing with healthy pregnant women, it is not surprising that practitioners are reluctant to recommend exercise to pregnant women suffering from some disorders, such as hypertension or pre-eclampsia, since guidelines include these disorders as absolute or relative contraindications to exercising during pregnancy.[5] Similarly, the PE recommendation for overweight pregnant women and pregnant women with obesity continues to be a debatable issue due to the low quality of evidence regarding its benefits.[2]

Finally, the safety or additional benefits of vigorous exercise for pregnant women and fetus health are widely debated. Although consistent evidence supports the beneficial effects of moderate PE in healthy pregnant women, the scarcity of studies addressing the risks and benefits of exercise at higher intensity prevents practitioners from recommending PE at higher dosages in terms of frequency, duration or intensity than recommended in clinical guidelines.[2 6]

Therefore, considering the myriad of systematic reviews and meta-analyses of randomised controlled trials (RCTs) addressing the impact of exercise during pregnancy on different maternal health outcomes, and the contradictory findings of these previous reviews, umbrella reviews represent an appropriate design to elucidate the reasons behind the conflicting findings of previous systematic reviews, and to provide clinicians and policymakers with an overall assessment of the evidence on this issue, which is necessary for both practitioners and pregnant women.[18]

OBJECTIVES

This umbrella review of systematic reviews and meta-analyses aims to provide an overview of the effect of PE during pregnancy on mothers' and children's health. Additionally, an updated meta-analysis of RCTs will be performed in order to assess the effect of PE interventions on some pregnancy outcomes for which new RCTs have been published and not included in previous systematic reviews and meta-analyses.

METHODS

This protocol was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols and the Cochrane Collaboration Handbook,[19 20] and has been registered in the PROSPERO database (registration number: CRD42019123410).

Search strategy

Screening and selection

Two investigators will independently and systematically search the following databases, from inception to August 2019, in order to identify systematic reviews and meta-analyses evaluating the effect of PE on mothers' and children's health: Medline, EMBASE, Web of Science, Cochrane database of systematic reviews, Epistemonikos, Prospero register and SPORTDiscuss. Furthermore, these databases will be screened to search for eligible RCTs published subsequently to the date the latest systematic review was conducted. The references of eligible reviews will also be manually searched. As the dates of searches are planned from September 2019 to November 2019, the date of the last meta-analysis and RCT included will be 31 August 2019. Since we are aware that meta-analysis and RCT till this date will be not included in the thesaurus search strategy, we will conduct both search techniques with thesaurus mapping and with free-text search.

Study records will be managed through the use of the Mendeley reference manager.

The search strategy will be conducted following the Participants, Intervention, Comparision and Outcomes (PICO) components (see the search strategy in tables 1 and 2).

Inclusion/exclusion criteria for study selection

The inclusion criteria for this umbrella review will be: (i) systematic reviews and meta-analyses of RCTs; (ii) RCTs not included in the most recently published systematic reviews selected for the umbrella review; (iii) control groups receiving usual prenatal care or another type of PE intervention and (iv) studies written in any language.

Table 1 Search strategy PubMed of systematic reviews and meta-analyses

Search set	Medline
#1	Pregnant
#2	Pregnancy
#3	Gravid
#4	Gestation*
#5	Maternal
#6	Fetus
#7	Neonate
#8	Newborn
#9	Child*
#10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
#11	Aerobic
#12	Sport
#13	Exercise
#14	Fitness
#15	'Physical exercise'
#16	'Physical activity'
#17	'Motor activity'
#18	11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
#19	Diabetes
#20	Diabetes mellitus
#21	DM
#22	'Gestational diabetes'
#23	'Glucose intolerance'
#24	Glucose
#25	Insulin
#26	Hyperglycemia
#27	Toxemia
#28	Preeclampsia
#29	Pre-eclampsia
#30	Eclampsia
#31	'Hypertensive disorders'
#32	'Blood pressure'
#33	'Weight retention'
#34	'Body Mass Index'
#35	BMI
#36	Labor
#37	Labour
#38	Delivery
#39	Caesarean
#40	'Prenatal depression'
#41	'Pre-natal depression'
#42	'Pre natal depression'
#43	'Postpartum depression'
#44	'Post partum depression'
#45	'Post-partum depression'
#46	'Postnatal depression'
#47	'Post natal depression'
#48	'Post-natal depression'
#49	'Puerperal depression'
#50	'Peripartum depression'
#51	'Depressive disorder'
#52	Depression
#53	Abortion
#54	Stillbirth
#55	'Fetal death'
#56	'Gestational age'
#57	Preterm
#58	'Preterm delivery'
#59	Prematur*
#60	'Birth weight'
#61	Macrosoma
#62	'Apgar score'
#63	'umbilical cord blood'
#64	'pH umbilical cord'
#65	19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64
#66	Meta
#67	Meta-analysis
#68	Review
#69	'Systematic review'
#70	66 OR 67 OR 68 OR 69
#71	10 AND 18 AND 65 AND 70

