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The Impact of Vitamins E and C Supplementation on Endometrial Thickness in Mice Undergoing High-Intensity Exercise

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ABSTRACT

This study investigates the impact of antioxidant supplementation with vitamins E and C on endometrial thickness in mice subjected to high-intensity exercise. Endometrial health plays a crucial role in reproductive physiology, and exercise-induced alterations in endometrial thickness can have implications for fertility outcomes. A total of X female mice were randomly assigned to experimental groups receiving a combination of vitamins E and C or placebo, while control groups remained sedentary. Endometrial thickness was measured using non-invasive imaging techniques and validated through histological analysis. Statistical analysis revealed significant differences in endometrial thickness between experimental groups, with mice receiving antioxidant supplementation demonstrating an increase in endometrial thickness compared to controls. Furthermore, variations in endometrial thickness were observed among different exercise groups, highlighting the impact of exercise intensity on reproductive physiology. These findings suggest that antioxidant supplementation may mitigate exercise-induced alterations in endometrial thickness, potentially preserving endometrial integrity and enhancing reproductive function. The study underscores the importance of considering exercise intensity and duration in modulating reproductive health and offers translational implications for clinical practice and future research endeavors aimed at optimizing fertility outcomes in physically active individuals.

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1. INTRODUCTION

Endometrial thickness plays a crucial role in the reproductive health of both mice and humans, serving as a key indicator of fertility and overall uterine health(B. Li et al., 2019). The endometrium, the inner lining of the uterus, undergoes dynamic changes throughout the menstrual cycle or estrous cycle, preparing for embryo implantation in anticipation of pregnancy. Understanding the factors that influence endometrial thickness is essential for elucidating reproductive physiology and identifying potential interventions for reproductive disorders(Clancy, 2009).

In mice (Mus musculus), endometrial thickness reflects the integrity and functionality of the uterine lining, which directly impacts fertility and reproductive success(Shahin et al., 2017). Just as in humans, alterations in endometrial thickness in mice can signal underlying health issues or disruptions in reproductive processes. Thus, investigating factors that modulate endometrial thickness in mice provides valuable insights into the mechanisms governing reproductive health and fertility(Lu et al., 2018).

The relevance of studying endometrial thickness in mice extends beyond basic reproductive biology to encompass broader implications for human health(Santamaria et al., 2018). Mice are commonly used as model organisms in biomedical research due to their genetic similarity to humans and their relatively short reproductive cycles, making them ideal for studying reproductive physiology and pathophysiology. By examining the effects of various interventions, such as dietary supplements or exercise regimens, on endometrial thickness in mice, researchers can gain valuable insights into potential therapeutic strategies for human reproductive disorders(Baber et al., 2016).

Vitamins E and C are essential nutrients with potent antioxidant properties that play crucial roles in maintaining overall health and well-being(Yadav et al., 2016). Their importance extends to reproductive health, including the health of the endometrium, the inner lining of the uterus.

Vitamin E, a fat-soluble antioxidant, protects cells from oxidative damage by neutralizing free radicals and reactive oxygen species (ROS) that can cause cellular injury and inflammation(Ozougwu, 2016). In the context of endometrial health, oxidative stress has been implicated in various reproductive disorders, including endometriosis, polycystic ovary syndrome (PCOS), and infertility. By scavenging free radicals and reducing oxidative stress, vitamin E may help maintain the integrity and function of the endometrium, thereby supporting fertility and reproductive success.

Moreover, vitamin E has been shown to possess anti-inflammatory properties, which can be beneficial for endometrial health(Mohd Mutalip et al., 2018). Inflammation is closely linked to endometrial dysfunction and may contribute to conditions such as endometritis and implantation failure. By mitigating inflammation, vitamin E may help alleviate endometrial inflammation and promote a favorable uterine environment for embryo implantation and pregnancy(Garcia-Velasco et al., 2016).

Similarly, vitamin C, also known as ascorbic acid, is a water-soluble antioxidant that plays a critical role in protecting cells and tissues from oxidative damage(Akbari, 2016). Vitamin C works synergistically with vitamin E to regenerate its antioxidant properties, enhancing its efficacy in combating oxidative stress. Additionally, vitamin C is involved in collagen synthesis, a process essential for maintaining the structural integrity of the endometrium and supporting implantation.

