Review

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Rare but Still There: A Scoping Review on Endometriosis-Associated Ovarian Cancer

Karl Livori[1,*], Jean Calleja-Agius[1]

[1]Department of Anatomy, Faculty of Medicine and Surgery, University of Malta, Birkirkara Bypass, MSD2080 Msida, Malta
*Correspondence: karl.livori.21@um.edu.mt (Karl Livori)
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Endometriosis is a medical condition affecting at least up to 10% of women of reproductive age. This condition occurs when ectopic endometrial glands and stroma implant outside the uterus and there are several theories regarding the underlying origins of the disease. Endometriosis is one of the major causes of severe dysmenorrhoea, chronic pelvic pain and infertility. While endometriosis is generally a non-malignant condition, it rarely may transform into an invasive cancer, and increase the risk for epithelial ovarian cancer, notably endometrioid or clear cell ovarian cancer. Despite the increased risk, the mechanisms behind the development of endometriosis-associated ovarian cancer (EAOC) are not yet well understood. Recent investigations have delved into the intricate interplay between endometriosis and EAOC, exploring pathways involving oxidative stress, inflammation, hyperestrogenism, and the discovery of genetic mutations within endometriotic lesions that hint at a transition towards invasive carcinoma. Efforts have been made to identify intermediary lesions between endometriosis and EAOC, which may enable earlier detection of endometriosis at risk of malignant transformation or even prevention of the transformation altogether. However, given the rarity of this malignancy, there is still the risk of late or missed diagnosis, with the risk of inappropriate management being offered to the patient, and the higher risk of poor prognosis and increased morbidity and mortality. This scoping review aims to summarize existing data on EAOC, with a focus on endometrioid and clear cell histologic subtypes. It also provides insights into its identification, prognosis, and delineating management strategies, seeking to provide a holistic understanding of the complexities surrounding EAOC, facilitating further research and the development of more effective prevention and treatment approaches.

Keywords: endometriosis; ovarian cancer; clear cell carcinoma; endometrioid carcinoma

Introduction

Endometriosis is a chronic, oestrogen-dependent, inflammatory disease defined by the implantation of ectopic endometrial glandular and stromal cells outside the uterine cavity. Endometriosis impacts about 5% to 15% of women [1]. It prevails in reproductive-age women, presenting with issues like severe dysmenorrhea, dyspareunia, infertility, and chronic pelvic pain. Among premenopausal women, endometriosis continues to be the leading cause of morbidity [2]. Although endometriosis is a non-malignant gynaecological condition, it shares some pathophysiological characteristics with cancer. Furthermore, histological, and epidemiological findings suggest that ovarian endometriosis may rarely contribute to the onset of epithelial ovarian cancer, specifically known as endometriosis-associated ovarian cancer (EAOC) [3].

Ovarian cancer is classified according to its cell type of origin, which might be epithelial, germ cell, or stromal. Epithelial ovarian cancers originate from the epithelial tissue that envelops the ovaries, accounting for around 85% of all ovarian cancers [3]. EAOCs represent only one rare subclass of epithelial ovarian cancers. Endometriosis is seen in 30%–55% of ovarian clear cell carcinoma (CCC) and 30%–40% of ovarian endometrioid carcinoma (EC), making EAOCs mostly comprised of clear-cell and endometrioid subtypes [3,4].

Research efforts have been made to identify intermediary lesions between endometriosis and EAOC, which may enable earlier detection of endometriosis at risk of malignant transformation or even prevention of the transformation altogether. However, given the rarity of this malignancy, there is still the risk of late or missed diagnosis, with the risk of inappropriate management being offered to patient, with the higher risk of poor prognosis and increased morbidity and mortality [5].

This scoping review aims to summarize existing data on EAOC, with a focus on endometrioid and clear cell histologic subtypes. It also provides insights into its identification, prognosis, and delineating management strategies, seeking to provide a holistic understanding of the complexities surrounding EAOC, facilitating further research and the development of more effective prevention and treatment approaches.

Methodology

English-language journals indexed in PubMed, and Google Scholar, published from 1996 to 2022, were searched for relevant articles addressing the clinical presentation, diagnosis, pathology, aetiology, prognosis, and management of endometriosis and EAOC. “Endometriosis”, “ovarian cancer”, “ovarian clear cell carcinoma”, “ovarian endometrioid carcinoma”, “chemotherapy”, and “radiotherapy” were among the targeted keywords. The references in the gathered articles were also reviewed for possibly relevant publications that were not found through database searches.

Epidemiology

Ovarian cancer ranks as the seventh most prevalent cancer among women around the world and the eighth highest contributor to cancer-related deaths [6]. Epidemiological studies imply that there is a higher incidence of ovarian cancer among women with endometriosis, up to 50% more compared to those without this condition. Women with endometriosis have a lifetime risk of around 1.9% for ovarian cancer, which is slightly higher than the 1.4% risk in those without endometriosis. This risk is particularly increased for ovarian clear cell carcinoma (CCC) or endometrioid carcinoma (EC), which is tripled or doubled, respectively [7].

