

INPLASY PROTOCOL

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Exercise as medicine for male reproduction management: a systematic review and network meta-analysis of randomized controlled trials

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ABSTRACT

Review question: In patients with male factor infertility, what is the impact of different exercise modalities, compared to non-exercise intervention, on markers of male reproductive function and performance as well as clinical outcomes (pregnancy and live birth rate)?

Rationale: The methodological quality of previously published systematic reviews in the field was low. They concluded that physical activity appeared to modulate human reproduction, but the effects on clinical outcomes yet were unclear. Our systematic review will use a rigorous methodology to identify, summarize and assess the quality of evidence from RCTs to inform clinicians of the treatment effects of physical exercise modalities in male factor infertility.

Methods: We will search the following databases for eligible articles: PUBMED, MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). We will perform a similar search using the same keywords in the other databases.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 March 2020 and was last updated on 26 March 2020 (registration number INPLASY202030008).

INTRODUCTION

Objectives / Review question: In patients with male factor infertility, what is the impact of different exercise modalities, compared to non-exercise intervention, on

markers of male reproductive function and performance as well as clinical outcomes (pregnancy and live birth rate)?

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the field was low. They concluded that physical activity appeared to modulate human reproduction, but the effects on clinical outcomes yet were unclear. Our systematic review will use a rigorous methodology to identify, summarize and assess the quality of evidence from RCTs to inform clinicians of the treatment effects of physical exercise modalities in male factor infertility.

Condition being studied: We will focus on male factor infertility. The illness normally is due to low sperm production, abnormal sperm function or blockages that prevent the delivery of sperm. Illnesses, injuries, chronic health problems, lifestyle choices, and other factors can play a role in causing male infertility.

METHODS

Participant or population: The population of interest is adults (25-45 years of age) with male factor infertility. We will exclude trials that are primarily conducted in women and animal studies.

Intervention: The studies of interest are the interventions in the field of physical exercise and human reproduction. We will include RCTs that examine the effects of different exercise modalities on one or several markers of male reproductive function. Trials must include a comparator or control group.

Comparator: We will identify randomized control trials comparing treatment effects of different exercise modalities versus a non-intervention control (non-exercise) group in adults with male factor infertility.

Study designs to be included: RCTs involving infertile patients that examined the effects of exercise or physical activity interventions on factors related to male reproduction.

Eligibility criteria: Articles will be included if they are independent original RCTs and evaluated the impact of one or more of the selected types of exercise interventions on human reproduction. Studies analyzed non-

human or female populations as well as studies considered other factors related to the human reproduction, in vivo analysis, or studies with focus on other diseases, case reports, reviews, author comments, abstracts will be excluded.

Information sources: PUBMED, MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) databases will be searched for the eligible articles using the keywords of interests. Requests for data will be sent to authors when detailed information is unavailable.

Main outcome(s): The key outcomes of interest for this review are as follows: Primary outcome - Pregnancy rate: the success rate for getting pregnant is the percentage of all attempts that lead to pregnancy, with attempts generally referring to menstrual cycles. Live birth rate: the number of deliveries that resulted in a live-born neonate.

Secondary outcomes - Semen quality: is a measure of the ability of sperm in semen to accomplish fertilization. Semen quality involves both sperm quantity and quality.

Additional outcome(s): Miscarriage rate, also known as spontaneous abortion and pregnancy loss, is the natural death of an embryo or fetus before it is able to survive independently.

Data management: We will perform data extraction independently and in duplicate using pre-tested data abstraction forms (DistillerSR). Data abstracted will include title, first author, relevant baseline patient data, intervention and comparator, results of key outcomes and data on methodological quality. Disagreements will be settled by discussion, and a third independent data abstractor if necessary.

Quality assessment / Risk of bias analysis: We will evaluate the methodological rigor of each trial using a modified Cochrane Collaboration tool for assessing the risk of bias. For each outcome in each included RCT, we will provide a description, comment and judgment of 'definitely yes', 'probably yes', 'probably not' and 'definitely

no' in each of the following domains: adequacy of sequence generation, allocation concealment, blinding of patients, blinding of clinicians, blinding of data collectors, blinding of data analysts, blinding of outcome adjudicators, selective outcome reporting and other biases. Two independent reviewers will perform the risk of bias assessment, with disagreements resolved by discussion, and a third reviewer if necessary. We will consider the risk of bias for each element to be 'high' when bias is present and likely to affect outcomes, and 'low' when bias is not present, or present but unlikely to affect outcomes. We will investigate the possibility of publication bias using a funnel plot, provided there are at least 10 included studies (RevMan). To test for funnel plot asymmetry, we will use the Egger test for continuous outcomes and the arcsine test for dichotomous outcomes.

Strategy of data synthesis: We will conduct a network meta-analysis to pool the effect sizes of several interventions and modalities obtaining from RCTs. We will use the R software program version 3.6.1. to analyze the data and depict the relevant graphs. Functions of netmeta and netmetabin package will implement in the software environment. The network graph will depict to see the overall structure of comparisons, allowing us to understand which treatments were compared with each other in the original data. Net split tables will generate to check for consistency in the network. This method splits our network estimates into the contribution of direct and indirect evidence, which allows us to control for inconsistency in specific comparisons in our network. In order to visualize the netsplit results, a forest plot will be used displaying all comparisons for which there was both direct and indirect evidence. The total inconsistency and heterogeneity of effect sizes directly will check using the full design-by-treatment interaction random-effects model. Fixed effect model will be used for homogenous and consistent data, while random-effects model will be used for heterogeneous data. Publication bias will test by the Begg-Mazumdar test of the

intercept to quantify the bias captured by the funnel plot and to test whether it is statistically significant.

Subgroup analysis: Subgroup analysis will perform according to age, ethnicity, different subtypes of male infertility disease, and duration of intervention.

Sensibility analysis: To discover the stability, reliability of the meta-analysis results and to identify the heterogeneity sources, sensitivity analysis will be used by the eliminating trials with a high risk of bias or excluding each study one by one. The meta-analysis will then be performed again and the results compared to the previous meta-analysis.

Language: There is no limitations set on language of publication.

Countries involved: Germany and Iran.

Other relevant information: We will review the reference lists of all identified RCTs, and published systematic reviews and review articles on the topic for potentially relevant trials.

Keywords: RCTs, exercise, infertility, physical activity.

Dissemination plans: Our findings will be disseminated through conference presentation and publication in a peer-reviewed journal. We will report this systematic review in accordance with the PRISMA statement.

Contributions of each author:

Author 1 - Conceived the idea for this systematic review. Developed the methodology for the systematic review protocol. Developed the search strategy and will screen potential studies, perform duplicate independent data extraction, risk of bias assessment, GRADE assessment, and data synthesis. Is the guarantor of the review.

Author 2 - Conceived the idea for this systematic review. Developed the methodology for the systematic review protocol. Developed the search strategy

and will screen potential studies, perform duplicate independent data extraction, risk of bias assessment, **GRADE** assessment and data synthesis. is the guarantor of the review.

Author 3 - Developed the search strategy and will screen potential studies, perform duplicate independent data extraction, risk of bias assessment, **GRADE** assessment and data synthesis. is the guarantor of the review. Will act as a third reviewer and arbitrator if necessary.