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REVIEW

# The role of maternal physical activity on in vitro fertilization outcomes: a systematic review and meta-analysis

Eleftheria Kakargia[1] · Eleftherios Mamalakis[2] · Maximos Frountzas[3] · Evangelos Anagnostou[4] · Charalampos Siristatidis[5]

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## Abstract

**Purpose** This systematic review is designed to summarize the evidence concerning the impact of maternal physical activity on the reproductive outcomes following assisted reproduction techniques (ART), namely in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI).

**Methods** We searched for eligible studies on PubMed, EMBASE databases and the Cochrane Library from their inception until September 2021. Our primary outcomes were live birth rate and miscarriage, while secondary ones included clinical pregnancy and implantation rates. The quality of the evidence was evaluated using a study-specific adaptation of the Robins I tool.

**Results** Quantitative data from 10 cohort studies (CS) and 2 randomized control trials (RCT), involving 3431 women undergoing ART treatments, were included in the analyses. The pooled results exhibited uncertainty regarding the effect of physical activity on live birth rate per woman (OR 1.15, 95% CI 0.92–1.43, $p = 0.23$, $I^2 = 61\%$, 9 studies) and miscarriage rates (OR 0.79, 95% CI 0.44–1.43, $p = 0.43$, $I^2 = 44\%$, 6 studies). However, physical activity was associated with significantly improved clinical pregnancy rate after ART (OR 1.39, 95% CI 1.08–1.79, $p = 0.0009$, $I^2 = 68\%$, 10 studies), whereas implantation rate after ART almost reached statistical significance (OR = 1.95, 95% CI 0.99–3.82, $p = 0.05$, $I^2 = 77\%$).

**Conclusion** The current evidence is still insufficient to firmly conclude on the effect of maternal physical activity on live birth, miscarriage and implantation rates. Although clinical pregnancy rates favored physical activity in this group of patients, these results must be undertaken with caution due to the low quality and the high heterogeneity of the studies included.

**Keywords** Assisted reproduction techniques · In vitro fertilization · Maternal physical activity · Exercise · Lifestyle

## Introduction

The impact of negative lifestyle behaviors has long been investigated in the setting of infertility and its treatment outcomes. Based on the latest international glossary on infertility and fertility care, infertility is defined as a disease characterized by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce, either as an individual or with his/her partner [1]. Most studied lifestyle-related factors include obesity, unhealthy diet, lack of physical activity, excess alcohol and caffeine consumption, smoking and psychological stress [2, 3].

Focusing on the aforementioned fitness-related factors, the beneficial effects of exercise in the whole spectrum of human life are undoubtable. Physical activity can contribute into maintaining a solid musculoskeletal system,

✉ Eleftheria Kakargia
elefkak@gmail.com

1 First Department of Internal Medicine, Medical School, National and Kapodistrian University of Athens, 401 General Military Hospital of Athens, Athens, Greece

2 Physiology Department, Medical School, National and Kapodistrian University of Athens, Athens, Greece

3 First Propaedeutic Department of Surgery, Medical School, National and Kapodistrian University of Athens, Hippokration General Hospital of Athens, Athens, Greece

4 Neurosurgery Department, Medical School, National and Kapodistrian University of Athens, 401 General Military Hospital of Athens, Athens, Greece

5 Second Department of Obstetrics and Gynecology, Medical School, National and Kapodistrian University of Athens, "Aretaieio" University Hospital, Athens, Greece

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while simultaneously it can prevent or even reverse the deleterious consequences of sedentary life and concomitant obesity acting as a shield against metabolic syndrome, hypertension, diabetes and their cardiovascular complications [4, 5].

However, it has long been demonstrated that the benefits of engaging into a lifestyle of increased physical activity are limited due to a j-curve pattern [6]. This implies that they diminish after an optimal level, which is different for every individual, while, this increased activity, when exaggerated, may cause more harm than good. This J-curve phenomenon has been mainly investigated in the context of cardiovascular and musculoskeletal health however, it seems to expand even in the field of human fertility.

The optimal dose of physical activity for maximizing health benefits is unknown, and even 2500 years ago, Hippocrates taught: "if we could give every individual the right amount of nourishment and exercise—not too little and not too much—we would have found the safest way to health" [7]. This suggests that there might be a dose range of physical activity that is optimal for improving well-being and life expectancy, with attenuation of these benefits when the amount of exercise is above or below this ideal range.

However, the available results in the medical literature are conflicting concerning the actual impact of exercise on IVF outcomes. Our objective is to identify, appraise and summarize the available data, aiming to provide a quantitative estimate on the impact of physical activity on the reproductive outcomes following assisted reproduction techniques (ART), namely in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) [8, 9] (Table 1).

