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Review Article

The Role of Oxidative Stress and Antioxidant Effects in Female Endometriosis: A Systematic Review

Ashish Ashish[1], Kusum Kusum[2], Sangeeta Rai[3], Kulsoom Zahra[4], Surendra Pratap Mishra[4] and Royana Singh[1]*

[1]*Department of Anatomy, Institute of Medical Science, Banaras Hindu University, Varanasi, India*

[2]*Department of Zoology, Institute of Science, Banaras Hindu University, Varanasi, India*

[3]*Department of Obstetrics and Gynaecology, Institute of Medical Science, Banaras Hindu University, Varanasi, India*

[4]*Department of Biochemistry, Institute of Medical Science, Banaras Hindu University, Varanasi, India*

***Corresponding Author:** Royana Singh, Department of Anatomy, Institute of Medical Science, Banaras Hindu University, Varanasi, India.

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Abstract

Endometriosis is an estrogen-dependent chronic inflammatory disease associated with substantial morbidity, including dyspareunia, dysmenorrhea, pelvic pain, multiple surgery, and infertility. This disease has a high impact on both woman's physical and mental well-being. The etiology of endometriosis is complex and multifactorial, influenced by genetic, epigenetic, elevated reactive oxygen species (ROS), and oxidative stress. These factors have been postulated to play an essential role in endometriosis pathogenesis. The mitochondria are central in cellular inflammation and also a source of reactive oxygen species (ROS) in endometriosis. They are targets of ROS, and many different cellular signals like NFκB are activated due to Retrogate mensuration and ROS. These signaling pathways are responsible for the activation of apoptotic pathways in the cells of Immunity like JNK, Caspases, and IKK. This review defines molecular events linking, oxidative stress, and mitochondria, which lead to Mitochondrial Dysfunction and Apoptosis instability, alterations associated with endometriosis, its mechanisms, and pathways related to oxidative stress in ectopic peritoneal lesions.

Keywords: Endometriosis; ROS; Mitochondrial Dysfunction; Infertility; Oxidative Stress

Introduction

Endometriosis is a common gynaecological affecting 10-15% of the women in their reproductive age. The most common symptoms of the disease are pelvic pain and infertility. Endometrisis is thought to arise from retrograde menstruation and implantation of endometrial tissue, mostly into the peritoneal cavity. It affects an estimated 1 in 10 women of reproductive age, constituting 200 million women worldwide, a total of 10% of the total female population. Endometriosis is the leading cause of infertility, with 30 to 50% of the total cases of infertility [1]. About 40% of total endometriosis cases have early disease onsets affecting younger women. In an estimate, approximately 25 million cases of endometriosis are prevalent in India [2]. Lack of awareness, miss and hit treatment of the disease, and the need for invasive surgery to establish a diagnosis lead to an average diagnostic delay of up to seven years [3]. This could be partially explained by the fact that the gold standard for diagnosis of endometriosis requires direct visualization of lesions at surgery followed by histological confirmation of endometrial glands and stroma in biopsies of suspected lesions [4]. Additionally, other factors that contribute to the diagnostic delay are the treatment of pain with oral contraceptives or nonsteroidal anti-inflammatory drugs and the assumption of dysmenorrhea as a regular event. Treatments are limited to hormonal therapy with many side-effects and complicated surgical removal of the disease, which

often needs to be repeated. Nowadays, growing evidence suggests that the remodeling of retrograde menstruation or endometrial tissues to the ectopic endometriotic lesions involves multiple epigenetic alterations, such as DNA methylation, histone modification, and microRNA expression. Many studies have shown that inflammation arises from retrograde menstruation, plays a central role in the development of endometriosis. It is marked by an inflammatory process associated with the overproduction of an array of inflammatory mediators such as metalloproteinases, prostaglandins, chemokines, and cytokines [5]. This review defines molecular events linking, Oxidative Stress, and mitochondria, which lead to Mitochondrial Dysfunction and Apoptosis instability, alterations associated with endometriosis, its mechanisms, and pathways relating to oxidative stress in ectopic peritoneal lesions.

