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Altered Mitochondrial Morphology and Reduced Cardiolipin Levels in Oocytes of Endometriosis Model Mice: Implications for Mitochondrial Dysfunction in Infertility

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Background: Women with endometriosis experience significantly reduced fertility, potentially linked to mitochondrial dysfunction. This study investigates the impact of endometriosis on oocyte mitochondrial morphology and cardiolipin levels, key indicators of mitochondrial health and function.

Material/Methods: Thirty-two healthy mice were randomly allocated into 2 groups: a control group (P0, n=16) and an endometriosis model group (P1, n=16). Endometriosis was induced via intraperitoneal injection of endometrial tissue, and oocytes were retrieved following superovulation. Mitochondrial morphology was analyzed using transmission electron microscopy, and cardiolipin levels were measured via ELISA. Statistical analyses included the Fisher exact test, Mann-Whitney U test, and Spearman correlation.

Results: Mitochondrial morphology in oocytes from the endometriosis group exhibited significant structural abnormalities, compared with controls ($P<0.001$). Class III and IV mitochondria, characterized by disrupted membranes and cristae, were predominantly observed in the endometriosis group. Cardiolipin levels were significantly reduced in the endometriosis group, compared with controls ($P<0.001$). A positive correlation (r=0.73, $P<0.001$) was identified between mitochondrial morphological changes and cardiolipin levels, indicating that structural mitochondrial damage was strongly associated with reduced cardiolipin levels.

Conclusions: Endometriosis induces significant mitochondrial abnormalities and decreases cardiolipin levels in oocytes, suggesting mitochondrial dysfunction as a critical factor in reduced fertility. These findings underscore the potential of targeting mitochondrial health to improve reproductive outcomes in women with endometriosis.

Keywords: Cardiolipins • Endometriosis • Fertility • Mitochondria • Oocytes

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Introduction

Endometriosis is a chronic inflammatory condition strongly associated with reduced fertility [1]. The mechanisms underlying this association remain poorly understood, particularly at the cellular and molecular levels. Mitochondria are essential organelles for oocyte development, playing a critical role in energy production, oxidative phosphorylation, and calcium homeostasis, all of which are vital for successful fertilization and embryo development [2,3].

Cardiolipin, a mitochondrial phospholipid unique to the inner mitochondrial membrane, is crucial for maintaining mitochondrial integrity and function [4]. It supports the activity of respiratory chain complexes and stabilizes supercomplexes involved in adenosine triphosphate (ATP) production. Oxidative stress and inflammation, hallmarks of endometriosis, can lead to cardiolipin oxidation, mitochondrial dysfunction, and impaired oocyte quality [5,6].

Emerging evidence suggests that mitochondrial dysfunction in oocytes may be a key factor linking endometriosis to infertility. Mitochondrial morphology, which reflects the structural and functional state of mitochondria, has been shown to alter dynamically in response to oxidative damage and inflammatory cytokines [5,6]. Despite its potential importance, the relationship between mitochondrial structural changes, cardiolipin levels, and endometriosis-induced infertility has not been fully explored.

This study addresses this gap by investigating how endometriosis affects mitochondrial morphology and cardiolipin levels in oocytes, providing insight into the role of mitochondrial dysfunction in reproductive failure. By understanding these mechanisms, we aim to identify potential biomarkers and therapeutic targets for improving fertility outcomes in women with endometriosis. This study is part of a research tree aimed at exploring the effects of endometriosis on oocyte quality in mice. Our previous paper [7] demonstrated that endometriosis is associated with decreased ATP levels in cumulus cells, reduced mitochondrial number, and impaired oocyte maturity in the cumulus-oocyte complex. Building on these findings, the present study focuses on the effects of endometriosis on mitochondrial morphology and cardiolipin levels in oocytes, further elucidating the mechanisms underlying oocyte quality reduction in endometriosis-induced infertility.

Material and Methods

Ethical Approval

This study used mice as experimental animals for endometriosis models. The animal model in this research were healthy adult female *Mus musculus* 2-month-old mice, weighing around 20 to 30 g. This study was conducted in accordance with international guidelines for the care and use of laboratory animals, including the ARRIVE guidelines. Ethical approval for the experimental protocol was obtained from the Research Ethics Committee at the Faculty of Veterinary Medicine, Airlangga University, Indonesia (reference No. 2.KEH.107.09.2022). All procedures were designed to minimize animal suffering and ensure humane treatment in accordance to the United Kingdom Animal Act 1986.