Reviews that did not systematically search the literature or not provide comprehensive data from individual studies will be excluded. Whenever more than one meta-analysis on the same outcome is eligible, the one with the largest number of included studies will be selected, but a sensitivity analysis will be conducted in order to assess concordance in the pooled estimates in terms of magnitude and direction of their duplicate analyses.

Participants

Women without absolute or relative contraindications to exercise as defined by the 2015 American College of

Table 2 Search strategy PubMed for randomised controlled trials

Search set	Medline
#1	Pregnant
#2	Pregnancy
#3	Gravid
#4	Gestation*
#5	Maternal
#6	Fetus
#7	Neonate
#8	Newborn
#9	Child*
#10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
#11	Aerobic
#12	Sport
#13	Exercise
#14	Fitness
#15	'Physical exercise'
#16	'Physical activity'
#17	'Motor activity'
#18	11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
#19	Diabetes
#20	Diabetes mellitus
#21	DM
#22	'Gestational diabetes'
#23	'Glucose intolerance'
#24	Glucose
#25	Insulin
#26	Hyperglycemia
#27	Toxemia
#28	Preeclampsia
#29	Pre-eclampsia
#30	Eclampsia
#31	'Hypertensive disorders'
#32	'Blood pressure'
#33	'Weight retention'
#34	'Body Mass Index'
#35	BMI
#36	Labor
#37	Labour
#38	Delivery
#39	Caesarean
#40	'Prenatal depression'
#41	'Pre-natal depression'
#42	'Pre natal depression'
#43	'Postpartum depression'
#44	'Post partum depression'
#45	'Post-partum depression'
#46	'Postnatal depression'
#47	'Post natal depression'
#48	'Post-natal depression'
#49	'Puerperal depression'
#50	'Peripartum depression'
#51	'Depressive disorder'
#52	Depression
#53	Abortion
#54	Stillbirth
#55	'Fetal death'
#56	'Gestational age'
#57	Preterm
#58	'Preterm delivery'
#59	Prematur*
#60	'Birth weight'
#61	Macrosoma
#62	'Apgar score'
#63	'umbilical cord blood'
#64	'pH umbilical cord'
#65	19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64
#66	Effectiveness
#67	'Program evaluation'
#68	'Randomized controlled trial'
#69	RCT
#70	'Controlled trial'
#71	Trial
#72	66 OR 67 OR 68 OR 69 OR 70 OR 71
#73	18 AND 18 AND 65 AND 72

Obstetricians and Gynecologists' recommendations for physical activity and exercise during pregnancy and the postpartum period.[5]

Patient and public involvement

No patients were involved.

Types of intervention

PE programme including any level of exercise intensity will be considered. When a meta-analysis includes studies with an extra intervention, such as a nutritional or behavioural intervention, only information on RCTs with

the PE intervention alone will be extracted. Women in the control group will be given usual prenatal care.

Types of outcome measures

Pregnancy outcomes that will be included in this umbrella review and update of RCTs are:

1. Gestational diabetes mellitus;
2. Hypertensive disorders of pregnancy;
3. Gestational weight gain;
4. Type of delivery;
5. Prenatal depression;
6. Postpartum depression;
7. Postpartum weight retention;
8. Spontaneous abortion (including stillbirths until 20 weeks of gestational age and/or weight fetus minor 500 g);
9. Maternal mortality.