## Materials and methods

We conducted a systematic review in accordance with Cochrane guidelines [10]. The review is presented using the structure suggested in Preferred reporting items for systematic review and meta-analysis (PRISMA) 2015 [11]. The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on May 12, 2021 (CRD42021245731) [12].

### Search strategy

The Centre for Review and Dissemination (CRD), Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines were followed throughout the process of completing this review [13–15]. The search filters were used for the PubMed, EMBASE databases and the Cochrane Library from their inception until September 2021. The search term combinations were Medical Subject Heading (MeSH) terms, text words and word variants for physical activity and in vitro fertilization. The full search strategy and combinations are illustrated in Fig. 1. Reference lists of relevant articles were hand-searched for potentially eligible studies ("snowball" procedure), so as to maximize the amount of synthesized evidence.

The following search algorithm was used as a basis, and was modified accordingly for each database: (physical activity OR physical active OR physical non-active OR exercise OR lifestyle OR lifestyle-related factors OR sedentary behavior) AND (in vitro fertilization OR IVF OR ICSI OR assisted reproduction techniques OR ART OR assisted

**Table 1** Risk assessment of included studies based on the Robins 1 tool

| | Confounding | Selection | Intervention classification | Deviation from interventions | Missing data | Measurement of outcomes | Selection of reported result | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|
| Läänelaid et al. [21] | Low | Low | Low | Low | Moderate | Low | Low | Moderate |
| Sõritsa et al. [27] | Low | Low | Low | Low | Low | Low | Low | Low |
| Ricci et al. [26] | Low | Moderate | Low | Low | Moderate | Low | Moderate | Moderate |
| Kiel et al. [19] | Serious | Low | Moderate | Low | Moderate | Moderate | Moderate | Serious |
| Gaskins et al. [18] | Moderate | Low | Low | Low | Low | Low | Moderate | Moderate |
| Evenson et al. [16] | Low | Serious | Moderate | Serious | Low | Low | Moderate | Serious |
| Palomba et al. [24] | Moderate | Serious | Moderate | Low | Low | Low | Low | Serious |
| Ramezanzadeh et al. [25] | Moderate | Low | Low | Low | Moderate | Low | Moderate | Moderate |
| Moran et al. [22] | Moderate | Low | Moderate | Low | Serious | Low | Moderate | Serious |
| Kucuk et al. [20] | Moderate | Low | Low | Low | Moderate | Low | Low | Moderate |
| Ferreira et al. [17] | Serious | Moderate | Low | Moderate | Low | Moderate | Moderate | Serious |
| Morris et al. [23] | Low | Moderate | Low | Moderate | Low | Moderate | Moderate | Moderate |

**Fig. 1** Full search strategy

| Group A | and | Group B |
|---|---|---|
| physical activity OR | | in vitro fertilization OR |
| physical active OR | | IVF OR |
| physical non-active OR | | ICSI OR |
| exercise OR | | assisted reproduction techniques OR ART OR |
| lifestyle OR | | assisted reproduction technologies OR |
| lifestyle-related factors OR | | assisted fertility OR |
| sedentary behavior | | assisted reproduction OR |
| | | infertility treatment |

reproduction technologies OR assisted fertility OR assisted reproduction OR infertility treatment).

## Study selection and data extraction

Guidelines suggest using a two-step process for selecting studies for inclusion in a review to reduce selection bias. This process involved the two researchers [EM, EA], analyzing each title and abstract independently. Any inconsistencies were discussed with leading author [EK] and resolved by team consensus. If multiple publications either from the same study group/author or using the same data, were identified, the most recent or most complete publication was used for data extraction, but information from all publications were used when necessary. The studies selected following review of titles and abstracts were then obtained and the full paper analyzed by the researchers. Various methods were used among the studies for the assessment of the level of PA (Table 4). Our study population was divided in two groups, the first one included women with regular activity and the second women with low activity or sedentary life. A study was considered eligible for this meta-analysis if it fulfilled the pre-defined inclusion criteria: (i) randomized controlled trials (RCT) and cohort studies (CS) with any sample size; (ii) women at reproductive age undergoing IVF or ICSI, (iii) studies reported in English up to September 2021. Studies reporting on cycles with donor oocytes were excluded, as an issue of embryo quality impairment might be introduced. Also studies with participants that were athletes were excluded, since they have been exposed to the effects of a significantly higher intensity of exercise and for a longer duration relative to the general population. Case–control studies as well as case series and case reports were excluded, to ensure a standard quality of the evidence to be analysed. When duplicate studies were identified, the most recent study was included unless the earliest version reported more relevant outcomes. Three reviewers (EM, EA, EK) independently evaluated citations for potential inclusion by screening titles and abstracts and assessed full publications to determine eligibility for final inclusion.