Ovarian CCC account for 5%–10% of all ovarian cancers in North America, making it the second most prevalent ovarian carcinoma [8]. Even so, CCC appears to occur more frequently in East Asia, specifically in Japan [9]. Like ovarian EC, CCC often manifest at an early stage, with the majority of patients presenting with Federation of International of Gynaecologists and Obstetricians (FIGO) stage I/II disease [10] and only a few cases presenting with peritoneal or nodal metastases [9,11]. Endometriosis, particularly atypical endometriosis, is correlated with at least 50% of CCC. Atypical endometriosis has a premalignant potential by having dysplastic characteristics with cellular atypia that differs from typical endometriosis [12].

Approximately 10% of ovarian epithelial cancers are ovarian EC. Most cases of EC are of low-grade and are detected at an early stage (FIGO stage I or II) [13]. Women in their perimenopausal or postmenopausal years are typically affected [14]. A relationship between endometriosis and EC can be noticed, with 20%–40% of EC cases being linked to endometriosis. Endometrial cysts also may sometimes give rise to EC. Additionally, there is a reported correlation between 15%–20% of ovarian EC and endometrioid adenocarcinomas of the endometrium [15,16].

Pathophysiology

Endometriosis and its Relation to EAOC

Despite advances being made, endometriosis remains an intricate and multifactorial illness in which diagnosis, biomarkers, and treatment remain ambiguous and sometimes controversial, with research still ongoing [17,18]. This is because there are different theories regarding its aetiology [19] (Fig. 1).

While endometriosis is not officially classified as premalignant, evidence from epidemiological, histological, and molecular studies suggests that it has the potential to become cancerous [20]. Endometriosis displays traits of unregulated cell growth, tissue invasion, and the ability to spread to other areas of the body, which are typical characteristics of neoplastic growth. The multiple molecular traits that endometriosis shares with invasive cancer include inflammation, tissue invasion, angiogenesis, immune cell dysfunction, enhanced local oestrogen production, apoptosis, and pro-survival properties [21]. However, endometriosis has restricted proliferation and invasiveness, unlike cancer [22]. Moreover, it does not directly cause catabolic problems and is not fatal [23].

Endometriosis and ovarian cancer have clinically significant parallels, some of which can impact cancer incidence rates. For example, clinical manifestations associated with increased risk include infertility and late menopause [24]. In contrast, total hysterectomy and bilateral salpingo-oophorectomy, oral contraceptives, and tubal ligation have reduced the risk of cancer development [25]. The specific manner by which tubal ligation reduces the chance of ovarian cancer is not well understood, but it may function as a physical barrier that prevents precancerous substances from travelling through the fallopian tubes to the ovaries (such as endometriosis, infectious agents, fallopian tube epithelial cells, or external carcinogens) [26].

The risk of ovarian cancer is 1.2 and is primarily raised among women with a long history of endometriosis (>10 years), however, the association is not well defined [27].

Aetiology of EAOC

There is evidence that several mechanisms could contribute to the conversion of endometriosis into a malignant form, but the processes by which this transformation occurs remain unclear [28]. To date, no precise mechanism or theory has been proposed to explain the underlying pathophysiology related to the relationship between endometriosis and ovarian cancer nor the pathogenesis of EAOC [29].

Histopathological Findings

Atypical Endometriosis – An Intermediatory Lesion?

In 1925, Sampson hypothesized that endometriosis could transform into cancer, even though he could not detect any intermediary lesions [30]. Czernobilsky and Morris built upon Sampson’s theory by introducing the concept