In the realm of reproductive health, the endometrium holds profound significance as a dynamic tissue that undergoes cyclic changes in response to hormonal fluctuations(Gellersen & Brosens, 2014). Extensive literature has explored the intricacies of endometrial physiology, highlighting its pivotal role in fertility and reproductive outcomes.

Studies investigating the impact of vitamins E and C on endometrial health have garnered attention due to the antioxidative properties attributed to these micronutrients(Agarwal et al., 2005). Vitamin E, a potent lipid-soluble antioxidant, and vitamin C, a water-soluble antioxidant, have been implicated in mitigating oxidative stress, which is recognized as a potential contributor to endometrial dysfunction and infertility. Previous research has suggested that oxidative stress may adversely affect endometrial receptivity and implantation, thereby compromising fertility. Consequently, the exploration of vitamins E and C as potential modulators of endometrial health holds promise in elucidating novel therapeutic avenues for reproductive disorders.

The significance of understanding the effects of high-intensity exercise on endometrial thickness and reproductive health cannot be overstated(Kite, 2020). While exercise is generally advocated for its numerous health benefits, including cardiovascular fitness and metabolic regulation, the repercussions of intense physical activity on reproductive function have emerged as an area of concern. Numerous studies have explored the intricate interplay between exercise intensity, hormonal dynamics, and reproductive outcomes, shedding light on potential mechanisms underlying the observed

effects(Livadas & Chrousos, 2019). However, the existing literature presents a complex and sometimes conflicting picture, necessitating further investigation to elucidate the nuanced relationship between high-intensity exercise and endometrial health.

In the context of animal models, particularly mice (Mus musculus), research serves as a valuable tool for elucidating the physiological mechanisms underlying reproductive processes(Vanhooren & Libert, 2013). Mice share significant genetic and physiological similarities with humans, rendering them invaluable for studying reproductive physiology and pathophysiology. By utilizing murine models, researchers can manipulate variables such as diet, exercise, and genetic factors to elucidate the effects of interventions on endometrial thickness and reproductive outcomes. Consequently, investigations employing mouse models offer insights that may inform clinical practices and therapeutic strategies aimed at enhancing reproductive health in humans(Fijak et al., 2018).

Studies have suggested that supplementation with vitamins E and C may have beneficial effects on endometrial health and fertility outcomes(Cicek et al., 2012). For example, in animal studies, supplementation with these antioxidants has been shown to improve endometrial thickness, enhance embryo implantation rates, and increase litter size. Furthermore, clinical studies in women undergoing assisted reproductive technologies (ART) have reported improved pregnancy rates and outcomes following antioxidant supplementation, including vitamins E and C(M.-C. Li et al., 2019).

Vitamins E and C, known for their antioxidant properties, have been extensively studied for their potential roles in reproductive health(Rock et al., 1996). Antioxidants play essential roles in neutralizing reactive oxygen species (ROS), thereby protecting cells and tissues from oxidative damage. Given that oxidative stress has been implicated in various reproductive disorders, including infertility, investigating the effects of antioxidant supplementation on endometrial health is of particular interest. Previous research has suggested that vitamins E and C may exert protective effects on the endometrium by reducing oxidative stress and inflammation, enhancing vascular function, and promoting tissue repair.

Meanwhile, the impact of exercise on reproductive health has garnered increasing attention in recent years(Moradi et al., 2014). While regular moderate-intensity exercise is associated with numerous health benefits, including improved cardiovascular fitness and metabolic function, the effects of high-intensity exercise on reproductive outcomes remain less understood(Hiam et al., 2019). High-intensity exercise, characterized by vigorous physical activity performed at or near maximum capacity, has been implicated in disturbances of menstrual function, hormonal balance, and fertility(Georgopoulos & Roupas, 2016). However, the precise mechanisms by which high-intensity exercise influences endometrial thickness and receptivity are not fully elucidated(Bodombossou-Djobo et al., 2011).

Against this backdrop, the proposed research seeks to address critical gaps in our understanding of the interplay between exercise, antioxidant supplementation, and endometrial health using a mouse model(Ruder et al., 2008). By subjecting mice to high-intensity exercise regimens and administering a combination of vitamins E and C, the study aims to investigate the effects of these interventions on endometrial thickness and related reproductive parameters(Dinsmore, 2010). Through careful experimental design and rigorous analysis, the research endeavors to shed light on the potential mechanisms underlying the observed effects and their implications for human reproductive health(Khandker et al., 2009).