Two reviewers (MF and EK) with methodological and content expertise independently extracted information on similar pre-defined forms on study setting and design, study population, intervention, outcomes and other relevant information. The list of data which were extracted is: name of first author, date of publication, location of study, funding (yes, no), mean age of participants, mean body mass index (BMI) of participants, mode, frequency, duration and intensity of physical activity before IVF/ICSI, number of participants in each arm, primary and secondary outcomes, results. The main outcomes under investigation were: 1. live birth and/or ongoing pregnancy; 2. pregnancy loss (Ectopic pregnancy, Miscarriage, Stillbirth). Additional outcomes that were also examined were clinical pregnancy rate, neonatal mortality, major congenital anomaly and gestational age at birth.

## Quality and risk of bias assessment

The studies' methodological quality and risk of bias was evaluated using a study-specific adaptation of the Robins I tool. RoB2 was not eventually used as the majority of studies included were cohort studies. Two reviewers (EA and EK) independently evaluated the risk of bias and rated studies by answering signifying questions of the template that lead to judgments of low, moderate, serious and critical overall risk of bias. Disagreement was resolved by the consultation of the last author (CS).

### Data synthesis and analysis

The statistical analyses were performed with Review Manager version 5.3 software (The Cochrane Collaboration). Confidence intervals (CIs) were set at 95%. Pooled odds ratios (ORs) along with their 95% CIs for the primary outcomes (implantation rate, clinical pregnancy rate, miscarriage rate and live birth rate) were calculated using the random effects model (Der Simonian–Laird). A quantitative analysis for secondary outcomes (neonatal mortality, major congenital anomaly, viable intrauterine pregnancy confirmed by US) was not conducted. The interpretation of results included the study selection strategy, the description of data tabulation, the quantitative analysis of primary outcomes, the qualitative analysis of secondary outcomes and the quality assessment of the included studies. Subgroups were defined according to the mode, frequency, duration and intensity of exercise as well as their categorization according to specific demographic characteristics of the participants and combination with other treatments.

## Results

### Search results

Through the initial database search and other sources, 335 articles were collected. After the removal of 79 records as duplicates and screening of 214 ones through their abstracts, 30 studies were identified as potentially eligible for inclusion and retrieved in full text. Eventually, 12 studies fulfilled the predetermined eligibility criteria, as shown in the PRISMA flow diagram (Table 2).

### Included studies

The present meta-analysis included 12 studies [16–27] that enrolled 3431 women in total, with intense or light physical activity before they undergo ART (IVF/ICSI) (Table 3). No differences were reported among the included studies regarding the baseline characteristics of women, such as age and BMI (Table 4). In addition, five of the included studies [17, 18, 23, 24, 26] utilized a validated self-administered questionnaire about the evaluation of the physical activity prior to ART. On the other hand, Ramezanzadeh et al. [25] used the classic International Physical Activity