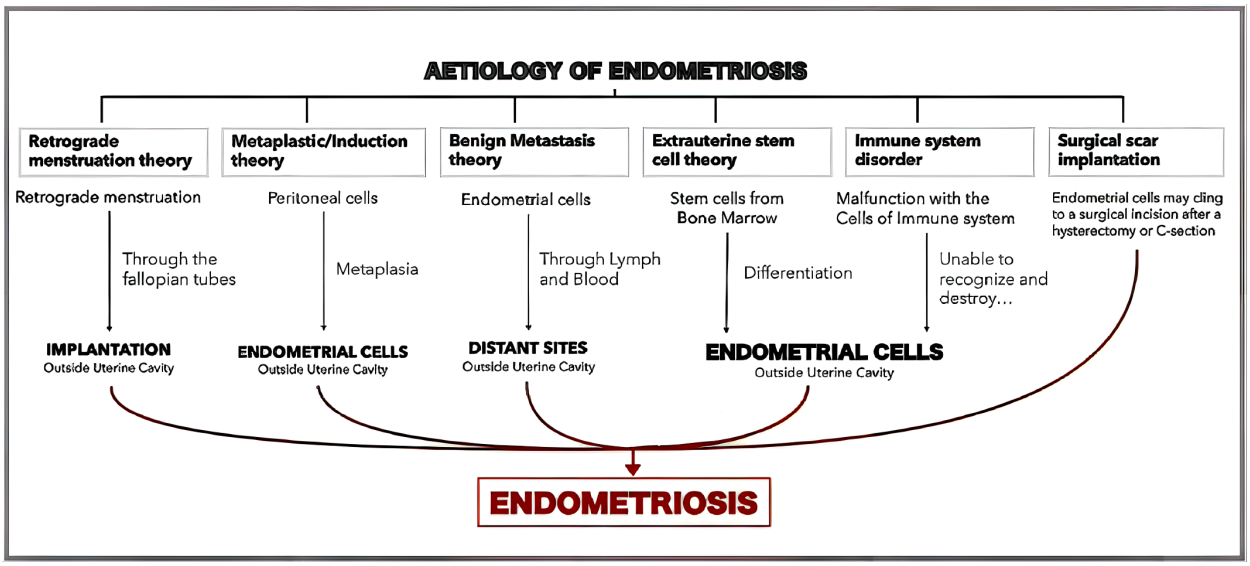

Fig. 1. Aetiology of Endometriosis. Although the specific mechanism of endometrial cell migration remains unknown, at least six significant concepts attempt to explain this phenomenon. Created with Microsoft PowerPoint – version 16.77, Microsoft Corporation, Redmond, WA, USA.

of an "intermediate stage" in the cancerous transformation process, called "atypical endometriosis", characterized by the degree of dysplastic histologic atypia [1]. Nowadays, pathologists use this term to describe endometriosis which displays characteristics that are neither benign nor malignant. These characteristics include large nuclei that are hyperchromatic or pale, a high nucleus-to-cytoplasm ratio, cellular crowding, stratification, and tufting [31].

It is unclear whether atypical endometriosis serves as a precursor to ovarian cancer or if it indicates an inflammatory histologic background [32]. Thus, the use of atypical endometriosis as a diagnostic criterion for pathology and therapeutic management is still a matter of debate.

Histological Classification of Ovarian Cancer and EAOC Subtypes

Based on their morphologic, histologic, and molecular characteristics, ovarian carcinomas are categorized as type I or type II [33]. Type I tumours tend to grow slowly, usually remain localized in the ovary or peritoneum upon diagnosis and emerge from pre-existing precursor lesions. Conversely, type II ovarian tumours are aggressive and fast-growing. It is thought that these tumours develop from poorly defined precursor lesions that form spontaneously before progressing into invasive malignancies [34]. As summarized in Fig. 2, ovarian cancers are also classified based on their origin cell type and histological subtypes.

Endometriosis is typically related to the onset of type I ovarian cancers [35], whereas it is unusual in type II ovarian cancers. Type I tumours, which include clear cell carcinoma, endometrioid carcinoma, and low-grade serous carcinoma, typically develop from endometriosis or borderline serous tumours usually manifest early [29].

Endometriosis is primarily associated with ovarian clear cell carcinoma (CCC) and ovarian endometrioid carcinoma (EC). It is histologically present in 30%–55% of ovarian CCC and 30%–40% of ovarian EC. Thus, these malignancies are recognized together as endometriosis-associated ovarian cancer (EAOC) [32]. Table 1 (Ref. [36–38]) summarizes the dissimilarities that exist between ovarian CCC and EC.

Despite this, endometriosis has been reported sporadically in low-grade serous carcinomas [39] and seromucinous carcinomas [8,28], even though they are not recognized as EAOCs. The clear cell and endometrioid subtypes are incredibly uncommon, accounting for just 12%–13% and 9%–11% of all epithelial ovarian malignancies, respectively [3].

Morphology of Ovarian CCC

The characteristic features of CCC are its complex papillae, which are covered by a dense hyaline material, and the presence of hyaline bodies. Furthermore, CCC is identifiable by its unique tubules, which are lined with transparent cytoplasmic cuboidal cells that contain eosinophilic secretions. Additionally, this cancer variant has clear cells with abundant clear cytoplasm, central nuclei, and discernible nucleoli, and can be low columnar, cuboidal, or polygonal in shape. Hobnail cells with either clear or eosinophilic cytoplasm are also commonly found in CCC. Overall, these features help differentiate CCC from other types of cancer [37].