Endometriosis Model Mice

Acclimatization took place 7 days prior to the experimental process, with a room temperature of approximately 22°C, humidity of 50% to 60%, and a maintained light-dark cycle (12 h/12 h). The mice were housed in plastic cages and had ad libitum access to water and standard feeding. After acclimatization, endometriosis was induced by intraperitoneal transplantation of endometrial tissue obtained from donor mice. Briefly, the endometrium was isolated, minced into 2 mm fragments, and suspended in saline solution before injection. Mice received cyclosporin A (0.2 mL intramuscularly) to suppress immune rejection, followed by endometrial tissue transplantation (0.1 mL intraperitoneally) and an estradiol injection (20 000 IU in 0.1 mL intramuscularly) to stimulate endometrial growth.

The mice were killed using a combination of ketamine hydrochloride (100 mg/kg) and xylazine (10 mg/kg) administered intraperitoneally to ensure rapid and painless sedation. Death was confirmed by the cessation of vital signs, including respiration and cardiac activity, as verified by trained personnel. This method complies with the recommendations of the American Veterinary Medical Association (AVMA) for humane killing of laboratory animals.

On day 14 after transplantation, the presence of endometriotic-like lesions was confirmed visually during necropsy. Ectopic lesions resembling endometriotic foci were identified in the peritoneal cavity, characterized by fluid-filled cysts and vascularized tissue, which are consistent with findings in validated mouse models of endometriosis. While histological confirmation was not performed, the induction method used in this study was based on extensively validated protocols in the literature, and the observed lesions during necropsy strongly supported the establishment of an endometriosis model.

Experimental Design

The sample size was calculated using the Lemeshow formula with a confidence level of 95%, power level of 90%, and standard deviation of 1.38, based on previous study by Dwiningsih et al [8]. Thirty-two healthy mice in this study were allocated randomly into 2 distinct cohorts (n=16): control cohort (P0): mice

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receiving a placebo; and treatment group 1 (P1): mice with an endometriosis model. Ovulation was induced through a superovulation protocol. Female mice received intraperitoneal injections of 5 IU pregnant mare serum gonadotropin followed by 5 IU human chorionic gonadotropin (hCG) 48 h later. After the hCG injection, the mice were paired with male mice, and successful mating was confirmed by the presence of a vaginal plug the next morning. Mice with confirmed vaginal plugs were killed 14 to 16 h after hCG injection. The oocytes were collected from the oviductal ampullae by flushing the fallopian tubes with prewarmed medium containing hyaluronidase, to separate cumulus cells. The retrieved oocytes were assessed under a stereomicroscope for maturity and morphology, ensuring the collection of intact metaphase II oocytes for subsequent analyses. The number of retrieved oocytes per mouse served as a proxy for ovulation.

Cardiolipin Level Analysis

Oocytes harvested from the fallopian tubes of killed mice were homogenized in phosphate-buffered saline (PBS) with a protease inhibitor. The homogenate was centrifuged at 3000 rpm for 20 min, and the supernatant was collected. Protein concentration was determined using a Bradford assay, to ensure consistent sample loading. The oocytes were quantitatively assessed, and an assay procedure was executed using the enzyme-linked immunosorbent assay (ELISA) with microtiter plates (Polysorp; Nunc, Life Technologies, Paisley, United Kingdom). These plates were subjected to a coating procedure overnight at a temperature of 4°C with 50 µg/mL of mouse cardiolipin (CL) sourced from the ELISA kit, catalog number: MBS055829 (MyBioSource, Inc, San Diego, CA, USA). The blocking procedure involved a 1% (w/v) bovine serum albumin (Sigma) solution in PBS for 1 h at 37°C, followed by a final rinse with PBS. The absorbance was subsequently recorded at a wavelength of 450 nm on the optical density (OD) using an ELISA reader within a timeframe of 15 min after the addition of stop solution. A known concentration of cardiolipin (from the kit standard) was used as positive control to assess the sensitivity of the assay. PBS without any sample was used as negative control to check for nonspecific binding or contamination in the assay. Absorbance was measured at 450 nm, and cardiolipin concentrations were determined using a standard curve (0-400 pg/mL). Results were expressed as a percentage of the positive control's OD. The OD and the concentration of cardiolipin were ascertained by computing the mean of the readings for each standard well and each sample well. The results were expressed as a percentage of the positive control, calculated using the formula: OD (sample)/OD (positive control) ×100.