Fetal and neonatal outcomes that will take part in this umbrella review and update of RCTs are:

1. Gestational age;
2. Preterm delivery;
3. Birth weight;
4. Apgar score at 1 and 5 min;
5. pH of umbilical cord blood;
6. Stillbirth;
7. Neonatal death.

DATA COLLECTION AND ANALYSIS

Selection of studies and data extraction

First, record titles and abstracts will be independently evaluated to identify eligible studies according to the inclusion and exclusion criteria. Then, the full-texts of possible eligible studies will be comprehensively reviewed by two investigators (GS-M and RP-L). Disagreements will be solved by consensus between them, but if disagreements persist, a third investigator will solve the conflict (BN-P). The two investigators will extract data (authorship, date, study characteristics, type of exercise, main outcome and quality assessment tool) from each included study. Data extraction forms have been designed ad hoc (see online supplementary files 1 and 2). Corresponding authors will be contacted when there are missing data or to clarify unclear information.

Assessment of risk of bias and methodological quality of included studies

The methodological quality of the included systematic reviews and meta-analyses will be evaluated using the AMSTAR 2 tool,[21] which was developed and validated to critically assess the quality of systematic reviews and meta-analyses. This instrument includes 16 criteria referring to relevant methodological aspects of studies. The quality of studies will be classified, according to the number of approved criteria, as follows: excellent, 15–16; very good, 12–14; good, 9–11; acceptable, 6–8 and deficient, 3–5.

The risk of bias (quality) for the RCTs selected for the updated systematic review and meta-analysis will be assessed following the Cochrane Collaboration's methodology. This tool is based on eight potential sources of bias: random sequence generation; allocation concealment; blinding of participants, of the evaluator, of the outcome assessment; incomplete outcome data; missing data and other.

Finally, the certainty of evidence and strength of recommendations for meta-analyses will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). This tool provides a rating of 'high', 'moderate', 'low' or 'very low' quality, and will provide a 'weak' or 'strong' recommendation. This will be accomplished using the GRADEpro software, and output tables will be added.

Data analysis

Tables will be designed to summarise the key characteristics of the included studies. Additionally, forest plots will be used to show results extracted from each meta-analysis.

Assessment of summary effects and heterogeneity

For each meta-analysis, the summary meta-analytic estimates and corresponding 95% CI will be calculated using both fixed-effects and random-effects models.[22 23] The 95% prediction intervals will also be estimated for the summary random-effects estimates, which will account for the between-study heterogeneity and as well as explaining the uncertainty for the effect that could be expected if a new study examines the same association.[24–26] Thus, this 95% prediction interval indicates the range where the true effect is expected for 95% of studies from the population of the included studies in the meta-synthesis or similar studies potentially conducted in the future. Additionally, for the largest RCT of each meta-analysis, the SD of the effect size will be calculated and scrutinised if the SD is <0.10.[27 28] Since a higher accuracy on detecting publication bias has been empirically demonstrated using 0.1 as the threshold for significance in the most well-known publication bias tests,[29] in our study the significance p values for Egger's test is setup at 0.1. When meta-analyses have continuous data, the estimated effect will be converted to their equivalent ORs using accepted calculation strategies. For other measures, such as the mean difference or the risk difference, a few general estimations will be needed, such as, Glass'Δ or RR, respectively.[30 31]

Among-study heterogeneity will be assessed using the I^2 statistic.[32] Usually, I^2 ranges between values of <25%, 25%–50%, 50%–75% and >75% which represent small, medium, large or very large amounts of heterogeneity, respectively.[25] The corresponding p values will also be considered. Studies with insufficient data to perform the analyses will be omitted from the data synthesis. When substantial heterogeneity will prevent the calculation of pooled estimates of outcomes, a systematic review or narrative synthesis will be undertaken.

Whenever possible, a meta-analysis will be conducted including the most recent RCTs on this issue not included in previous meta-analyses, and pooled effect size estimates were calculated with their 95% CIs. Moreover, when several studies have been published after the latest meta-analysis,

we will first conduct an additional meta-analysis including only the most recent studies, and then we will carry out the umbrella review that will include the newest one. Additionally, for outcomes of studies where a meta-analysis will not be possible, a narrative synthesis of the results will be presented.