Morphology of Ovarian EC

Most EC demonstrate a papillary or glandular appearance that is similar to uterine endometrioid adenocarcino-

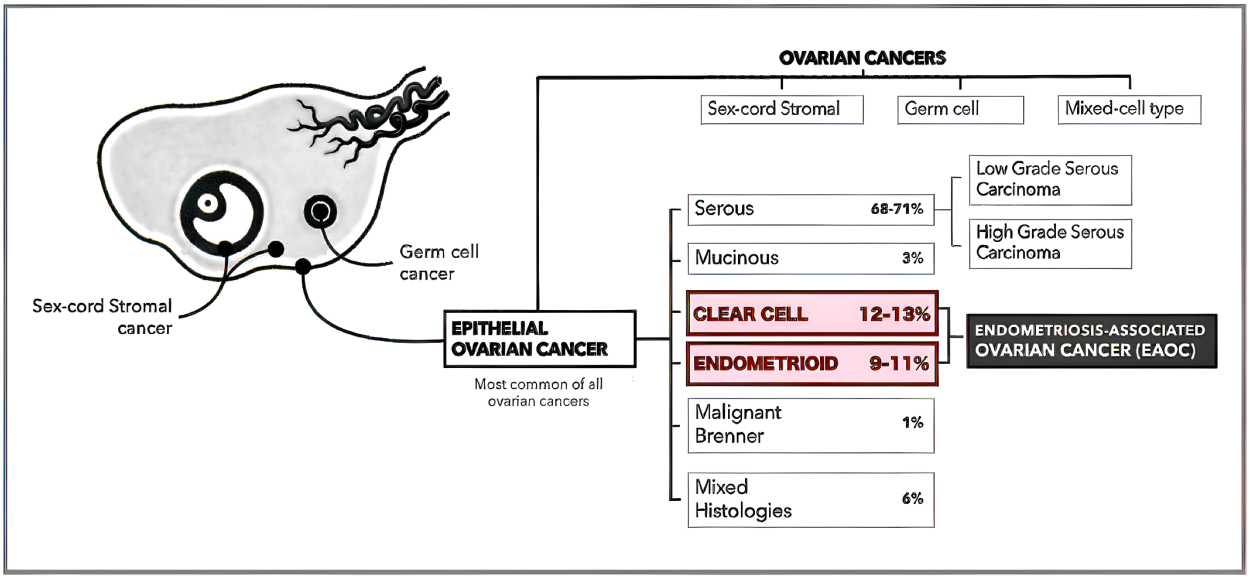

Fig. 2. Summary of Histological Subtypes of Ovarian Cancers. Ovarian cancers are also classified based on their origin cell type and histological subtypes. Endometriosis is primarily associated with ovarian clear cell carcinoma (CCC) and ovarian endometrioid carcinoma (EC). Created with Microsoft PowerPoint – version 16.77, Microsoft Corporation, Redmond, WA, USA.

mas. The epithelium consists of layered, non-mucinous glandular epithelial cells with nucleoli, and in roughly half of the instances, squamous differentiation occurs. As the grade of EC increases, the level of atypia, the degree of nuclear stratification, and the extent of glandular clustering to form solid masses also increase [37]. In addition, clear cells can be present in EC, and they may have a glandular or squamous appearance. Nevertheless, the nuclear grade attributes of clear cells present in EC that are less advanced, combined with the structural qualities of CCC, aid in distinguishing them from CCC [37].

Immunological Findings

Abnormal Immunological Findings in Endometriosis

Iron-induced oxidative stress (redox imbalance), inflammation, and hyperestrogenism have all been proposed as important links between endometriosis and cancer [40]. The pathogenesis of endometriosis can be influenced by alterations in cellular, humoral, and innate immunity (Fig. 1).

The clearance of ectopic endometrial tissue in the peritoneal cavity may be impeded in women with endometriosis due to the presence and function of peritoneal macrophages and the reduced cytotoxicity of natural killer and T cells, thus promoting immunological tolerance to implanted endometrial cells in the peritoneal cavity [41]. However, it is still unclear if the immunological abnormalities in patients with endometriosis are the cause or a subsequent outcome [25].

In addition, the promotion of implantation and growth of ectopic endometrium may be facilitated by the elevated levels of cytokines and growth factors that are secreted by immune or endometrial cells. These substances induce angiogenesis and proliferation, which can enhance the development of ectopic endometrium. Aside from the immune cells' impaired capability to mediate endometrial cell clearance, the inherent resistance of ectopic endometrial cells is an intriguing concept in the genesis of endometriosis [28].

Endometriosis and ovarian cancer share parallel immunological similarities, such as elevated levels of the transcription factor forkhead box P3 (Foxp3) and regulatory T lymphocytes (Tregs), which result in immune system dysfunction and the formation of illness. Targeting and reprogramming Tregs may thus become essential for treating both conditions [41]. Tregs are a subset of cells that work to suppress immune system activation and maintain immunological tolerance to self-antigens. They are functionally characterized by Foxp3, which regulates Tregs formation and is essential for sustaining their immune-suppressive activity [42].

Elevated occurrence of Tregs in the peritoneal fluid of women with endometriosis, which could potentially lead to a malfunction of other immune cells. This increased frequency of Tregs in the peritoneum might be a compensatory anti-inflammatory response and may explain the impaired cellular immune responses in the area. Additionally, Tregs have been associated with poor prognosis in ovarian cancer [43].