Analysis of Transmission Electron Microscopy

The ultrastructural characteristics of mitochondria within the isolated oocyte cells were systematically investigated using transmission electron microscopy (TEM). The initial step involved fixing the cells in a solution comprising 2.5% glutaraldehyde and 3% sucrose within a 0.1 M sodium cacodylate buffer (pH 7.4) for a full day at 4°C, succeeded by a further fixation duration in the same mixture for 3 h at 4°C. Following that, the cells underwent a treatment involving 2% osmium tetroxide and 2.5% K3 Fe(CN)6 mixed in 0.1 M cacodylate buffer (pH 7.4) for 30 min while kept at 4°C. The samples were then dehydrated using a graded series of ethanol for 15 min, embedded in Spurr's resin (Spurr Low-Viscosity Embedding Kit (EM0300), Sigma-Aldrich, St. Louis, MO, USA) for 24 h at ambient temperature, and subsequently analyzed using a JEOL 1010 transmission electron microscope. Moreover, the sample was subjected to centrifugation at 3000 rpm for a duration of 5 min, commensurate with its pellet cell type [9,10].

Mithocondrial Ultrastructure Staining

The oocyte sample was well embedded in the capsule then the sample was cut using a machine Ultramicrotome PowerTome XL Ultramicrotome RMC and a special diamond knife to make a cut thickness of 50 to 70 nm. The sheet of oocyte was glued on a copper plate or 200 mesh grid then stained with uranyl acetate (10288, BDH Chemicals Ltd) and triple-lead citrate (10242, BDH Chemicals). The sample was observed under an electron microscope FEI Tecnai G2 S-Twin with a voltage of 80 kV using a magnification of 15 000 times to show an image of the mitochondrial ultra-structure, with cristae and mitochondrial membranes in each sample obtained [9,10]. Mitochondrial morphology is systematically categorized into 4 distinct classifications for analytical purposes: class I: mitochondria are characterized by a well-defined outer membrane and exhibit multiple elongated cristae within the surrounding densely packed matrix; class II: fragmented mitochondria, which display dilated crista junctions and possess an electron-transparent intra-crystalline compartment, interspersed with regions of electron-dense matrix; class III: distinguished by prominent morphological anomalies and partial integrity loss of the outer membrane; and class IV: characterized by pronounced morphological deterioration and alterations, encompassing significant swelling, with edema and ruptured mitochondria exhibiting indistinct cristae structures. [11]. To ensure that observed changes were not attributable to fixation artifacts, meticulous sample preparation protocols were followed, including immediate fixation of oocytes in glutaraldehyde and post-fixation with osmium tetroxide to preserve ultrastructure integrity. Consistent results were observed across multiple replicates, further supporting the validity of the findings.

Statistical Analysis

The data were analysed using SPSS version 24 software. The Kolmogorov-Smirnov test was used to analyze all datasets for their adherence to normal distribution. Parametric datasets

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underwent analysis using the Fisher exact test to examine variations in the morphology of mitochondrial oocytes. The Mann-Whitney U test was used to evaluate differences in cardiolipin concentrations within non-parametric datasets. The Spearman correlation analysis was performed to elucidate the influence of morphological alterations in mitochondrial oocytes on the concentrations of cardiolipin. A criterion for statistical significance was established at $P \leq 0.05$.