Epidemiology

The accurate assessment of endometriosis burden requires detailed information related to its occurrence and incidences in the general population, but it is not known because its diagnosis is often overlooked by clinicians. Due to miss treatments, it takes an average of 7-10 years to get diagnosed in most of the women, and a general lack of awareness about the illness itself contributes further [6]. It has been estimated that every 1 out of 10 women, during their reproductive years (between puberty to menopause), is suffering from endometriosis, with more recent research proposing up to 30-50% women with infertility. It is immensely challenging to assess the rate of endometriosis in general female population because the definitive diagnosis requires surgical visualization [7]. Accordingly, one has to access many different population samples and modes of disease diagnosis for estimation – all influenced by present symptoms and access to care. Despite these limitations, in a study of a large group of women in their first laparoscopic examination in 10 countries, across five countries showed that endometriosis is a common global problem, with an incidence ranging from 35% to 100% in symptomatic women [8]. Although the lack of reliable data confirms that the prevalence of this disease varies among different ethnic groups as any experimental variations cannot be extracted from differential access to health care [4]. The symptoms of endometriosis include painful ovulation and periods, dyspareunia, chronic pelvic pain, heavy menstrual flow, infertility, fatigue, and it impacts severely on general physical, mental, and social wellbeing of women. The disease has an increased rate of recurrence after bilateral oophorectomy (removal of the ovaries) or in postmenopausal women, particularly in those who have undergone hormone replacement therapy. Despite the existing data as well as the case reports, accurate prevalence is not known because of the lack of clinical evidence and reliable data [9]. The incidence of clinically diagnosed endometriosis in Rochester, Minnesota, was 187 per 100,000 person-from years 1987 to 1999 [10]. In a similar study, in 1989, among whom a 10-year incidence of laparoscopically confirmed significant cases with endometriosis were 298 per 100,000 people. The Endometriosis Society of India estimated about 25 million cases of endometriosis are prevalent in India [11].

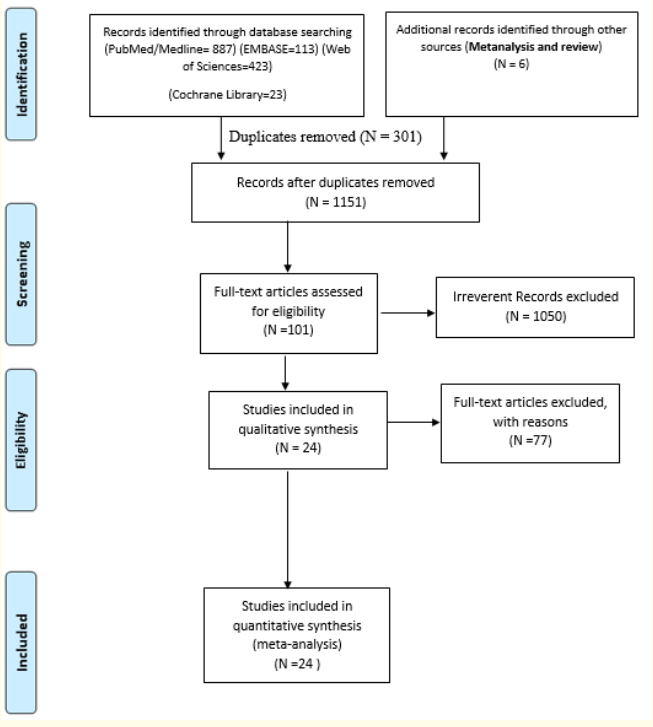

Figure 1: Flow diagram; expanding the relevant search terms related articles were selected, for a comprehensive systematic review (PRISMA protocol 2009).

Types of endometriotic lesions

Endometriosis is characterized as the appearance at ectopic locations of endometrial tissues. The most common involvement is in the peritoneum (deep endometriotic and superficial implants) and ovaries (endometrioma or endometriotic cysts), although cases of pulmonary and cerebral endometriosis are also known. According to clinical point of view, there are three distinct central lesions depending on their location: peritoneal implants (P.I., on the surface of the peritoneum), ovarian endometriomas (OMAs, in the ovary), and rectovaginal nodules (RVN; in the Pouch of Douglas and rectovaginal septum). From a histological point of view, all three types of lesions share common features, as the presence of stromal and epithelial endometrial cells, chronic bleeding, and signs of inflammation [12].

Endometriosis classification system

Numerous proposed systems to classify endometriosis exist at present. These include those by American society for reproductive Medicine (rASRM, 1979) [13]. The number, size, location of peritoneal endometrial implants, plaques, endometriomas, and adhesions imposed ASRM to revise and chart their classification into a point system with a scoring system to translate the disease into its differential stages. The classification has been revised, modified, and renamed as revised American Society for Reproductive Medicine (rASRM) for classification of endometriosis. Mainly, all of these classifications divide endometriosis disease into four stages related to the increasing severity of the ovarian lesions, particularly the number of endometrial implants, their depth, and adhesion formation [14]. The main objective of this classification system is to predict disease severity, based on a numerical scale and the chance for conception after treatment.