Combining immune factors like increasing inflammation, proliferation, and angiogenesis may aid in the implantation and development of ectopic endometrial cells. Endometriosis has also been thought to be an autoimmune illness due to the presence of autoantibodies [44]. However, the relationship between endometriosis and autoimmunity remains intangible.

Table 1. Summary of the dissimilarities that exist between ovarian CCC and EC.

Frequency	Ovarian clear cell carcinoma 12%–13% [36]	Ovarian endometrioid carcinoma 9%–11% [36]
Key morphological features	Multiple complex papillae, dense hyaline basement membrane that expands the papillary cores, hyaline bodies, atypical hobnail cells, limited cellular stratification, and a low mitotic rate [37].	Glandular architecture with squamous differentiation and resembling uterine endometrioid adenocarcinomas.
		The epithelium is made up of nonmucinous glandular cells that are stratified and contain nuclei that may have nucleoli [37].
	EC may occasionally include clear cells that have a glandular or squamous appearance. However, the less advanced nuclear grade qualities of clear cells found in EC and the distinguishing structural attributes of CCC aid in distinguishing them from CCC [37].	
Diagnosis	Early [38]	Early [38]
Molecular abnormalities	*PIK3CA, ARID1A*, microsatellite instability. Little association with *PTEN* gene and *KRAS* [37]	*β-Catenin/CTNNB1*, *PTEN* gene, microsatellite instability. Little association with *PIK3CA, KRAS and ARID1A* [37]
Pattern of spread	Often confined to ovary [37]	Often confined to pelvis [37]
Response to chemotherapy	High response to chemotherapy [37]	Low response to chemotherapy [37]
Prognosis	Intermediate – relatively good prognosis for early stage, poor prognosis for advanced stage [38]	Favourable [38]

CCC, clear cell carcinoma; EC, endometrioid carcinoma; *PTEN*, Phosphatase and tensin homolog; *ARID1A*, adenine-thymine-rich interactive domain-containing protein 1A; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *PIK3CA*, Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *CTNNB1*, Catenin beta 1.

Redox Imbalance and Iron-Induced Oxidative Stress

The concept of redox imbalance has recently been proposed to unify several components involved in the pathophysiology of endometriosis and related cancers [29]. According to the retrograde menstruation theory, repeated instances of retrograde menstruation led to haemorrhage in the pelvic cavity and endometriotic cysts, as well as the release of haemoglobin (Hb), free iron, and haem. In addition, consistent exposure to high haem concentrations causes the production of reactive oxidative species (ROS) in tissues [29] through the *Fenton reaction*:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \bullet \cdot OH \text{ (ROS)}$$

Subsequently, ROS contribute to infertility and carcinogenesis by increasing oxidative stress, inducing DNA methylation (DNA damage) and mutations activating anti-apoptotic pathways, and altering the expression of stress signalling pathways [45].

It is noteworthy that haem iron constitutes the majority of iron observed in endometriotic cysts, as opposed to free iron. The process of antioxidant conversion generates superoxide (O_2-) to convert haem iron to metHb. Notably, nitric oxide levels, which assist in the process from oxyHb to metHb, are raised in the serum and peritoneal fluid of individuals with endometriosis. Consequently, metHb can cause the production of free ROS, which can cause DNA damage [29]. However, EAOC displays a downregulation of metHb, indicating that there is an imbalance between oxidative stress and antioxidants that favours antioxidants in EAOC [46].

As a result, iron metabolism has a two-fold impact on the malignant transformation of endometriosis. Firstly, by-products of haem metabolism trigger the generation of ROS and oxidative stress, and subsequently, the synthesis of antioxidants takes place [46].

Inflammation

Chronic pain and infertility are most likely caused by local and systemic inflammatory responses. As a result, the presence of inflammation and hormonal imbalance in endometriotic implants may play a part in the development of cancer [47]. Therefore, the presence of chronic inflammation, which is often seen in endometriosis, can lead to the development of various types of cancer. This is similar to what occurs in certain cases of Barrett's oesophagus, where abnormal cell growth progresses from metaplasia to dysplasia and eventually cancer [48].

It is believed that this chronic inflammation can trigger the growth and spread of endometriotic tissue, which may result in a transition from benign to intermediate or "atypical" endometriosis at the histological level [49]. A chronic inflammatory disorder like endometriosis is believed to be capable of establishing an immunological microenvironment rich in cytokines and growth factors [29,49]. Ele-

vated levels of interleukin (IL)-1, 6, 8, 10, tumour necrosis factor-alpha (TNF-α), and vascular endothelial growth factor (VEGF) have been detected in the peritoneal fluid of women with endometriosis. These pro-inflammatory cytokines may play a role in macrophage activation and increased angiogenesis. These cytokines can potentially promote tumour development by triggering uncontrolled mitotic division, growth, and differentiation. Even so, the interaction of these cytokines and growth factors with endometriotic cells may initiate a cascade of biological processes that finally lead to angiogenesis, extracellular matrix remodelling, and malignant transformation [50].