Results

TEM revealed significant differences in mitochondrial morphology and density between oocytes from the control and endometriosis groups. Mitochondria in the control group exhibited intact double membranes and well-defined cristae (class I), whereas oocytes from the endometriosis group predominantly showed damaged mitochondria with disrupted membranes,

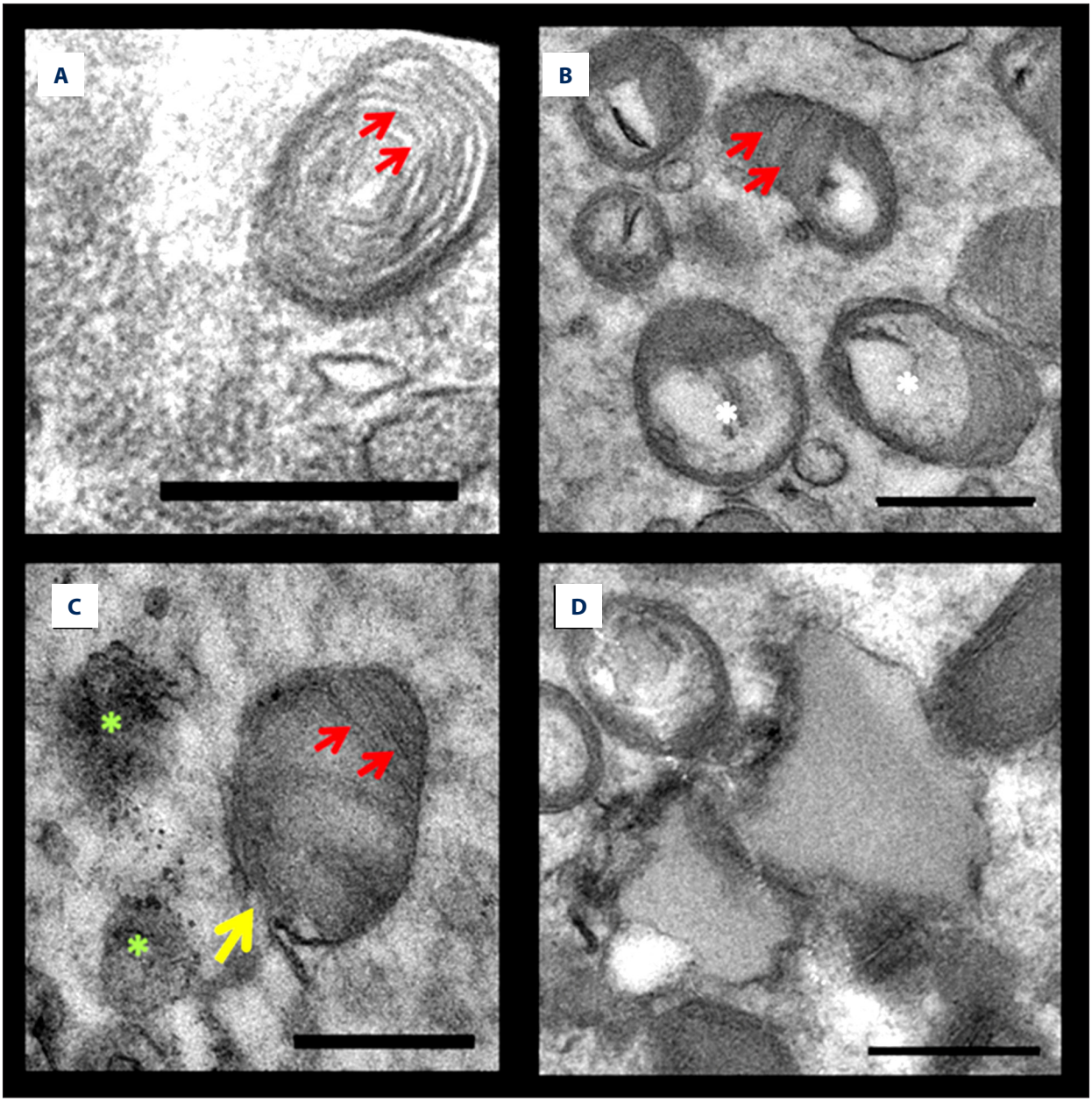

Figure 1. Representative transmission electron microscopy images of oocytes. (**A**) Mitochondria from control mice show intact membranes and well-defined cristae. (**B-D**) Mitochondria from endometriosis-induced mice exhibit disrupted membranes and swollen cristae. Red arrow: cristae; yellow arrow: outer membrane; white asterisk: swollen cristae; green asterisk: materials of mitochondria burst out. (Bar 500 nm; Magnification 15 000×; FEI Tecnai G2 20 S-Twin, 80 kV.). *This figure was generated using Microsoft PowerPoint, Microsoft, Washington, USA.*

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Table 1. Morphology of mice mitochondrial oocytes in each group.