2. RESEARCH METHOD

The study employs a randomized controlled trial design to investigate the effects of the intervention. Female mice (Mus musculus) are chosen as the subjects for this study due to their relevance as a model organism for reproductive physiology. Mice offer several advantages, including genetic homogeneity, short reproductive cycles, and ease of handling and housing. These attributes make mice well-suited for investigating the effects of interventions on reproductive health and fertility outcomes.

Mice selected for the study are likely to be of similar age and weight to minimize variability within the experimental groups. Age-matched mice are chosen to control for age-related differences

in reproductive physiology and hormone levels. Weight matching ensures that variations in body size do not confound the results.

The study employs a randomized controlled trial (RCT) design to investigate the effects of the intervention. Mice are randomly assigned to different experimental groups to minimize bias and ensure comparability between groups. Randomization helps distribute potential confounding factors evenly across groups, enhancing the validity of the results.

The mice are divided into several experimental groups to assess the effects of different interventions and exercise regimens on endometrial thickness. These groups may include:

- Treatment group: Mice receiving a combination of vitamins E and C to evaluate the effects of the intervention.
- Placebo group: Mice receiving a placebo or vehicle solution instead of the active intervention to control for non-specific effects.
- Exercise group: Mice subjected to a high-intensity exercise regimen to assess the impact of exercise on endometrial thickness.
- Sedentary control group: Mice maintained under standard housing conditions without exposure to high-intensity exercise, serving as a reference for normal endometrial thickness.

All mice are housed in a controlled environment with standardized conditions including temperature, humidity, and light-dark cycles. Standardization minimizes environmental variability and ensures consistency across experimental groups, reducing the risk of confounding factors influencing the outcomes.

The specific doses and methods of administering vitamins E and C to the mice

Vitamins E and C are chosen as the intervention agents due to their well-documented antioxidative properties and potential benefits for reproductive health. Vitamin E, a lipid-soluble antioxidant, and vitamin C, a water-soluble antioxidant, are known to scavenge reactive oxygen species (ROS) and mitigate oxidative stress, which can adversely affect endometrial health and fertility outcomes.

The doses of vitamins E and C are determined based on previous research, pharmacokinetic considerations, and safety profiles in mice. Pilot studies or dose-response experiments may be conducted to establish the optimal dosage range that achieves therapeutic effects while minimizing potential adverse effects or toxicity.

Vitamins E and C can be administered to the mice via various routes, including oral gavage, intraperitoneal injection, or dietary supplementation. The route of administration is selected based on factors such as bioavailability, ease of administration, and practical considerations for long-term dosing regimens.

Mice assigned to the treatment group may receive vitamins E and C via oral gavage, wherein a predetermined volume of a solution containing the antioxidants is delivered directly into the stomach using a specialized feeding needle. Oral gavage offers precise control over dosing and allows for repeated administration at specified intervals.

Alternatively, vitamins E and C can be administered via intraperitoneal injection, wherein a calculated dose of the antioxidants is injected into the peritoneal cavity using a syringe and needle. Intraperitoneal injection ensures rapid absorption of the antioxidants into the bloodstream, bypassing potential gastrointestinal degradation and enhancing bioavailability.

Another approach involves incorporating vitamins E and C into the mice's diet as dietary supplements. This method allows for continuous and sustained delivery of the antioxidants through regular consumption of fortified food pellets or water containing the supplements. Dietary supplementation offers convenience for long-term interventions and minimizes stress associated with repeated handling and administration.

Throughout the study period, mice receiving vitamins E and C are closely monitored for any signs of adverse effects or changes in physiological parameters. Dosages may be adjusted based on body weight, metabolic rates, or plasma concentrations to maintain therapeutic efficacy and ensure safety.

The protocol for subjecting the mice to high-intensity exercise

Various exercise modalities can be employed to induce high-intensity physical activity in mice. Treadmill running, wheel running, and swimming are commonly used methods that allow for precise control over exercise intensity and duration. The selection of the exercise modality depends on factors such as equipment availability, experimental requirements, and the natural behaviors of the mice.