Hyperestrogenism

Since the endometrium is a primary tissue that is targeted by progesterone and oestrogen, any significant disturbance in the hormone-tissue axis can have a considerable impact on the functioning of the endometrium. Both endometriosis and ovarian cancer are progressive conditions that rely on oestrogen for growth, making oestrogen a mitogen for these diseases.

Lacey *et al*. [51] (2002) suggested that oestrogen may be carcinogenic to the ovary, as early menarche and late menopause were correlated with higher incidences of ovarian cancer. Despite this notion, laboratory findings fail to substantiate this hypothesis, and there is no established mechanism that links oestrogen to ovarian carcinogenesis. Nevertheless, there is evidence that oestrogen participates in the development of endometriosis and the expansion of inflammation [52]. Increasing levels of oestrogen can promote the proliferation of endometriotic tissue and may be related to the malignant transformation of endometriotic cysts.

In this regard, an important ectopic endometrial cell abnormality, namely the pathologic expression of P450 aromatase, increases the conversion of androgens to oestrogens triggering cumulative oestradiol synthesis [53]. The enzyme 17-hydroxysteroid dehydrogenase type 1 is present in endometriotic lesions, which can convert estrone to the more potent oestrogen, oestradiol. In contrast, endometriotic lesions lack the enzyme 17-hydroxysteroid dehydrogenase type 2, which is responsible for converting oestradiol to estrone, leading to further accumulation of oestradiol. As a result of increased production and decreased inactivation, the combined effect is a robust local accumulation of oestradiol [54].

Increased levels of oestradiol can also stimulate the production of Cyclooxygenase 2 (COX-2) in ectopic endometrial cells, leading to the overproduction of prostaglandin E. In turn, this stimulates the activity of aromatase, which contributes to the accumulation of oestradiol. Moreover, prostaglandin E itself has been associated with the development of tumours, and higher levels have been observed in ovarian cancers [55].

Conversely, progesterone is naturally an oestrogen antagonist that inhibits cancer growth and may trigger apoptosis. Ovarian cancer specimens show a significant reduction in expression of the two progesterone receptor isoforms, increasing the potential for proliferation [56]. Furthermore, given progesterone's well-documented anti-inflammatory properties, its decreased effect in ectopic endometriotic cells may exacerbate the proinflammatory microenvironment surrounding the ovary – rendering them more vulnerable to DNA damage and mutations, which further encourages malignant transformation even further [57].

Genetic and Epigenetic Findings

There is substantial evidence linking endometriosis to cancer, particularly in cases of endometriotic and clear cell ovarian carcinomas. As a result, it is thought that alterations in the expression of tumour suppressor genes and oncogenes in the ectopic endometrium might contribute to the spread of endometriotic lesions beyond the uterus [58]. In fact, mutations in tumour-suppressing genes and oncogenes have been observed both in ovarian cancers and endometriotic lesions [42,59]. These mutations frequently result in pathologically produced proteins disrupting cellular functions. However, the precise processes remain unclear.

Loss of Heterozygosity (LOH)

Loss of heterozygosity (LOH) is a genetic mutation characterized by the loss of one copy of a gene or a group of genes. Loss of heterozygosity might inactivate tumour suppressor genes, potentially leading to cancer genesis [39]. Increased incidences of LOH have been documented in isolated endometriosis lesions and EAOC. For instance, LOH at 10q23.3 was detected in 27.3% of Clear cell carcinoma and 42.1% of Endometrioid carcinoma [58].

Carcinogenic Mutations in EAOC

Current knowledge suggests that endometriosis and EAOCs have distinct gene mutations and biological processes that differentiate them from non-EAOCs. These genes are categorized as either tumour suppressor genes or oncogenes [49].

Genetic mutations in both copies of a tumour suppressor gene result in undesirable cells which proliferate uncontrollably, resulting in cancer. Tumour suppressor genes such as *PTEN* gene, *P53*, and adenine-thymine-rich interactive domain-containing protein 1A (*ARID1A*) have been identified as factors in forming EAOCs, and are detected in 5%, 20%, and up to 50% of EAOCs, respectively [49]. An oncogene is a mutant gene with the capability to cause cancer. Activated oncogenes can induce apoptotic cells to survive and multiply, leading to unregulated cellular growth and division, which contributes to cancer formation [49]. Table 2 (Ref. [40,60–65]) summarizes the tumour suppressor gene mutations related to EAOC, while Table 3 (Ref. [52,60,63,66]) summarizes the oncogenic mutations related to EAOC.

Table 2. Tumour suppressor gene mutations related to endometriosis-associated ovarian cancer (EAOC).