**Table 2** Research results

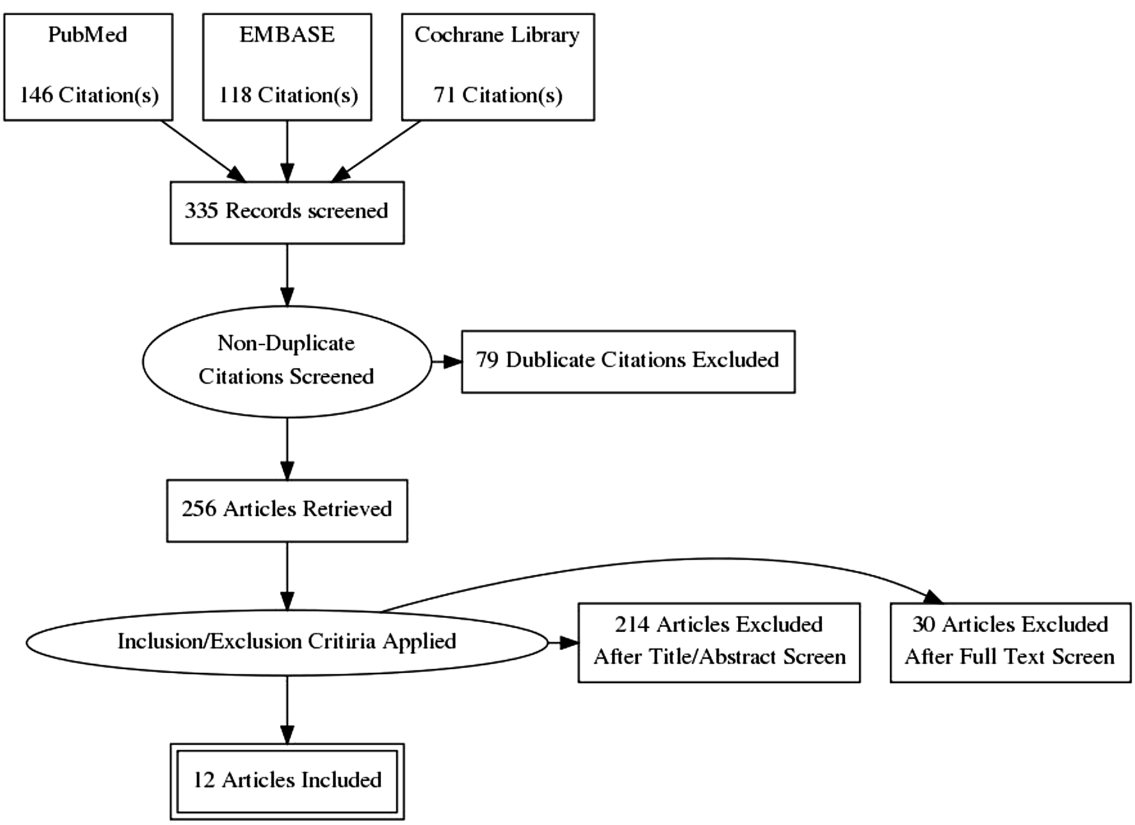

**Table 3** Study characteristics

| References | Type of study | No of patients | Study origin | Inclusion criteria | Treatment |
|---|---|---|---|---|---|
| Morris et al. [23] | Cohort | 1305 | USA | Women undergoing IVF | IVF |
| Ferreira et al. [17] | Cohort | 436 | Brazil | Women undergoing ICSI | ICSI |
| Kucuk et al. [20] | Cohort | 131 | Turkey | Women undergoing their first non-donor ICSI | ICSI |
| Moran et al. [22] | RCT | 38 | Australia | Overweight/obese women undergoing IVF with GnRH agonist protocols who had undergone at least one ART cycle | IVF |
| Ramezanzadeh et al. [25] | Cohort | 236 | Iran | Women undergoing IVF, age 18–40, use autologous oocytes | IVF |
| Palomba et al. [24] | Cohort | 216 | Italy | Obese women undergoing their first ART | IVF/ICSI |
| Evenson et al. [16] | Cohort | 121 | USA | Women undergoing IVF | IVF |
| Gaskins et al. [18] | Cohort | 273 | USA | Women undergoing ART, age 18–46 | IVF/ICSI |
| Kiel et al. [19] | Pilot RCT | 18 | Norway | Overweight women undergoing ART, age > 18, undergoing ART | IVF/ICSI |
| Ricci et al. [26] | Cohort | 492 | Italy | Women undergoing IVF | IVF |
| Sõritsa [27] | Prospective | 101 | Estonia | Women undergoing ART receiving fresh embryo transfer | IVF/ICSI |
| Läänelaid et al. [21] | Cohort | 64 | Switzerland | Women undergoing ART for the first time | IVF/ICSI |

Questionnaire (IPAQ) and Kucuk et al. [20] used the short form of it, whereas Moran et al. [22] included patients that participated in the Comprehensive Lifestyle Intervention Program (CLIP) and the assessment of their physical activity was based on CLIP questionnaires. Finally, two of the included studies [21, 27] evaluated physical activity using a combination of wearable accelerometers and questionnaires.

## Data tabulation

Data on variables of interest were tabulated in three structured forms. Table 3 briefly describes the characteristics of each study, including the study type, the number of patients enrolled, the country of origin and the inclusion criteria as well as the kind of treatment (IVF or ICSI) that was utilized by the women of each study. In addition, Table 4 presents the baseline characteristics of the patients enrolled, such as their age and their BMI, as well as the definition of the activity prior to the utilized ART and the means of evaluation of their activity. Finally, Table 5 summarizes the pregnancy outcomes after ART utilization, such as the implantation rate, the clinical pregnancy rate, the miscarriage rate and the live birth rate.

## Primary outcomes

The meta-analysis of the nine included studies [16, 18, 20–24, 26, 27] that reported the live birth rate after ART demonstrated a trend of high live birth rate among physically active women, but no statistically significant association was observed (OR 1.15, 95% CI 0.92–1.43, $p = 0.23$, $I^2 = 61\%$, Fig. 2). Moreover, a trend towards the association of the physical inactivity and the high miscarriage rate after ART was outlined, but it was proved statistically insignificant (OR 0.79, 95% CI 0.44–1.43, $p = 0.43$, $I^2 = 44\%$, Fig. 3) after the meta-analysis of the six included studies that described the miscarriage rate after IVF/ICSI [17, 18, 20, 22–24].

## Secondary outcomes

The meta-analysis of the ten included studies [16–20, 22, 24–27] that reported the pregnancy rate after ARTs demonstrated a significant correlation between the physical activity and high pregnancy rate after IVF/ICSI (OR 1.39, 95% CI 1.08–1.79, $p = 0.0009$, $I^2 = 68\%$, Fig. 4). On the other hand, the association between physical activity and implantation rate after ARTs almost reached statistical significance (OR 1.95, 95% CI 0.99–3.82, $p = 0.05$, $I^2 = 77\%$, Fig. 5), as the meta-analysis of the three included studies that reported implantation rate after IVF/ICSI demonstrated [20, 24, 25].