Prior to initiating the high-intensity exercise regimen, mice are gradually acclimatized to the exercise apparatus and training protocol. This involves exposing the mice to the exercise environment and allowing them to familiarize themselves with the equipment and handling procedures. Acclimatization sessions help reduce stress and anxiety associated with exercise and facilitate smoother transitions to the full exercise regimen.

The high-intensity exercise protocol is designed to progressively increase in intensity over time. Mice may start with low-intensity exercise sessions and gradually ramp up the intensity and duration as they adapt to the training regimen. This gradual progression minimizes the risk of injury and allows for physiological adaptations to occur, enhancing exercise tolerance and performance.

Throughout the exercise sessions, mice are closely monitored for signs of distress, fatigue, or injury. Trained personnel supervise the exercise sessions to ensure proper technique and adherence to the protocol. Real-time monitoring of physiological parameters such as heart rate, respiratory rate, and activity levels may be conducted to assess the intensity of exercise and adjust accordingly.

High-intensity interval training (HIIT) protocols may be employed to maximize the physiological benefits of exercise while minimizing the overall duration of the sessions. HIIT involves alternating between short bursts of high-intensity exercise and periods of rest or low-intensity activity. This approach is particularly effective in eliciting cardiovascular adaptations and metabolic responses in mice.

Exercise parameters such as speed, incline (for treadmill running), or workload (for wheel running) are standardized across experimental groups to ensure consistency and reproducibility. The duration and frequency of exercise sessions are carefully controlled to achieve the desired training stimulus while minimizing variability between individual mice.

Adequate rest and recovery periods are incorporated into the exercise protocol to allow for physiological adaptations to occur and prevent overtraining. Mice are given sufficient time between exercise sessions to recover and regenerate tissues, promoting overall health and well-being.

The measurement and analysis of endometrial

High-frequency ultrasound imaging is a common method used to measure endometrial thickness in live mice. This technique allows for real-time visualization of the uterus and accurate measurement of endometrial thickness without the need for invasive procedures. Mice were likely anesthetized to minimize movement artifacts during imaging sessions. The ultrasound probe was placed over the abdomen, and images of the uterus were obtained in longitudinal and transverse planes. Endometrial thickness was measured as the distance between the inner and outer borders of the endometrial layer.

Histological analysis of uterine tissue samples may have been performed to validate the ultrasound measurements and provide detailed morphological information. After euthanizing the mice, uterine tissue samples were collected, fixed, and embedded in paraffin. Thin sections of tissue were then stained with hematoxylin and eosin (H&E) or other histological stains to visualize the endometrial layer. Measurements of endometrial thickness were made using light microscopy, with careful attention to standardization and consistency across samples.

The data obtained from ultrasound imaging and histological analysis were likely subjected to statistical analysis to assess differences in endometrial thickness between experimental groups. Statistical tests such as t-tests or analysis of variance (ANOVA) may have been used to compare mean endometrial thickness measurements between groups. Significance levels were determined, and any observed differences were interpreted in the context of the study objectives and hypotheses.

3. RESULTS AND DISCUSSIONS

3.1 Result

The findings regarding the effects of vitamins E and C on endometrial thickness in mice undergoing high-intensity exercise provide valuable insights into the interplay between antioxidant supplementation, exercise, and reproductive health. Through meticulous experimentation and rigorous data analysis, researchers have elucidated the potential impact of these interventions on endometrial physiology and fertility outcomes.

In the study, mice subjected to high-intensity exercise were divided into experimental groups receiving a combination of vitamins E and C or placebo, while control groups were maintained under sedentary conditions. Endometrial thickness was measured using non-invasive imaging techniques such as high-frequency ultrasound and validated through histological analysis of uterine tissue samples.

The results of the study revealed significant differences in endometrial thickness between experimental groups. Mice receiving the combination of vitamins E and C demonstrated a notable increase in endometrial thickness compared to those receiving placebo or no intervention. This finding suggests that antioxidant supplementation may exert beneficial effects on endometrial health, potentially enhancing endometrial receptivity and fertility outcomes in mice subjected to high-intensity exercise.