Mitochondria	Endometriosis	Control	Total	*P* value
Intact mitochondria (class I)	2	16	18	<0.001
Damaged mitochondria (class II-IV)	14	0	14	
Total	16	16	32	

Table 2. Cardiolipin level of oocytes in each group.

Cardiolipin level	Endometriosis	Control	*P* value
Mean	3.73 (0.24)	4.59 (0.2)	<0.001
Range	4.28-4.96	3.14-4.15	

Mann-Whitney test.

Table 3. Correlation between morphological change in mitochondrial oocytes with cardiolipin level of oocytes in each group.

Correlation	R	*P* value
Correlation between morphological change in mitochondrial oocytes with cardiolipin level of oocytes in each group	73%	<0.001

R – correlation coefficient. Spearman correlation test.

swollen structures, and disorganized cristae (classes II, III, and IV). Representative TEM images are shown in **Figure 1**. Endometriosis-induced mice exhibited a 87.5% reduction in intact mitochondrial morphology, compared with controls. The findings from the Fisher exact test demonstrated a statistically significant disparity in the mitochondrial oocyte morphology between the 2 cohorts ($P<0.001$). Notably, the group affected by endometriosis displayed a markedly reduced variation in mitochondrial morphology in comparison with the control group ($P<0.05$), as illustrated in **Table 1**.

The results obtained from the Mann-Whitney analysis showed a notably significant difference in cardiolipin levels across the 2 participant groups ($P<0.001$), where the cohort diagnosed with endometriosis displayed a markedly reduced concentration of cardiolipin, compared with the control group ($P<0.05$), as shown in **Table 2**.

The correlation between morphological alterations in mitochondrial oocytes and cardiolipin levels within the oocytes of endometriosis-affected mice is shown in **Table 3**.

Discussion

The outcomes of the correlation analysis indicated a significant positive correlation between morphological changes in mitochondrial oocytes and oocyte cardiolipin levels ($P<0.001$), with a morphological change rate of 73% in relation to cardiolipin levels, as presented in **Table 3**.

The findings indicated a substantial disparity in mitochondrial morphology between the oocytes of the 2 groups ($P<0.001$), with the endometriosis group exhibiting notably reduced mitochondrial morphology, in contrast to the control cohort ($P<0.05$). This phenomenon may be ascribed to endometriosis, wherein an inflammatory response prompts the body to mobilize monocytes, particularly macrophages, to eliminate endometrial cells and debris. The binding of TNF-α induces an elevation in the generation of reactive oxygen species (ROS) by the mitochondria, which triggers the activation of permeability transition pores, resulting in the subsequent expansion of the mitochondrial matrix. Consequently, it results in mitochondrial malfunction.

Numerous studies indicate that mitochondria modify their shape and cristae in reaction to oxidative stress. Mitochondria adapt to oxidative damage by adopting an extended morphology. The elongated structure with enlarged cristae is used for enhanced metabolic bioenergetics, glycolysis, and ROS generation. Chen et al [12] said that mitochondrial cristae are the primary sites for oxidative phosphorylation. ROS are chiefly produced by the mitochondrial electron transport system throughout the process of oxidative phosphorylation, mainly via the respiratory chain complexes I and III. The enlargement

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of cristae spaces transpires with the stimulation of oxidative phosphorylation and heightened ROS production. Mitochondria are believed to use 90% of cellular oxygen, with 2% of that oxygen being reduced by electrons to generate ROS [12-14].

Mitochondria in endometriosis stromal cells are situated adjacent to the nucleus or the plasma membrane, exhibiting increased elongation, rounded cristae, and elevated electron matrix density. Mitochondria in ectopic endometriosis displayed 60% class I morphology, infrequently presented class II morphology, and a subset was categorized as class III morphology, due to distinctive cristae morphology. Mitochondria in situ in endometriosis and control samples exhibited class I morphology. They possess an oval morphology characterized by parallel cristae and prominent intracristal gaps [12].