## Quality assessment

Risk of bias was assessed for all included studies, ten cohort studies and 2 RCTs, using the Robins I tool. The results of the quality assessment are presented in Table 3. Among the twelve studies, five were classified as having a serious overall risk of bias [16, 17, 19, 22, 24], six were classified as having a low risk [18, 20, 21, 23, 25, 26] and one was classified as having a low risk [27].

**Table 4** Patient characteristics

| References | Age (years) | BMI (kg/m$^2$) | Never smoker | Type of activity—intervention | Evaluation of activity |
|---|---|---|---|---|---|
| Morris et al. [23] | (Median, 10th and 90th percentile): 35 (30,41) | 22.2 (19.5,28.3) | 1305 (100%) | Categories (0) No exercise, (1) 1–3 h per weeks 1–9 years, (2) > 4 h per weeks 1–9 years, (3) 1-3 h per weeks 10–30 years, (4) > 4 h per weeks 10–30 years | Self-administered questionnaire |
| Ferreira et al. [17] | 35 ± 4.8 | 23 ± 3.5 | | Regular PA: practice of physical activity: at least 1 h of activity three times a week | Self-administered questionnaire |
| Kucuk et al. [20] | 33.7 ± 5.2 | 24.7 ± 4.7 | | Low, moderate and high physical activity as defined by the IPAQ working group | International Physical Activity Questionnaire short form (IPAQ-sf) |
| Moran et al. [22] | | | | Exercise and diet intervention versus control | Patients participated in the Comprehensive Lifestyle Intervention Program (CLIP) |
| Ramezanzadeh et al. [25] | (Age < 25: 93/236 age 25–30 94/236, age > 30 49/236) | | | More than 3 h/week moderate-intensity exercise or 5 h/week low-intensity exercise versus not | International Physical Activity Questionnaires |
| Palomba et al. [24] | 37.3 ± 3.6 | 216 (100%) obese | | Regular Physical Activity VERSUS not regular | Self-administered semiquantitative general health questionnaires formulated on the basis of a well-validated international questionnaire |
| Evenson et al. [16] | 67 (55.4%) < 35 years | 71 (58.7%) normal | 96 (82.1%) | Total activity index ≥ 10.6 versus < 10.6 | Questionnaire on past year physical activity |
| Gaskins et al. [18] | 35.3 ± 3.9 | 24.0 | | Physical Activity per week (> 2.5 h versus ≤ 2.5) | Validated questionnaire |
| Kiel et al. [19] | Exercise group 33.1 ± 5.9, Control group 31.7 ± 4.3, *p* value 0.58 | Exercise group 28.9 ± 2.4, Control group 31.2 ± 1.3, *p* value 0.03 | | HIT (high-intensity interval training) for 10weeks | |
| Ricci et al. [26] | (age < 35: 136/492 age 35–39 243/492, age > 40 113/492) | (BMI < 18.5: 47/492, BMI 18,5–24.9:369/492, BMI 25–29.9:46/492, BMI > 30: 30/492) | 272 | Number of hours per week (< 2 h/weeks, 2–4 h/weeks, > 5 h/weeks) | Questionnaire |
| Sõritsa [27] | 33.5 ± 4.1 | 23.9 ± 4.4 | 57 | Light AND moderate to vigorous/MVPA [Energy expenditure 1.5–3 metabolic equivalents are considered light intensity, > 3 MVPA summing moderate and vigorous] | Wearing accelerometer for 14 days and questionnaires 1–6 months before ET |
| Läänelaid et al. [21] | 32.4 ± 4.1 | 23.1 ± 3.7 | 57 | Total volume of PA (total counts/wear time in minutes, cpm); time (min/day) spent in 2 groups: low light if 101–759 cpm AND moderate to vigorous if ≥ 1952 cpm | Wearing accelerometer and questionnaire |