Severe with many deep implants large cysts on one or both ovaries with dense adhesions. Limitation of this ASRM staging system is that the scoring includes only intraperitoneal endometriosis, and it under-represents other manifestations of endometriosis such as extraperitoneal lesions in the bowel or bladder. Therefore, ASRM classification and scoring are currently under investigation to reflect the multifaceted aspects of endometriosis and its impact on fertility. Further, to overcome the limitation related to spontaneous pregnancy prediction after surgery for endometriosis, the Endometriosis Fertility Index (EFI) score has been developed. EFI score is also based on a punctuation system that takes into account both surgical factors assessed during surgery (representing half of the points and involving fallopian tubes, fimbriae, and ovaries) and historical factors of the woman (involving age, years of infertility and whether a prior pregnancy occurred). The endometriosis fertility index EFI ranges from 0–10, with 0 representing the poorest prognosis and 10 the best prognosis. Importantly, the EFI score has been validated in French, Italian (Garavaglia., *et al*. 2015), Belgian, and India cohorts [15].

Etiology of endometriosis

The origin of endometriosis is yet unknown. However, multiple theories exists that explained the causes and pathophysiology of the disease. These theories can be grouped into those proposing a uterine origin of implants and those proposing an extrauterine origin of endometriotic lesions.

Sampson's Implantation Theory (uterine origin of endometriosis)

There are two theories that accounts for uterine origin of endometriotic lesions, namely the theory of retrograde menstruation and the theory of benign metastasis (both hematogenous and lymphatic).

Initially proposed by the American gynecologist J.A. Sampson in 1927, the theory of retrograde menstruation and implantation and is the most widely accepted. Sampson suggested that the endometrial tissue gets transported back through the fallopian tubes during menstruation, where it is capable of reaching the abdominal cavity by retrograde flow through the fallopian tubes, leading to intra-abdominal pelvic implants. 90% of healthy women documented that retrograde menstruation occurs in reproductive age with patent fallopian tubes followed by peritoneal implantation, and further supports the location of endometriotic lesions [16].

Theories regarding a non-uterine origin of endometriosis

Four theories accounts for non-uterine origin of endometriosis, namely coelomic metaplasia theory, induction theory, embryonic Müllerian rests theory, and the recently proposed extrauterine bone-marrow progenitor theory [17]. Both coelomic metaplasia and induction theory propose that endometriotic lesions are the results of the transformation of normal peritoneum under the influence of appropriate stimulus (e.g., endocrine disruptors for coelomic metaplasia and endogenous hormonal or immunologic factors for induction theory). The idea that estrogen could also induce the formation of endometriotic lesions has been developed by the theory of embryonic Müllerian rests. In contrast to the induction theory, proposes that specific agents released from shed endometrium induce undifferentiated mesenchyme to develop into endometriosis under the influence of estrogen at the beginning of puberty (Russell, 1899). Finally, the more recently proposed theory of bone marrow progenitors suggests that extrauterine bone marrow mesenchymal stem progenitors and endothelial progenitors may differentiate into endometriotic tissue. These theories are backed by clinical findings of histologically proven endometriotic tissue in patients without menstrual endometrium (e.g., women with Rokitansky-Kuster-Hauser syndrome) and men with prostate cancer undergoing treatment with high-dose of estrogens [18].

Antioxidants and mitochondrial dysfunction

Antioxidants are biological compounds that inhibit oxidation, oxygen-derived molecular species formed as intermediary products. Antioxidants are versatile molecules that play a role in cellular response with virtually all cellular components. When antioxidants are present above a critical threshold, they can induce a significant structural, chemical reaction that can produce free radicals and functional cell damages [19]. Mitochondrial potential dysfunction underlies the endless cycle of oxidative stress and inflammation,

which increases oxidative stress under inflammatory conditions resulting in possible mitochondrial dysfunction. This dysfunctional mitochondria triggers an amplified oxidative burst and propagates inflammation**.** ROS (reactive oxygen species), such as superoxide anion peroxides, hydrogen peroxide, and the hydroxyl radical singlet oxygen, and alpha-oxygen are characterized as oxidants. During in-vivo studies of biological oxidation, electron leakage from the inner mitochondrial membrane has been identified as the main source of ROS; it can mediate redox signaling or, in excess, causes cell injury and even cell death. Free radicals induce oxidative stress that can lead to retrograde menstruation by an imbalance between antioxidant defense and Pro-oxidant burden caused by an inadequate or excess inflammation. Sustained exposure to ROS damages the mitochondria and compromises the electron transport system (ETS). Mitochondrial membrane potential, a source of ROS, could also be a target of ROS under pathological conditions. Specifically, the opening of the mitochondrial membrane permeability transition pore (MMPTP), which in turn causes the release of cytochrome C are located in the mitochondrial matrix to the cytoplasm, activates pro-apoptotic caspases [20]. Aberrant mitochondrial morphology may lead to enhanced ROS formation, which, in turn, may deteriorate mitochondrial health and attack most of the biomolecules, proteins, including lipids and nucleic acids, resulting in various forms of cell damages. The imbalance in the ratio of the antioxidants to ROS can result in a variety of pathological processes within the body. Specifically, ROS comprises a class of radical and nonradical oxygen derivatives that play a significant role in reproductive biology.