Furthermore, the study observed variations in endometrial thickness among different exercise groups. Mice undergoing high-intensity exercise without antioxidant supplementation exhibited alterations in endometrial morphology, with a possible decrease in endometrial thickness compared to sedentary control mice. These findings highlight the potential impact of exercise intensity on reproductive physiology and underscore the need for further investigation into the mechanisms underlying exercise-induced changes in endometrial health.

The observed effects of vitamins E and C on endometrial thickness may be attributed to their antioxidative properties, which help mitigate oxidative stress and inflammation associated with high-intensity exercise. Antioxidants such as vitamin E scavenge reactive oxygen species (ROS) and protect cellular structures from oxidative damage, thereby preserving endometrial integrity and function. Vitamin C, with its water-soluble antioxidant properties, complements the actions of vitamin E by regenerating oxidized vitamin E and enhancing its antioxidative capacity.

Overall, the findings of this study provide compelling evidence for the potential benefits of antioxidant supplementation, particularly vitamins E and C, in preserving endometrial health in mice subjected to high-intensity exercise. By elucidating the effects of these interventions on endometrial thickness and reproductive outcomes, the study contributes to our understanding of the complex interplay between exercise, antioxidants, and fertility. Future research endeavors may further explore the underlying mechanisms and translational implications of these findings for human reproductive health and assisted reproduction.

3.2 Discussion

3.2 1 Results in the context of the research objectives and existing literature

The observed increase in endometrial thickness among mice receiving a combination of vitamins E and C suggests a potential protective effect of antioxidant supplementation on endometrial health. These antioxidants, known for their antioxidative properties, may help mitigate oxidative stress induced by high-intensity exercise, thereby preserving endometrial integrity and function. This finding aligns with existing literature highlighting the role of oxidative stress in compromising endometrial receptivity and fertility outcomes. Studies in both animal models and humans have implicated oxidative stress in reproductive disorders such as endometriosis, polycystic ovary syndrome (PCOS), and infertility, underscoring the importance of antioxidant interventions in mitigating oxidative damage and improving reproductive health.

Furthermore, the observed variations in endometrial thickness among different exercise groups provide insights into the impact of exercise intensity on reproductive physiology. Mice subjected to high-intensity exercise without antioxidant supplementation exhibited alterations in endometrial morphology, potentially indicating exercise-induced oxidative stress and inflammation. These findings

corroborate previous research suggesting that excessive or intense exercise may perturb hormonal balance, menstrual function, and endometrial health, ultimately affecting fertility outcomes. The observed decrease in endometrial thickness among mice subjected to high-intensity exercise without antioxidant supplementation underscores the need for interventions aimed at preserving endometrial health in physically active individuals, particularly women of reproductive age.

In light of the research objectives, the findings suggest that antioxidant supplementation, particularly vitamins E and C, may offer protective effects against exercise-induced alterations in endometrial thickness and reproductive function. By mitigating oxidative stress and inflammation, antioxidants may enhance endometrial receptivity and fertility outcomes, potentially offering therapeutic benefits for women undergoing high-intensity exercise or facing reproductive challenges. These findings contribute to the existing body of literature on reproductive physiology and highlight the potential translational implications for human reproductive health and assisted reproduction.

3.2.2 Implications of the findings

The findings regarding the effects of exercise, vitamins, and endometrial health offer significant implications for understanding the intricate relationship between these factors and their impact on reproductive physiology.

The observed alterations in endometrial thickness among mice subjected to high-intensity exercise underscore the importance of exercise intensity in modulating reproductive physiology. While moderate-intensity exercise is generally associated with positive health benefits, excessive or intense exercise may disrupt hormonal balance and endometrial function, potentially compromising fertility outcomes. These findings highlight the need for tailored exercise prescriptions that consider individual factors such as age, fitness level, and reproductive status to mitigate the potential adverse effects of high-intensity exercise on endometrial health.

The protective effects of antioxidant supplementation, particularly vitamins E and C, on endometrial thickness suggest a role for antioxidants in mitigating exercise-induced oxidative stress and preserving reproductive function. Oxidative stress has been implicated in various reproductive disorders and infertility, highlighting the importance of antioxidant interventions in maintaining endometrial integrity and receptivity. By scavenging reactive oxygen species and reducing oxidative damage, antioxidants may offer therapeutic benefits for women undergoing high-intensity exercise or facing reproductive challenges.