**Table 5** Reproductive outcomes

| References | Implantation rate | Clinical pregnancy rate | Miscarriage rate | Live birth rate |
|---|---|---|---|---|
| Morris et al. [23] | | | OR 1.93 [0.94, 1.80] | OR 0.80 [0.58, 1.11] |
| Ferreira et al. [17] | | OR 1.83 [1.15, 2.90] | OR 0.30 [0.08, 1.10] | |
| Kucuk et al. [20] | OR, 95% CL 1.75 [1.04, 2.96] | OR 2.29 [1.13, 4.65] | OR 0.25 [0.06, 0.97] | OR 3.21 [1.5, 6.85] |
| Moran et al. [22] | | OR 3.00 [0.80, 11.31] | OR 1.19 [0.19,7.46] | OR 1.91 [0.48,7.6] |
| Ramezanzadeh et al. [25] | OR, 95% CL 1.14 [0.68, 1.92] | OR 0.97 [0.55, 1.72] | | |
| Palomba et al. [24] | OR, 95% CL 3.94 [2.09, 7.45] | OR 1.08 [O.74, 1.59] | OR 0.87 [0.12, 6.21] | OR 4.02 [1.62,9.98] |
| Evenson et al. [16] | | OR 2.91 [1.20, 7.04] | | OR 2.54 [0.99, 6.55] |
| Gaskins et al. [18] | | OR 2.91 [1.20, 2.73] | OR 0.97 [0.39, 2.40] | OR 1.60 [0.98, 2.60] |
| Kiel et al. [19] | | OR 3.3 [0.52, 21.6] | | |
| Ricci et al. [26] | | OR 1.08 [O.74, 1.59] | | 1.07 [0.71,1.62] |
| Sõritsa [27] | | OR light PA 1.01 [0.71–1.43] OR VMPA 0.98 [0.95–1.01] | | OR light PA 0.96 [0.65,1.41] OR VMPA 0.99 [0.96,1.02] |
| Läänelaid et al. [21] | | | | OR light PA 0.641 [0.329,1.251] OR VMPA 0.737 [0.396,1.373] |

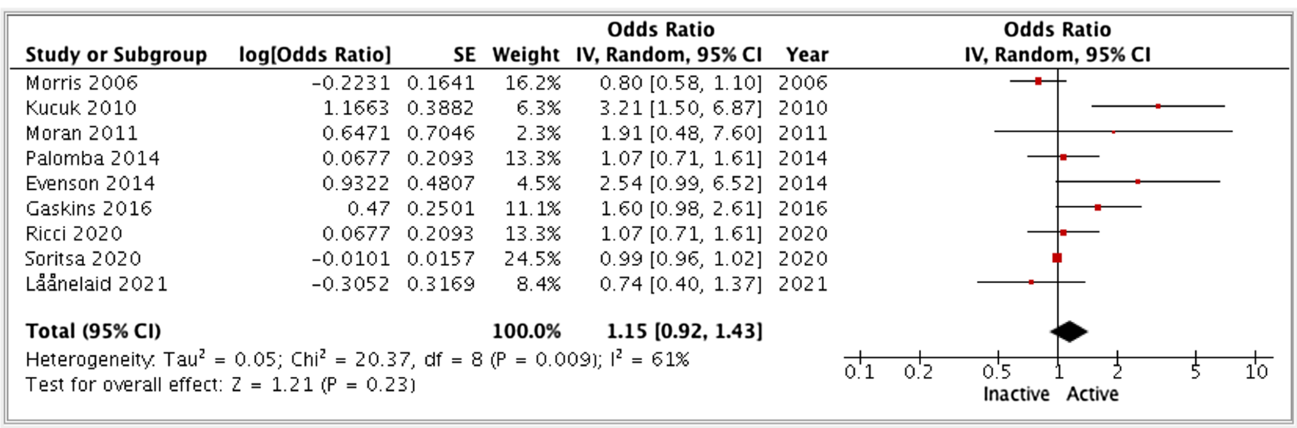


**Fig. 2** Odds ratio according to live birth rate. The overall effect was not statistically significant ($p > 0.005$); vertical line, no difference point between two groups; squares, odds ratios; diamonds, pooled odds ratio for all studies; horizontal lines, 95% CI

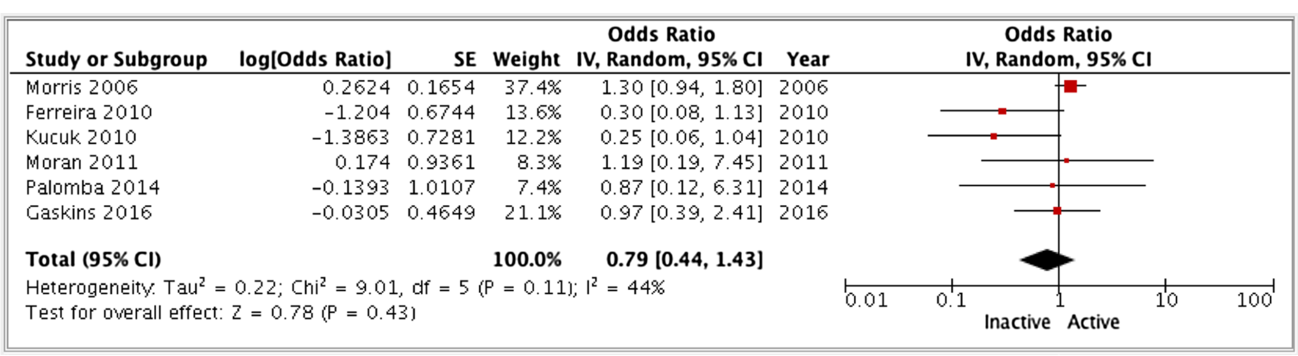


**Fig. 3** Odds ratio according to miscarriage rate. The overall effect was not statistically significant ($p > 0.05$); vertical line, no difference point between two groups; squares, odds ratios; diamonds, pooled odds ratio for all studies; horizontal lines, 95% CI