Pathophysiology of oxidative stress and endometriosis

Oxidative stress can occur when there is an excess of free radicals and antioxidants in our body cells, which imbalances free radicals and antioxidants capacity. When reactive oxygen species concentration is not controlled by internal defense mechanisms such as antioxidants (tocopherols, glutathione, and ascorbic acid) or enzymes involved in oxygen radical scavenging (catalase(CAT), glutathione peroxidase (GPX), superoxide dismutase (SOD), then oxidative damages occur to proteins, lipids, and DNA, which could lead to cytotoxicity, genotoxicity, and even carcinogenesis when damaged (or mutated) cells proliferate. Oxidative stress could result in a damaging effect on female abilities, fertility by affecting fertilization, folliculogenesis, signaling molecules, oocyte maturation, embryo development, ovulation, tubal function, and implantation (Figure 2). Thus, oxidative stress is considered as a cause of female infertility; this is particularly notorious in cases of endometriosis [21].

The components of refluxed blood (retrograde menstruation), includes apoptotic endometrial tissue, desquamated menstrual cells, lysed erythrocytes, apoptosis of T and B cells and released iron, leading to inflammation in the peritoneal cavity. This, in turn, activates macrophage release of reactive oxygen species (ROS), leading to oxidative stress via the respiratory burst. Refluxed blood promotes the autoxidation and Fenton reaction, terminating in the production of hydroxyl radical, the most potently destructive ROS. Fenton reaction producing hemoglobin from the ferrous Fe2+ (oxyhemoglobin) with the iron of ferric Fe3+ (methemoglobin) production of excess (ROS) such as O2− and -OH. Haemoglobin, iron derivatives, and heme in endometriotic cysts cause distortion in the homeostatic redox balance.

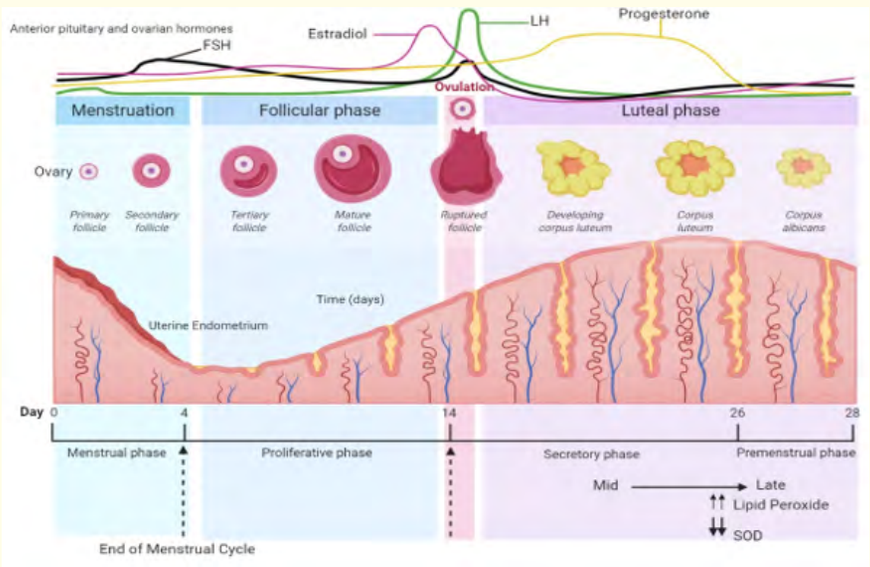

Figure 2: Inflection of redox balance throughout the menstrual cycle.

Iron and oxidative stress

Heme and iron derivatives to induced oxidative stress play a fundamental role in the endometriotic lesions during retrograde menstruation [22]. Excess oxidative stress could trigger an influx of iron that modifies lipids and proteins, leading to DNA damage and cell death. Reversible binding of heme oxygen to hemoglobin to transferrin to regulates erythrocytes. Thus, body and dietary iron have important beneficial effects on tissue homeostasis [23]. A study have confirmed HNF-1β overexpression in endometriotic foci. HNF-1β increases the survival of endometriotic cells under iron-induced condition suggested that oxidative stress may have activation of forkhead box (FOX) transcription factors and endometriosis-specific expression of microRNAs. A recent study confirmed by Alizadeh., *et al*. 2015 A high level of serum iron may promote O.S. in patients with endometriosis.