Tumour suppressor gene mutations	
PTEN	The *PTEN* gene encodes for a phosphatase known as Phosphatase and tensin homolog (PTEN), which is commonly mutated in many cancers, especially in ovarian EC. PTEN inactivation occurs early in carcinogenesis, and it plays a crucial role in the malignant progression of endometriosis. Endometriotic cysts commonly include *PTEN* somatic mutations [60].
ARID1A	*ARID1A* gene codes for the BAF250a protein, a component of the SWI/SNF chromatin remodelling complex [40]. Mutations in *ARID1A* have been identified in both ovarian CCC (46%–95%) and ovarian EC (30%) [61]. The high incidence of *ARID1A* mutations in EAOCs clearly implies that it plays a role in the malignant transformation of endometriosis [62].
P53	*P53* is a negative regulator of the cell cycle and is involved in the development of several cancers. *P53* expression is absent in benign endometriosis but significantly present in benign endometriotic lesions adjacent to endometrioid or clear cell carcinoma [60]. There is some controversy regarding whether mutations in the *P53* are present in atypical endometriosis [63].
BRCA1 *BRCA2*	The *BRCA1* and *BRCA2* genes are essential early-onset tumour suppressors. *BRCA1* and *BRCA2* gene mutations have been linked to the progression of several human malignancies, including ovarian cancer. However, there are limited evidence on their impact on endometriosis [64,65].

PTEN, Phosphatase and tensin homolog; *ARID1A*, adenine-thymine-rich interactive domain-containing protein 1A; *BRCA1*, Breast cancer gene 1; *BRCA2*, Breast cancer gene 2

MicroRNAs and Microsatellite Instability

MicroRNAs (miRNAs) are short RNA sequences that do not code for proteins and are believed to play a part in the inhibitory control of target genes during the progression of the cell cycle Studies revealed that miRNA dysregulation is linked to endometriosis. These miRNAs may have an impact on the proposed molecular pathways created by the genes they target, implying that miRNAs may be necessary for the development of endometriotic lesions [49].

The miRNAs associated with endometriosis may potentially regulate various processes such as inflammation, hypoxia, tissue repair, cell proliferation and growth, apoptosis, extracellular matrix remodelling, and angiogenesis. Additionally, certain miRNAs are linked to the onset of malignant endometriosis. In fact, specific miRNAs were shown to be downregulated in ovarian CCC and EC, with lower expression in recurrent versus primary ovarian malignancies [49].

As a result, miRNAs may possibly serve as biomarkers to categorize tumours or differentiate between endometriosis-associated cancer and non-endometriosis-associated cancer. Nevertheless, the usefulness of miRNAs in evaluating ovarian cancer associated with endometriosis is currently unknown.

Microsatellite instability is described as a shift in the size of short tandem repeat sequences in a tumour relative to normal tissue from the same patient, indicating mismatch repair gene inactivation [49]. Microsatellite instability is a notable characteristic of ovarian CCC [37].

Epigenetic Abnormalities in EAOC

Research is still ongoing to understand the influence of epigenetic gene regulation in endometriosis and EAOC. Despite an incomplete understanding of the relationship between various epigenetic modifications, it is established that EAOC might display physiological variations caused by the activation or suppression of genes through epigenetic means [29].

The transcription factor hepatocyte nuclear factor 1-beta (HNF1β)-positive cells have been identified in CCC and the surrounding endometriosis, but not in EC. HNF1β is primarily involved in glycogen synthesis, anti-apoptosis, antioxidative defence, and chemotherapy resistance. In addition, HNF1β is overexpressed in CCC, resulting in enhanced glycolysis and lactate production. This prevents cancer cells from producing excess reactive oxidative species (ROS), giving them a survival advantage. Then again, HNF1β increases glutathione production and antioxidants, further promoting CCC survival [29].

The oestrogen receptors Oestrogen Receptor alpha (ERα) and Oestrogen Receptor beta (ERβ) are highly expressed in ovarian EC. The level of expression is significantly higher than that of CCC [46]. Several factors, including epigenetic factors such as methylation and acetylation, as well as haem binding, may have an impact on the expression of the oestrogen receptor. Endometriosis causes hypomethylation of ERβ, which causes the protein (receptor) to be overexpressed, whereas ERα is reduced in endometriosis [67]. ER upregulation and a hyperestrogenic state may lead to malignant transition of endometriosis into EC; however, this is unrelated to CCC.

Association with Lynch Syndrome

Endometriosis has also been linked to Lynch syndrome, which is a hereditary genetic condition that enhances the risk of developing various kinds of cancer. Patients with Lynch syndrome (an autosomal dominant disorder) have an ovarian cancer risk of 10% to 12%. One of

Table 3. Oncogenic mutations related to EAOC.

