

Title: Studying the Complex Relationships Between Physical Activity and Infertility

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Abstract

This article provides commentary on the accompanying review, “Modifiable Risk Factors and Infertility: What are the Connections?” by Rossi and colleagues. This commentary focuses specifically on the association between physical activity or exercise and infertility, given the equivocal evidence as summarized by the review paper. Several methodologic issues related to this research topic are discussed, including clarifying the components of physical activity to assess in research studies (e.g., type, intensity, frequency, duration), considering the optimal way to measure physical activity, and investigating important potential modifiers of the relationships including age and body mass index. Researchers should also consider whether sedentary behavior is another potentially important modifiable factor to explore in relation to infertility. Given that unexplained infertility remains of widespread global concern, establishing modifiable risk factors remains an important area for research.

Keywords: conception, exercise, fertility, in vitro fertilization, pregnancy, recreational activity, sedentary behavior

The accompanying article “Modifiable Risk Factors and Infertility: What are the Connections?” by Rossi and colleagues¹ reviewed the link between infertility and a range of modifiable risk factors, including diet, caffeine, alcohol, tobacco, body mass index, stress, psychological state, environment, and exercise. Much of their review draws on evidence from epidemiologic studies, as there are few randomized clinical trials on the topic. The authors identified several methodologic issues related to studying modifiable risk factors with infertility, including clarity in defining clinical outcomes, recall bias, selection bias, and establishing causality. This commentary focuses specifically on the association between physical activity or exercise and infertility, given the equivocal evidence on this topic as presented by Rossi et al.¹ We discuss some of the methodologic issues specifically related to this research topic and describe how future studies could address these issues.

First, it is critical to clarify what the exposure under study will be, in this case physical activity or exercise, and discerning whether type, intensity, frequency, and duration should be collected. Physical activity is defined as any body movement produced by skeletal muscles that requires energy expenditure.² Exercise is a subset of physical activity that is planned, repetitive, and structured and usually has a goal to maintain or improve at least one component of physical fitness.² Different types of physical activity (e.g., recreational, household, child or adult care, transportation, work) or exercise (e.g., aerobic, strengthening, low impact) may be differentially associated with infertility. Likewise, the intensity of physical activity (e.g., light, moderate, vigorous) may also be important. Vigorous physical activity has been hypothesized to be detrimental,³⁻⁵ whereas moderate physical activity may potentially be beneficial. Dose response should also be clarified by assessing both frequency and duration of the physical activity or exercise. Studying the various types of physical activities, assessing their influence over a range of intensities, and ascertaining dose response can help clarify the association of physical activity with infertility.

Second, how the exposure will be measured should be considered. In the six studies reviewed by Rossi et al.,¹ all relied on self-reported physical activity or exercise⁶⁻¹¹ and only one additionally utilized accelerometry.¹¹ Accelerometry is a form of objective measurement designed to capture movement, with monitors usually worn at the hip or wrist. So long as the device is worn, these monitors can overcome measurement challenges related to recall bias. Reliance on only self-reported physical activity can lead to under-estimates of the strength of association between the exposure and outcome due to measurement error. Use of **difference measures**

[KE1]between studies also leads to inconsistent results, potentially providing weaker evidence for causality, and an underestimate of the public health impacts of physical activity. Therefore, the use of accelerometers in future studies may better capture details about frequency, duration, and intensity of daily physical activity that is challenging to accurately capture with self-reported instruments.

Third, it is important to assess whether the relationship between physical activity and infertility is moderated by key factors such as a woman's body mass index (BMI) or age. There is evidence to suggest a link between infertility and being at either end of the weight spectrum (e.g., underweight, overweight, or obese).¹² Whereas exercise may contribute to negative energy balance, resulting in amenorrhea and irregular ovulation,¹³ being physical active may be beneficial to the fertility of women who are overweight or obese. For example, a small intervention conducted in infertile obese women found that physical activity was associated with improved fertility when combined with weight loss.¹⁴ Additionally, in a cohort study of over 5,000 women, there was an inverse association between vigorous physical activity and fecundability among those with BMI in the healthy range (<25 kg/m²), but a weak positive association between higher levels of vigorous physical activity and fecundability in overweight and obese women.¹⁵

Though all six studies reviewed by Rossi et al.¹ included age as a potential covariate, few conducted subgroup analyses to assess interaction. In Norwegian women, higher duration of activity (>60 minutes/week) was associated with lower fertility, but only when the sample was limited to women under 30 years.⁸ This suggests that variables such as BMI and age may moderate the relationship between physical activity and infertility may be missed when instead treating them only as potential confounders. However, only studies with sufficient statistical power can adequately explore these modifiers.

Finally, it is interesting to note that the Rossi et al.¹ review did not identify studies on the association between sedentary behavior and infertility. Sedentary behavior comprises time spent in periods of little or no movement while awake (e.g., sitting).¹⁶⁻¹⁸ Sedentary behavior is another potentially important modifiable risk factor for infertility, and is not equivalent to "lack of physical activity", since one can be physically active but also accumulate large amounts of sedentary time. As a broad category, sedentary behavior is very challenging to self-report, since it is common and interspersed throughout the day. This may be why it has yet to be

assessed in relation to infertility. However, self-reported measures of sedentary behavior exist, including assessment of sitting, television viewing, and computer use, and sedentary behaviors can be explored in detail using accelerometers. Future studies may therefore benefit from including measures of both sedentary behavior and physical activity to determine whether both have an independent association with infertility.

Although recommendations exist for physical activity during pregnancy,¹⁹ there are no clear guidelines on physical activity for women who are trying to conceive. Biological evidence supports the hypothesis that physical activity may impact infertility, since those who engage in vigorous physical activity may have an increased risk for infertility due to anovulation and possibly implantation failure.³⁻⁵ However, the relationship is likely complex and studies with adequate statistical power are needed to explore potential moderators such as BMI and age. The measurement of physical activity and exercise can be enhanced by clarifying what exposure is being measured and to consider including accelerometry in addition to self-reported measures, to more precisely explore the relationship between physical activity behaviors and fertility. Research may also benefit from an exploration into sedentary behavior and infertility. Given the wide range of physical activity exposure measures, in combination with differing covariates and fertility outcomes used across studies, it is not surprising that firm conclusions about the influence of physical activity on fertility cannot be drawn at this time. However, given the benefits of physical activity to health, and that unexplained infertility remains of widespread concern globally, establishing the optimum type, duration, intensity, and frequency of physical activity for conception remains an important area for research.

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