Fenton reaction

Accumulated refluxed menstrual blood inflammatory components contain numerous lysed erythrocytes in the serum of women with endometriosis [24]. The Iron toxicity is the production of a wide variety of damaging free radical species by the Fenton reaction, leading to deregulation of cellular processes, cell dysfunction, and eventually to apoptosis or necrosis through protein, lipid peroxidation, and DNA damages leading to the generation of ROS which is the product of the reaction between NO and superoxide anion (O2−) [25].

$$--Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH\cdot + OH^-$$

Interactions between the superoxide (SO) anion and hydrogen peroxide (H_2O_2) Superoxide radical is associated with the formation of Fe^{2+} and H_2O_2 and, in turn, produces ·O.H. However, Oxidative stress elevates the number of erythrocytes found in the peritoneal Mesothelium cavity of women producing adhesions for ectopic endometrial cells (Figure 3) [26].

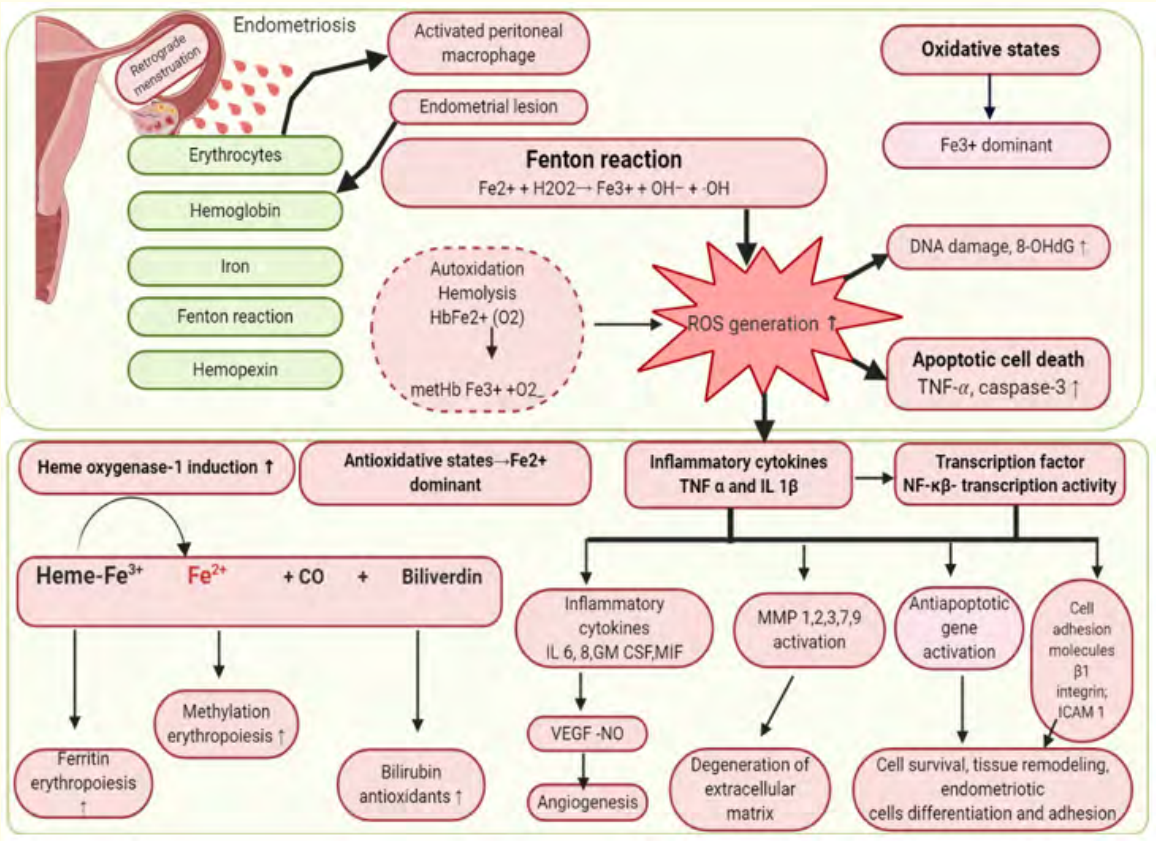

Figure 3: The Role of retrograde menstruation, iron, and oxidative stress, inflammatory cytokines, and vascular endothelial growth factor in the pathogenesis of endometriosis.

The ferritin elevated in the course of the disease quickly binds with an iron into the peritoneal cavity, contributes to the Fenton reaction generating hydroxyl (O.H.) radical, and inducing oxidative stress. Heme oxygenase-1 levels were found to be higher in ectopic endometrium, especially in the red lesions and lower peritoneal mesothelium in macrophages [27]. Decreased expression of the HO-1 enzyme does not allow the final byproduct of heme breakdown, bilirubin, to form, and its antioxidant capacity is missing in these women. Moreover, a recent study proposed another role of OH-1 in endometriosis pathophysiology. Significantly increased OH-1 levels were observed in endometriomas compared to ectopic endometrial tissue of endometriosis and non-endometriosis patients. Increased OH-1 is proposed to induce autophagy [28]. Autophagy is a catabolic defensive mechanism in which macromolecules are confiscated and subsequently degraded. Wide activation of autophagy is lethal to the cells, resulting in autophagic cell death. Overall, iron overload causes increased proliferation of endometrial lesions and progression of the disease, which means that this mechanism could be a therapeutic target. By decreasing levels of iron, the levels of O.S. resulting from free iron in the peritoneal cavity can also be controlled [28].

