

# High-Intensity Exercise Training for Improving Reproductive Function in Infertile Patients: A Randomized Controlled Trial



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## Abstract

**Objective:** The purpose of this RCT was to investigate whether a 24-week program of high-intensity exercise was beneficial for improving reproductive function in infertile male patients.

**Methods:** Infertile men ( $n = 433$ ) were randomly assigned to exercise ( $n = 218$ ) and non-exercise ( $n = 215$ ) groups. The seminal markers of inflammation and oxidative stress, semen quality parameters, sperm DNA fragmentation, and pregnancy rate were measured at baseline, at the end of week 12, at the end of week 24, and at 7 and 30 days during recovery. Exercise programs included a treadmill running protocol, three times a week, at an intensity  $>70\%$  to  $85\%$  of maximal oxygen consumption.

**Results:** The exercise group reported significantly attenuated inflammatory biomarkers (interleukin-6 and tumour necrosis factor- $\alpha$ ), oxidative stress (reactive oxygen species and malondialdehyde), and antioxidants (superoxide dismutase, catalase, and total antioxidant capacity) ( $P < 0.05$ ), and these changes coincided with favorable improvements in semen parameters, sperm DNA integrity, and pregnancy rate ( $P < 0.05$ ). These findings indicate that our exercise training program was adequate to elicit improvements in markers of male reproductive function in infertile patients.

**Conclusions:** We concluded that a high-intensity exercise program could be recommended as an adjunct lifestyle approach to male factor infertility treatment or used in combination with other therapies.

## Résumé

**Objectif :** Cet ECR visait à déterminer si un programme d'exercice à haute intensité de 24 semaines pouvait améliorer la fonction reproductrice des hommes infertiles.

**Key Words:** High-intensity exercise training, male factor infertility, cytokines, randomized controlled trial, redox status

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**Méthodologie :** Des hommes souffrant d'infertilité ( $n = 433$ ) ont été aléatoirement répartis en deux groupes : un groupe suivant le programme d'exercice ( $n = 218$ ) et un groupe témoin ( $n = 215$ ). La présence de marqueurs d'inflammation et de stress oxydatif dans le sperme, les indices de la qualité séminale, la fragmentation de l'ADN spermatique et le taux de grossesse ont été évalués au début de l'essai, à la fin de la 12<sup>e</sup> et de la 24<sup>e</sup> semaine, puis après 7 et 30 jours de récupération. Le programme prévoyait un protocole de course sur tapis roulant à une intensité de 70 à 85 % de l'absorption maximale d'oxygène, à réaliser trois fois par semaine.

**Résultats :** Dans le groupe suivant le programme d'exercice, une amélioration statistiquement significative ( $P < 0,05$ ) a été observée quant aux biomarqueurs d'inflammation (interleukine 6 et facteur de nécrose tumorale alpha) et de stress oxydatif (dérivés réactifs de l'oxygène et malonalaldéhyde) et à la quantité d'antioxydants (superoxyde dismutase, catalase et capacité antioxydante totale), tandis que la qualité du sperme, l'intégrité de l'ADN spermatique et le taux de grossesse ont augmenté ( $P < 0,05$ ). Ces résultats indiquent que notre programme d'exercice est parvenu à améliorer les indicateurs de la fonction reproductrice masculine chez les patients infertiles.

**Conclusion :** Il conviendrait de recommander un programme d'exercice à haute intensité comme complément au traitement de l'infertilité masculine.

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## INTRODUCTION

Male factor infertility is considered to be responsible as the primary cause or a contributory factor in up to 50% of infertile couples and is caused mainly by disruption in the process of spermatogenesis, leading to no or incomplete spermatozoa.<sup>1</sup> Cell-mediated immunity has been known to affect spermatogenesis through cytokines and may play a key role in male factor infertility.<sup>2</sup> Several studies have reported a negative association between cytokine levels in the seminal plasma and standard semen quality

parameters and sperm DNA integrity.<sup>3–6</sup> A growing body of evidence also suggests that inflammation in the semen could be linked to oxidative stress.<sup>7</sup> Earlier studies have pointed out a central role of oxidative stress, either in perturbation of sperm cell function or in the etiology of sperm DNA damage.<sup>8,9</sup> A high level of DNA fragmentation in sperm cells has been shown to represent a critical factor that may have serious consequences for pregnancy or during subsequent embryonic development.<sup>10,11</sup> Therefore, it seems possible that protective approaches against oxidative stress and inflammation may be useful therapeutic strategies in the treatment of male infertility.