The findings of our investigation have highlighted a significant difference in the comparative analysis of cardiolipin concentrations between the 2 groups, exhibiting a statistically significant disparity ($P<0.001$), with the endometriosis cohort showing reduced levels, compared with the control group ($P<0.05$). Cardiolipin is a major mitochondrial phospholipid, essential for sustaining mitochondrial activity, encompassing membrane architecture, oxidative phosphorylation, ATP synthesis, mtDNA biogenesis, mitochondrial fusion, fission, and autophagy (mitophagy) [15]. Reduced levels of cardiolipin, a mitochondrial breakdown product, result from damage to mitochondrial oocytes in endometriosis, in which mitochondrial oocytes exhibit decreased activity due to elevated inflammatory markers, particularly TNF-α. The interaction of TNF-α to its receptor activates procaspase 8, converting it into active caspase 8, which then induces mitochondrial damage via the apoptotic pathway [16]. This phenomenon will precipitate oxidative damage to cardiolipin and diverse membrane phospholipids, thereby resulting in an increased permeability to protons and ions, which subsequently reduces ATP synthesis [17]. Consequently, ROS generation can lead to oxidative degradation of mitochondrial lipid membranes [18]. Oxidized cardiolipin will initiate a loss of electron transport function when ROS/reactive nitrogen species damage occurs [7].

In this study, we performed a correlation analysis between mitochondrial oocyte morphology and cardiolipin levels in oocytes, revealing a significant positive correlation ($P<0.001$), with a correlation rate of 73% between mitochondrial oocyte morphology and cardiolipin levels. Mitochondria serve as the principal origin of ROS and ATP production. Mitochondria in endometriosis are subjected to prolonged oxidative stress, necessitating the production of enough energy for lesion proliferation [12]. Oxidative stress possesses the capacity to elicit the oxidation of cardiolipin, hence altering its physicochemical characteristics. The alteration of cardiolipin is a first indicator of the apoptotic process mediated through an increase in the concentrations of ROS. Augmented levels of ROS possess the capacity to cause detrimental effects on mitochondria in neurones deprived of growth factors, leading to a reduction in cardiolipin levels. Oxidation of cardiolipin can result from the activity of oxidative enzymes, including the activation of lipoxygenase. Lipoxygenase activity induces morphological alterations in mitochondria, due to modifications in cardiolipin. Lipoxygenase elevates the oxidative index, leading to the release of cytochrome c. Furthermore, the by-products of lipoxygenase oxidation, specifically linoleic and arachidonic acids, might directly influence mitochondrial apoptosis [19].

As a key phospholipid in mitochondrial membranes, the oxidation of cardiolipin under oxidative stress conditions, as observed in our study, underscores its potential as a biomarker for mitochondrial dysfunction in endometriosis. Targeting cardiolipin integrity through antioxidants or mitochondrial stabilizers could offer novel therapeutic avenues for enhancing fertility in patients with endometriosis.

This study presents a well-designed exploration of mitochondrial morphology and cardiolipin levels in oocytes within an endometriosis model, leveraging a controlled experimental design with adequate sample sizes to enhance reliability. Detailed methodologies, including TEM and ELISA, provided high-resolution insights into mitochondrial alterations. This study demonstrated that endometriosis significantly affects mitochondrial morphology and cardiolipin levels in oocytes, highlighting a potential mechanism for reduced fertility associated with this condition. The observed morphological alterations and lowered cardiolipin concentrations in the mitochondria of endometriosis-afflicted mice suggest that mitochondrial dysfunction may play a key role in the impaired oocyte quality linked to endometriosis. Additionally, the positive correlation between mitochondrial morphological changes and cardiolipin levels reinforces the idea that oxidative stress and inflammation in endometriosis can lead to mitochondrial damage, further affecting reproductive health. These findings provide a foundation for future research on targeted therapies to improve mitochondrial function in the reproductive cells of women with endometriosis, potentially enhancing fertility outcomes. However, there are limitations, including the challenge of translating mouse model findings to human physiology, which can affect applicability. The focus on a limited set of biomarkers and the study's acute rather than chronic approach constrains the broader understanding of the long-term mitochondrial effects of endometriosis. The findings of this study require further clinical studies to confirm applicability to women with endometriosis.

Conclusions

This study reveals that endometriosis disrupts mitochondrial structure and reduces cardiolipin levels in oocytes, suggesting

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mitochondrial dysfunction as a key factor in decreased fertility. These findings highlight the potential of targeting mitochondrial health to improve reproductive outcomes for women with endometriosis.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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