Peritoneal fluid(P.F)

Peritoneal oxidative stress is currently argued in a number of studies and thought to be a major constituent of the endometriosis inflammation. The development of peritoneal Endometriotic lesions involves multiple etiology, immunological, and inflammatory factors, an increase in ROS production by P.F. mononuclear cells. Peritoneal oxidative stress regulates the expression of numerous genes encoding cytokines, immunoregulators, and cell adhesion molecules [15]. The peritoneal concentration of macrophages appears to be higher in women with endometriosis, and they may release prostaglandins, cytokines, growth factors, and other enzymes. Studies suggested that chronic stimulation of P.F. macrophages induces the release of ROS. One of the important hallmarks of macrophages is its high heterogeneity, allowing them to be activated to a different function, endogenous and exogenous inducers in the microenvironment, play an important role in the proinflammatory cytokines such as interleukin-1β (IL-1β), IL-12, tumor necrosis factor-α (TNF-α), and superoxide anions during the endometriotic disease [29]. A study by Anne Van Langendonckt., *et al*. concluded that ROS induced by macrophages, increases peritoneal levels of oxidized low-density lipoproteins, altered expression of antioxidant enzymes, endometrial pro-oxidant and consumption of peritoneal fluid and vitamin E. During endometrial inflammation highly pro-oxidant factors, such as heme and iron, into the peritoneal cavity, as well as apoptotic endometrial cells, are well-known inducers of oxidative stress. Other studies by Santulli., *et al*. shows a significant correlation between pelvic pain symptom scores and peritoneal protein [30].

Oxidative stress markers in women with endometriosis

Oxidative mechanisms involving LDL are higher in women with endometriosis. It consists of the oxidation of poly-unsaturated fatty acid-containing lipids of the lipoprotein [31]. In a study using chemiluminescence analysis, Y. Wang., *et al*. found that women with idiopathic infertility and women with endometriosis both had higher concentrations of ROS than tubal ligation control patients. This group found no correlation between the stage of endometriosis and ROS concentrations. Overall, the increase in ROS concentrations in patients with endometriosis was not significant, suggesting that in patients with the disease, ROS may not directly cause infertility [32]. A study by GrzegorzPolakto determines iron metabolism markers and their influence on oxidative stress parameters in the peritoneal fluid of endometriosis. Hemoglobin and iron levels are associated with oxidative status, values were significantly higher, and antioxidant values were significantly lower in the peritoneal fluid with endometriosis in comparison to the reference groups [33]. A study by Vivian Polak., *et al*. measured the level of lipid peroxidation (malondialdehyde, malondialdehyde with copper addition, and cholest-3,5-dien-7-one) in 21 women with endometriosis-related infertility. The level of lipid peroxidation level is not one of the factors responsible for women with endometriosis-related infertility and controls [33].

Oxidative stress (O.S.) and endometriosis

Oxidative stress is a phenomenon caused by environmental factors, including an imbalance between reactive oxygen species (ROS) and antioxidants, and it also affects fertility in women suffering from endometriosis. ROS have biological importance in reproduction. Serving as signaling molecules, they modify reproductive processes such as tubal function, oocyte maturation, and folliculogenesis [31]. The progression of endometriosis is clearly investigated the oxidative stress prognostic markers. Serum, peritoneal fluid, follicular fluid, ovarian cortex, and endometrial tissue (ectopic and eutopic) are all related to oxidative stress, which results in inflammatory responses in the peritoneal cavity [34]. According to several studies, increased antioxidant concentrations is signifi-

cantly and positively related to the prevention of endometriosis onset. One of the main effects of oxidative stress on endometrial cells is cell proliferation. Inducers of O.S. may include erythrocytes, apoptotic endometrial cells, and undigested endometrial cells in the menstrual effluent [35]. These factors may cause activation and recruitment of mononuclear phagocytes. Activated macrophages induce O.S., lipid peroxide formation, and other byproducts resulting from the interaction of apolipoproteins with peroxides. O.S. leads to a localized pelvic inflammatory reaction resulting in increased concentrations of cytokines, growth factors, and other pro-inflammatory mediators [36]. A study by Ana A. Murphy Lysophosphatidyl Choline, a Chemotactic Factor for Monocytes/T-Lymphocytes, mediates some of the clinical sequelae associated with endometriosis [37].