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Ferreira 2010 | 0.6043 | 0.237 | 12.0% | 1.83 [1.15, 2.91] | 2010 |
| Kucuk 2010 | 0.8286 | 0.3604 | 7.8% | 2.29 [1.13, 4.64] | 2010 |
| Moran 2011 | 1.0986 | 0.6744 | 3.1% | 3.00 [0.80, 11.25] | 2011 |
| Ramezanzadeh 2012 | −0.0305 | 0.2895 | 10.0% | 0.97 [0.55, 1.71] | 2012 |
| Evenson 2014 | 1.0682 | 0.452 | 5.8% | 2.91 [1.20, 7.06] | 2014 |
| Palomba 2014 | 0.077 | 0.1929 | 13.9% | 1.08 [0.74, 1.58] | 2014 |
| Gaskins 2016 | 0.5339 | 0.2392 | 11.9% | 1.71 [1.07, 2.73] | 2016 |
| Kiel 2018 | 1.1939 | 0.9428 | 1.7% | 3.30 [0.52, 20.94] | 2018 |
| Ricci 2020 | 0.077 | 0.1929 | 13.9% | 1.08 [0.74, 1.58] | 2020 |
| Soritsa 2020 | −0.0202 | 0.0159 | 20.0% | 0.98 [0.95, 1.01] | 2020 |
| **Total (95% CI)** | | | **100.0%** | **1.39 [1.08, 1.79]** | |

Heterogeneity: Tau² = 0.08; Chi² = 28.15, df = 9 (P = 0.0009); I² = 68%
Test for overall effect: Z = 2.57 (P = 0.01)

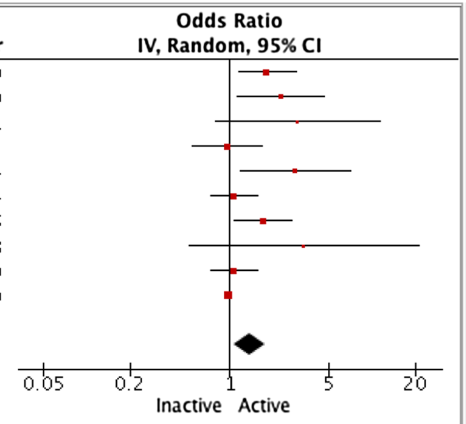


**Fig. 4** Odds ratio according to pregnancy rate. The overall effect was statistically significant ($p < 0.05$); vertical line, no difference point between two groups; squares, odds ratios; diamonds, pooled odds ratio for all studies; horizontal lines, 95% CI

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Kucuk 2010 | 0.5596 | 0.2655 | 34.3% | 1.75 [1.04, 2.94] | 2010 |
| Ramezanzadeh 2012 | 0.131 | 0.2636 | 34.4% | 1.14 [0.68, 1.91] | 2012 |
| Palomba 2014 | 1.3712 | 0.3235 | 31.2% | 3.94 [2.09, 7.43] | 2014 |
| **Total (95% CI)** | | | **100.0%** | **1.95 [0.99, 3.82]** | |

Heterogeneity: Tau² = 0.27; Chi² = 8.87, df = 2 (P = 0.01); I² = 77%
Test for overall effect: Z = 1.93 (P = 0.05)

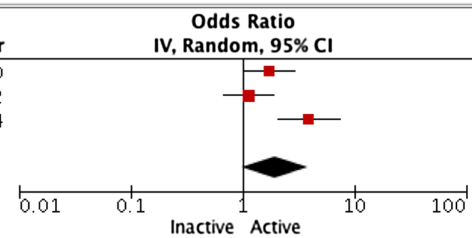


**Fig. 5** Odds ratio according to implantation rate. The overall effect was almost statistically significant ($p = 0.05$); vertical line, no difference point between two groups; squares, odds ratios; diamonds, pooled odds ratio for all studies; horizontal lines, 95% CI

## Discussion

Quantitative data from 12 studies, involving 3431 women undergoing IVF treatments, were included in the analyses. The pooled results showed that we are uncertain of the effect of physical activity on live birth rate per woman and miscarriage rates when compared with less active women. However, physical activity was associated with significantly improved pregnancy rate after ARTs, whereas implantation rate after ARTs almost reached statistical significance. The overall quality of the evidence varied from low to very low, mainly due to serious limitations of the nature of included studies and imprecision.