The health benefits of a physically active lifestyle are widely recognized, and there is abundant evidence supporting the significance of regular physical exercise as an important strategy for reducing the risk of chronic diseases.<sup>12</sup> In recent years, numerous studies have linked the health benefits of regular EX and physical activity, among others, to favourable modulations of inflammatory mediators<sup>13</sup> and changes in cellular or tissue redox status.<sup>14</sup> The protective effects of a physically active lifestyle on male reproduction have also been reported in healthy humans.<sup>15</sup> Studies from our laboratory have shown that, in healthy humans, chronic, intense EX may affect markers of male reproductive function, among others, by alterations in seminal markers of inflammation and oxidative stress.<sup>15</sup> However, this has not been systematically tested before in infertile patients. Therefore, we hypothesized that intensive EX training would affect seminal markers of inflammation and oxidative stress in infertile patients and that changes would be related to markers of male reproductive function and reproductive performance in infertile patients. Thus, this RCT aimed to evaluate the effects of 24 weeks of high-intensity EX on proinflammatory cytokines, peroxidative and antioxidative biomarkers, semen quality, sperm DNA integrity, and pregnancy rate in sedentary, infertile patients.

## ABBREVIATIONS

EX	exercise
IL	interleukin
MDA	malondialdehyde
ROS	reactive oxygen species
SOD	superoxide dismutase
TAC	total antioxidant capacity
TNF	tumour necrosis factor
TUNEL	terminal deoxynucleotidyl transferase dUTP nick end labelling
VO <sub>2max</sub>	maximal oxygen consumption

## MATERIALS AND METHODS

### Experimental design and patients

We excluded 675 infertile men from the original cohort of 1108 sedentary patients (aged 25 to 40 years) attending the infertility clinic. All patients had a history of infertility >1 year with no indication of hormonal, infective, or physical causes. The exclusion criteria were as follows: participating in a regular EX program or accumulating 25 minutes or more of moderate physical activity on most days of the week; history of chronic illness, serious systemic diseases, testicular varicocele, and genital infection; history of use of antioxidants supplements that could alter the hypothalamic-pituitary-gonadal axis; history of use of cigarettes and alcohol in the last 6 months; irregular eating patterns and history of depressive illness; abnormal physical and sexual development; working in a profession in which the activity might influence reproductive capacity; and history of relevant previous surgery. All female partners of the infertile patients were subjected to gynaecologic assessment by a specialist and had normal results on fertility evaluation. All patients who met the inclusion criteria were required to stop all medical therapy  $\geq 12$  weeks before study initiation.<sup>8,16–18</sup>

Each patient provided three semen samples at 3-week intervals. All semen samples were evaluated in the same laboratory and, on the basis of the fifth edition of the WHO laboratory manual for the examination and processing of human semen,<sup>19</sup> were classified into groups of asthenozoospermic (progressive sperm motility <32% motile); asthenoteratozoospermic (progressive sperm motility <32% motile, sperm morphology <4% normal); oligoasthenozoospermic (sperm concentration <15  $\times 10^6$  sperm/mL, progressive sperm motility <32% motile); oligospermic (sperm concentration <15  $\times 10^6$  sperm/mL); and oligoasthenoteratozoospermic (sperm concentration <15  $\times 10^6$  sperm/mL, progressive sperm motility <32% motile, sperm morphology <4% normal), for a total of five infertile subgroups. In addition, patients were not included if they presented with azoospermia, leukocyte concentration >10<sup>6</sup>/mL of ejaculate, specimens with hyperviscosity, and incomplete semen analysis results. Each patient underwent history and physical and laboratory evaluation, with any clinically significant abnormalities in any of these tests leading to exclusion from the study. A certificate attesting to the patient's ability to participate in the study protocol was provided by the physician and served as the final screen for participation in the study.

Eligible patients (asthenozoospermic, n = 88; asthenoteratozoospermic, n = 85; oligoasthenozoospermic, n = 89; oligospermic, n = 86; and oligoasthenoteratozoospermic, n = 85) were further randomly assigned to either EX or non-

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