Subgroup analysis and meta-regression

In the new meta-analysis, we will carry out subgroup and meta-regression analyses to examine influence of potential mediators such as gestational weight gain on the main outcome. We will also conduct meta-regression analysis on some intervention (length of intervention, duration of intervention sessions) and women (BMI, gestational age at delivery or birth weight) related variables. Finally, subgroup analyses by categorical variables as, type and intensity of exercise or weight status will be conducted.

Small studies effect assessment

Small study effects usually indicate publication or other reporting biases, although these effects may also reflect chance, genuine heterogeneity or other differences between large and small studies.[33] The existence of a potential small study effect will be assessed, if small studies tend to show larger estimates of effect size in contrast to larger studies, using the regression asymmetry Egger's test for continuous outcomes, and Harbord's test for dichotomous ones. A p value <0.10 will be used to show evidence of small-study effects.[34]

Excess of significance evaluation

The excess significance test will be used to evaluate whether the observed number of studies (O) included in each meta-analysis with statistically significant results (positive studies, p<0.05) is different than the expected number of studies with significant results (E).[35] The effect size of the largest study (smallest SE) in a meta-analysis will be used to calculate the statistical power of each component study.[36] Furthermore, the largest study effect will be assumed to be the true effect. A two-sided p<0.10 will be considered statistically significant.

Then, the comparison between the observed and the expected number of studies will be done separately for each meta-analysis, and it will be amplified to groups including many meta-analyses when the observed and the expected values from each meta-analysis will be summed.

All statistical analyses and power calculations will be performed using STATA V.15.1 software (StataCorp, College Station, Texas, USA).

DISCUSSION

Concluding remarks

A positive effect of PE on some pregnancy outcomes has been reported more or less consistently by recent systematic reviews and meta-analyses.[2–4 9 16] This umbrella review is expected to provide a comprehensive and rigorous review of the reported evidence regarding the influence of prenatal exercise on maternal health by synthesising the results of previous systematic reviews and meta-analyses, and conducting an updated meta-analysis of RCTs.

The proposed umbrella review has several strengths. First, this protocol aims to overcome the inconclusive evidence about the effect of PE on overweight pregnant women and pregnant women with obesity; for this, a subgroup analysis with these groups of women will be carried out. Second, we aim to elucidate the safety and benefits of physical activity at intensity levels significantly higher than the moderate-intensity usually recommended. Finally, this umbrella review will provide a definitive support to the evidence to recommend PE during pregnancy in some prevalent disorders, such as hypertension, pre-eclampsia or gestational diabetes.

Strengths and limitations

The main anticipated limitations of this umbrella review include the low-medium quality level of some studies due to small sample sizes or non-blinded data extraction. Furthermore, pregnant women who participate in these studies are volunteers, so they usually have higher levels of compliance than pregnant women from the general population. Thus, these facts could be potential sources of bias. Another potential limitation would be the heterogeneity among the included studies that could lead to bias in the results. Therefore, a random-effects model will be considered for medium-high heterogeneity reviews. Furthermore, we will be cautious when conducting sensitivity analyses based on methodological quality, analysis and interpretation of the results.

Ethics and dissemination

Ethical approval will not be needed for this review protocol because data will be extracted from published studies and there will be no concerns about privacy. The best way to disseminate information will be through conducting dissemination plan, which include: (i) to present findings of this umbrella review in international obstetric conferences; (ii) publishing the results in a peer-reviewed international journal interested in improving clinical practices with scientific evidence and (iii) to upload briefing entries to social networks in order to improve decision-makers and guidelines developers.

Consequently, this umbrella review will have important clinical and public health implications, because it will aim to provide support for recommendations to advise mothers to engage in PE programme as an effective and safe strategy to experience healthier pregnancies, especially in populations at risk in their pregnancies, such as overweight women or women with obesity and those with hypertensive disorders of pregnancy.

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Contributors VM-V and GS-M designed the study. VM-V is the principal investigator and guarantor. RP-L, GS-M and VM-V are the main coordinators of the protocol. GS-M, RP-L, BN-P and IC-R will conduct the study. IC-R, VM-V and CA-B will provide statistical and epidemiological support. GS-M wrote this protocol manuscript with the support of VM-V, RP-L and BN-P. All the authors revised and approved the final version of the manuscript.

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