Over the last decades, the percentage of obese women resorting to IVF has been increased in parallel to the worldwide increase of obesity per se [28, 29]. As far as IVF is concerned, obese women face a significantly higher risk of cycle cancellation, lower success rates of implantation and clinical pregnancy and lower live birth rates [30]. Potential underlying mechanisms mainly take place throughout the HPO axis. In particular, increased adipose tissue and insulin resistance are responsible for increased levels of estrogens which exert negative feedback leading to higher LH secretion and thus impairing the ovulation process [31]. Oocytes in this setting are characterized by critical spindle and chromosomic anomalies. Furthermore, developing blastocysts are exposed to a worse metabolic profile and biochemical environment. On the other hand, adaptation of weight reduction strategies has demonstrated significant chances of success in natural conception and improved clinical pregnancy outcomes in IVF [32]. Therefore, before any attempt of ART an improved BMI should be sought for.

Apart from the established detrimental effects of obesity on fertility and the obvious necessity to manage it before initiating an IVF procedure, exercise per se and not as a simple therapeutic mean against obesity have been studied in the context of improving ART outcomes. Advocates of exercise have suggested that it could improve IVF outcome through a number of possible mechanisms, including stimulation of beta-endorphins release, which could influence steroid hormone secretion; improvement of endometrial receptivity; and, of course, dealing with obesity which has been found to exert detrimental effects on fertility as it has been associated with lower ovulation frequency, worse oocyte quality, higher frequency of early miscarriage and preterm birth, reduced rates of spontaneous and assisted conception and poorer endometrial receptivity.

The results of this systematic review and meta-analysis are in accordance with the reviews currently existing in the literature. At the present time, only one systematic review and meta-analysis was designed to explore the effects of maternal physical activity before IVF/ICSI cycles, which was published in 2018. Rao et al. showed that, as far as implantation and miscarriage rates were concerned, there was no significant difference among those undertaking regular exercise compared with less physically active women. On the other hand, clinical pregnancy rate exhibited an overall increase in the physically active population.

The trials included in the present review are of substantially higher quality compared to the ones included in the aforementioned review. We added four studies, three of which showed positive results regarding clinical pregnancy rate [19, 26, 27], and three showed positive results regarding live birth rate [21, 26, 27]. Therefore, the results of the present meta-analysis differ from the earlier meta-analysis.

Regarding the results of our study and focusing on primary outcomes, the potential association between increased physical activity and live birth rate after ART was assessed in a meta-analysis of the nine included studies and no statistical significance was observed. On the other hand, a meta-analysis of six included studies was performed to investigate the correlation of miscarriage rate after IVF/ICSI with regards to physical activity level. Similarly, only a trend towards physical inactivity and a higher miscarriage rate after ARTs was noticed without statistical significance.

Concerning the secondary outcomes, a meta-analysis of ten studies, which was conducted to assess the potential correlation between physical activity and pregnancy rate after IVF/ICSI exhibited statistically significant positive association. On the other hand, the association between physical activity and implantation rate after ARTs almost reached statistical significance in the particular meta-analysis including three of the studies.

Taking into account the results of the present meta-analysis, no definite conclusions can be drawn regarding the potential positive impact of physical exercise on the outcomes of IVF or ICSI. The authors believe that more theory- based, large-size, randomized and multicenter trials should be conducted before a final decision is made on whether to choose the intensity, the type and the duration of exercise in an attempt to improve IVF outcomes.

## Study limitations

The systematic nature of the present study required that all studies that met the inclusion criteria should be part of it; therefore, a great heterogeneity was observed among included studies in the terms of type of activity and its evaluation. Unfortunately, the effect of these parameters on our primary outcomes was not possible to be investigated. In addition, due to the small number of patients in the included studies, our conclusions should be interpreted with caution.

## Conclusion

Over the last decades, the percentage of obese women resorting to IVF has been increased in parallel to the worldwide increase of obesity and sedentary lifestyle. The present meta-analysis was performed in an attempt to assess the potential association between increased levels of maternal physical activity and an improvement of IVF outcomes. According to our results, exercise is not associated with a statistically significant improvement of live birth rate and decrease of miscarriage rate, although significantly correlated with improved implantation and clinical pregnancy rates. The authors believe that more randomized and multicenter trials of a larger scale are necessary before establishing a final conclusion.

**Author contributions** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by EK, EM, MF and EA. The first draft of the manuscript was written by EK and all authors commented on previous versions of the manuscript. CS supervised and guided the whole initiative. All authors read and approved the final manuscript.

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## Declarations

**Conflict of interest** The authors have no relevant financial or non-financial interests to disclose.

**Ethical approval** The authors declare that the present manuscript is not a result of original research on human subjects but a review of the current literature thus an ethics approval is not required.

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