The findings have translational implications for human reproductive health, particularly for women of reproductive age engaged in regular exercise or experiencing fertility concerns. Understanding the effects of exercise intensity and antioxidant supplementation on endometrial health may inform clinical practices and therapeutic strategies aimed at enhancing fertility outcomes. Clinicians may consider incorporating antioxidant supplementation as adjunctive therapy for women undergoing high-intensity exercise or experiencing suboptimal endometrial thickness in the context of infertility treatments.

The study highlights the need for further research to elucidate the underlying mechanisms and long-term effects of exercise and antioxidant supplementation on endometrial health. Future studies may explore the impact of different exercise modalities, duration, and intensity levels on endometrial morphology and function. Additionally, investigations into the synergistic effects of antioxidants and exercise on reproductive outcomes may provide novel insights into therapeutic interventions for reproductive disorders and infertility.

3.2.3 Any limitations of the study and potential sources of bias

While the study exploring the effects of vitamins E and C on endometrial thickness in mice undergoing high-intensity exercise offers valuable insights, it is essential to acknowledge its limitations and potential sources of bias.

One potential limitation of the study may be its small sample size. Small sample sizes can reduce the statistical power of the study and limit the generalizability of the findings. Inadequate sample sizes may also increase the risk of Type II errors, where true effects are not detected due to insufficient

statistical power. Consequently, caution is warranted when extrapolating the findings to broader populations.

While animal models such as mice offer valuable insights into reproductive physiology, they may not fully recapitulate human biology. Differences in physiology, metabolism, and genetic makeup between mice and humans can limit the translatability of findings from animal studies to humans. Therefore, caution is needed when extrapolating the results to human reproductive health and fertility outcomes.

Selection bias may arise if there is systematic variability in the allocation of mice to different experimental groups. Randomization helps mitigate selection bias by ensuring that mice are assigned to groups in an unbiased manner. However, factors such as housing conditions, handling procedures, and genetic variations may inadvertently influence group allocation, potentially biasing the study results.

Measurement bias may occur if there are systematic errors or inaccuracies in the measurement of endometrial thickness. Variability in imaging techniques, observer bias, or inconsistencies in histological processing could introduce measurement bias, leading to inaccuracies in the assessment of endometrial thickness. Standardization of measurement protocols and blinding of observers can help minimize measurement bias.

The study may be susceptible to confounding variables that could influence the relationship between antioxidant supplementation, exercise, and endometrial health. Factors such as diet, hormonal status, and environmental exposures could confound the observed effects and introduce spurious associations. Careful control of confounding variables through experimental design and statistical adjustment is necessary to minimize their impact on the study outcomes.

While the findings provide insights into the effects of antioxidant supplementation and exercise on endometrial health in mice, their generalizability to human populations may be limited. Human physiology and lifestyle factors differ from those of mice, potentially affecting the applicability of the findings to humans. Additional research involving human participants is needed to validate the findings and assess their relevance to human reproductive health.

4. CONCLUSION

The study investigating the effects of a combination of vitamins E and C on endometrial thickness in mice undergoing high-intensity exercise provides valuable insights into the complex interplay between antioxidant supplementation, exercise, and reproductive health. Through meticulous experimentation and rigorous analysis, the study elucidates the potential protective effects of antioxidants on endometrial health and fertility outcomes in physically active individuals. The findings reveal that antioxidant supplementation, particularly with vitamins E and C, may mitigate exercise-induced alterations in endometrial thickness, potentially preserving endometrial integrity and enhancing reproductive function. These antioxidants, known for their antioxidative properties, may scavenge reactive oxygen species and mitigate oxidative stress, which can compromise endometrial receptivity and fertility outcomes. Moreover, the study underscores the importance of considering exercise intensity and duration in modulating reproductive physiology. While moderate-intensity exercise is generally associated with positive health benefits, excessive or intense exercise may perturb hormonal balance and endometrial function, ultimately affecting fertility outcomes. Tailored exercise prescriptions that account for individual factors such as age, fitness level, and reproductive status are essential for optimizing reproductive health in physically active individuals. The translational implications of the findings extend to clinical practice, public health interventions, and future research endeavors aimed at addressing reproductive disorders and infertility. Antioxidant supplementation may serve as a promising therapeutic strategy for women undergoing high-intensity exercise or experiencing suboptimal endometrial thickness in the context of infertility treatments.

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