A recent study by Scuterio G., *et al*. from the University of Ferrara, Italy, a systematic review explores the functions of oxidative stress in the development of endometriosis.ROS possibility contributes to the development of endometriosis-associated cancer by targeting deregulated epigenetic factors or upregulating antioxidants. These changes may evoke the restoration of cell survival and subsequent malignant transformation [31]. Women with endometriosis, if they have an increased level of iron, can generate ROS. ROS may regulate epigenetic processes such as DNA methylation, histone acetylation, and histone methylation. Persistent upregulation of antioxidants may result in the restoration of cell survival and subsequent malignant transformation [31]. A review Study by Vitale., *et al*. concluded that several pro-inflammatory mediators such as metalloproteinases, chemokines, prostaglandins, cytokines, ROS, and free radicals, Vitamin A, Vitamin C, Vitamin E, and selenium in their follicular fluid have been associated with stage progression of endometriosis. Retrograde menstruation inflammation through the pelvic cavity, seem to be associated with highly prooxidant factors such as heme and iron (mainly from blood) [38]. A new study by Dr.Hariyono Winarto from the University of Indonesia in Jakarta identified increased oxidative stress that might contribute to a higher risk of ovarian cancer in women with endometriosis and investigated the ARID1A gene expression in human tissue samples. A study by Dr.Asemi group summarized the importance of key factors in the endometriosis pathogenesis. Endometriosis is a chronic disease, and inflammatory factors, including interleukin-1β (IL-1β), IL-6, and IL-8, enhances the proliferation of endometriotic cells in the endometriotic tissue. NF-κB, signaling pathway is regulated by various inflammatory signaling pathways, and are increased in both ectopic and eutopic endometrium [39].

NF-kappa B activation and endometriosis

The NF-kb pathway is a central signaling node in inflammatory cytokine stimulation and T Cells activation. Out of the five family members, p65 is the most ubiquitous and is expressed at high levels in most of the cell types; it can also dimerize with any of the other four family members to form an active transcriptional factor [38]. The Crucial Role of Sirt1 in the adaptive immune system was initially concentrated on T-cell activation. NF-kb dimers, however, have distinct functional and temporal parts in the immune response. The coordinated regulation of these NF-kb pathways is highly complex and dependent on many factors. In regards to the Sirt1 regulation of the NF-kb pathway, it was initially shown that Sirt1 deacetylates p65 at lysine 310 residue (K310), and this deacetylation of p65 leads to reduced NF-kb transcriptional activity. NF-κb function in T cells retrograde mensuration leads to mitochondrial dysfunction and activation of stress pathways. In previous studies during the past few years have underscored the central Role of NF-kb in the pathophysiology of endometriosis [40]. This Involvement of NF-kb in pathophysiology and inflammation appears to reflect the close integration and coevolution of highly mediated gene transcription promotes inflammation, invasion, angiogenesis, cell proliferation and inhibits apoptosis of endometriotic cells and pathogen sensing systems. Ikkb is situated at the focal point of signaling pathways induced downstream of cytokine receptors [e.g., tumor necrosis factor (TNF), interleukin (IL)-1 receptor, TLRs, and metabolic stress sensors and controls the expression of NF-kb-regulated inflammatory genes, such as TNF, IL-1b, and IL-6. IKK family kinases play a central role in both endometrial dysfunction and endometriotic lesions through multiple mechanisms. Nuclear factor-kappa B (NF-kappa B) plays a pivotal role in the immune and inflammatory response.

Effect of NF-kappa B activation on endometriosis and development

The nuclear factor kappa B (NF-kappa B) is ubiquitously expressed in human endometrial epithelial and stromal cells transcription factor playing vital roles in innate Immunity during menstruation. Nuclear factor-kappa B is physiologically and pathophysiology activated in the human endometrium and an important role in endometrial cell physiology. *In vitro* and *in vivo* studies constitutive activation of the NF-kappa B pathway to be activated in ectopic endometrial Cells, pelvic macrophages linking this inflammatory pathway in peritoneal endometriosis (Figure 4).

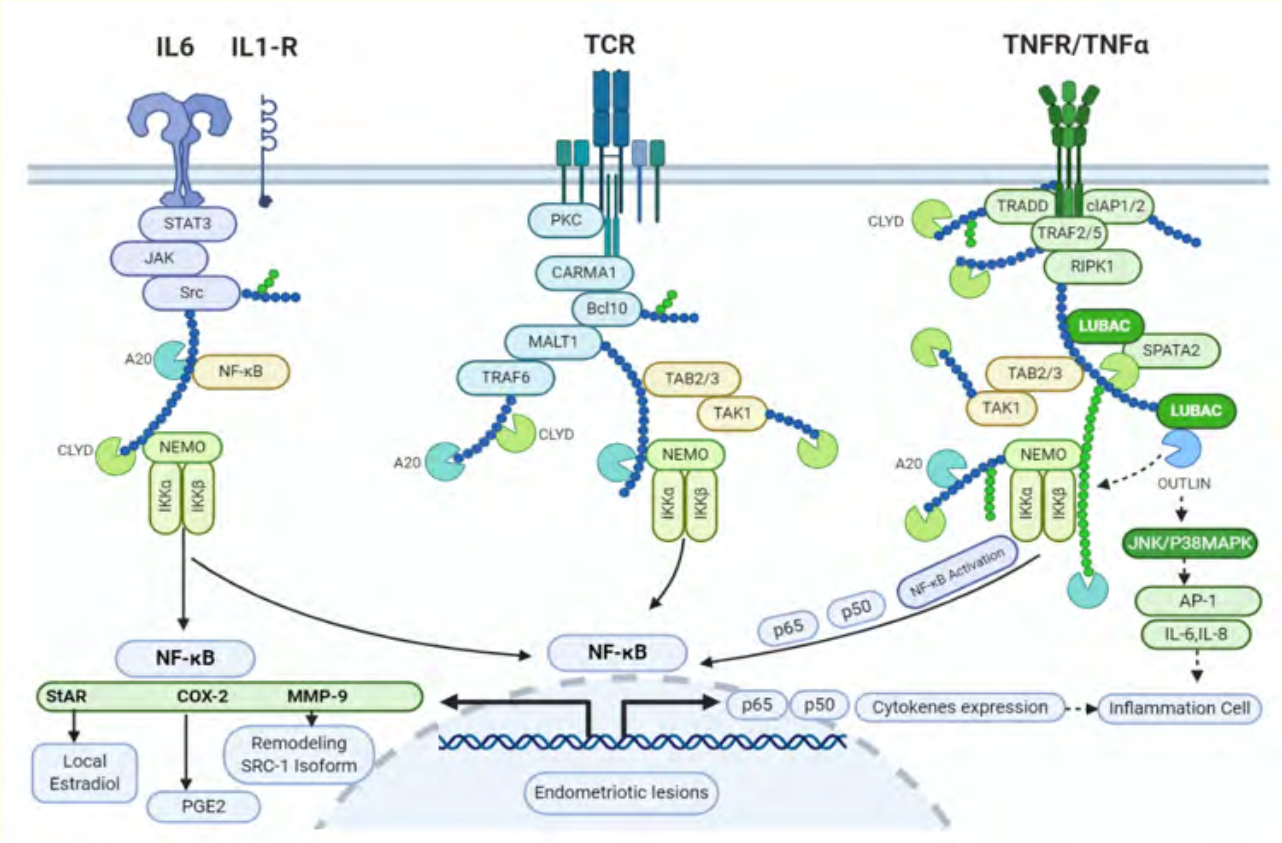

Figure 4: Activation of the NF-κB pathway in Endometriosis due to increased ROS, leading to mitochondrial dysfunction and apoptosis.

In vitro study shows basal and stimulated NF-kappa B activation have been demonstrated in endometriotic stromal cells, with endometriotic cells showing IL-1 beta, TNF-alpha or lipopolysaccharide-dependent NF-kappa B activation, positively modulating the proinflammatory cytokines RANTES, macrophage migration inhibitory factor (MIF), IL-8, IL-6, TNF-alpha, intercellular adhesion molecule (ICAM)-1, granulocyte-macrophage colony-stimulating factor and MCP-1. *In vivo*, constitutive activation of NF-kappa B has been evidenced in endometriotic lesions in endometriosis patients. Concentrations of active p65-containing dimers and ICAM-1 expression were found to be significantly higher in red endometriotic lesions than black lesions, while expression of the NF-kappa B inhibitor I-kappa B alpha was similar in red and black lesions, confirming the more extensive inflammatory pattern of red lesions. NF-kappa B-dependent activation of proinflammatory genes, such as RANTES, ICAM-1, IL-1 or TNF-alpha, may provide positive feedback to the pathway, thus self-perpetuating macrophage recruitment and the inflammatory response in the peritoneal cavity of endometriosis patients [40].

Conclusion

Endometriosis can effectively increase oxidative stress leading to mitochondrial dysfunction and increased permeability of mitochondrial membranes. The transcription factor NF-κb regulates multiple aspects of inflammatory responses. NF-κb plays a critical role in regulating the existence, activation, and differentiation of immune cells and inflammatory and also regulates NF-κb and other inflammatory pathways. Activation of these pathways leads to increased mitochondrial permeability and other changes leading to apoptosis in Cells of immunity inflammation associated with endometriosis patients; decreased Immunity leads to mortality and morbidity in a large number of patients. This is an of the further research area, and various pharmacological agents blocking and modulating this (NF-κb) pathways should be investigated for

their effect on stabilizing effect on mitochondria and Immunity in general.

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Ethical Approval

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Informed Consent

Consent statement is not applicable for this review manuscript.

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