Oncogenic mutations	
KRAS	Type I ovarian cancers often have mutations in the *KRAS* oncogene. Nevertheless, research suggests that *KRAS* gene mutations are not typically observed in endometriosis, nor atypical endometriosis [52]. Nevertheless, *KRAS* gene mutations are often detected in ovarian EC, although the prevalence of these mutations can differ among studies [60].
Bcl-2	The significant expression of this anti-apoptotic protein in malignant endometriosis (ranging from 42%–73%) is considerably higher compared to benign endometriosis (23%). This suggests that the protein may be involved in the initial phases of cancer development [60].
PIK3CA	The presence of mutations in the *PIK3CA* gene, identified in both nonatypical and atypical endometriosis, is believed to be an early occurrence in the development of cancer, likely at the onset of malignant transformation in endometriosis [63].
CTNNB1 *β-catenin*	*CTNNB1* mutations and overexpression are particularly prevalent in ovarian EC (around 50%). Ovarian EC with *CTNNB1* mutations is of lower grade and has a better prognosis. This data suggests that *CTNNB1* mutations happen early in the carcinogenesis of ovarian EC [66]. Thus, the clinical use of *CTNNB1* as a marker for diagnosing early-stage endometrioid carcinoma should be studied further.

KRAS, Kirsten rat sarcoma viral oncogene homolog; *Bcl-2*, B-cell lymphoma 2; *PIK3CA*, Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *CTNNB1*, Catenin beta 1.

the gene mutations associated with EAOC and Lynch syndrome is MutL homolog 1 (MLH1), which is responsible for DNA repair [68].

Risk Factors

Risk factors that increase the incidence of retrograde menstruation, as well as genetic or hereditary factors, are important contributors to the development of endometriosis. For instance, risk factors for endometriosis include early onset of menstruation, never having given birth, abnormal uterine bleeding, abnormal levels of oestrogen, and having a low body mass index, amongst others [69]. Besides that, endometriosis and EAOC share similar risk factors like regular periods, lower parity, and earlier menarche. Thereby, endometriosis appears to be particularly a risk factor for ovarian cancer, especially EAOC [70]. The presence of oestrogen, particularly a state of excessive oestrogen, is a recognized risk factor for both atypical endometriosis and EAOC, as previously described [31].

Aging is also a risk factor for EAOC. According to Wang *et al*. [71] (2014), women over 50 with endometriosis have a greater risk of epithelial ovarian cancer than young women under 30 with endometriosis Furthermore, although postmenopausal endometriosis is uncommon, people on hormone treatment are at risk. Hormone therapy, specifically oestrogen therapy, is often believed to stimulate the growth of endometriosis and increase the risk of ovarian carcinogenesis. This is especially true in cases of postmenopausal endometriosis, and therefore, oestrogen therapy should only be administered in combination with progesterone [27]. Additionally, obesity and unopposed oestrogen therapy after hysterectomy were found to contribute to the development of EAOC [72].

While only a small percentage of women with endometriosis (0.3–1.6%) develop ovarian cancer, it is crucial to identify, document, and carefully monitor women who are at risk for EAOC. The leading risk factors for EAOC consist of the following: endometriosis present for an extended duration, endometriosis diagnosed at an early age, endometriosis related to infertility, and the existence of an enlarging ovarian endometrioma Contrastingly, adequate exercise, hormonal contraception, childbirth, tubal ligation, and hysterectomy were preventive against ovarian cancer in endometriosis patients [29].

Certain dietary factors may also influence the development and progression of endometriosis. For instance, diets high in trans fats, red meat, and caffeine have been associated with an increased risk of endometriosis [73]. On the other hand, a diet rich in omega-3 fatty acids, fruits, and vegetables may help to reduce the risk [74]. There is evidence that a gluten-free diet and a low-nickel diet may alleviate pain in women with endometriosis [75].

Signs and Symptoms

Presentation/Symptoms and Examination Findings

About 25% of all ovarian cancers are detected at an early stage (stage I) and this might be due to the presence of certain specific signs and symptoms [76]. There are a few case studies which describe the presentation of patients with EAOC. In Yang *et al*. [77] (2021), a 54-year-old postmenopausal lady had a palpable pelvic lump for months. She was also experiencing feelings of abdominal fullness,

loss of appetite, and frequent urination. Cancer antigen 125 (CA-125) levels were normal. A 22.5 by 9.7 by 10 cm cystic lesion was discovered using sonography and pelvic magnetic resonance imaging (MRI). The patient was diagnosed with FIGO stage IIIA EAOC, which contained two distinct subtypes: endometrioid and mucinous cells.

In Sao *et al.* [78] (2020), a 60-year-old nulliparous postmenopausal lady presented with lower abdomen fullness and pain for six months. She had dysmenorrhea for ten years prior to her menopause at the age of 52. In the previous month, she had generalized discomfort, loss of appetite, and a weight drop of 6 kg. A bulky lump was felt in the lower abdomen. CA-125 levels in the serum were elevated to 1265.4 U/mL (normal: 0–35 U/mL). Ultrasonography showed two ovarian masses. The left ovarian tumour was larger (11 $\times$ 8 $\times$ 7 cm) than the right ovarian tumour (4.5 $\times$ 3.2 $\times$ 2.7 cm).

The left ovary was found to have clear cell carcinoma with endometriosis areas, displaying clear cytoplasm, psammoma bodies, and hobnail cells. The tumour exhibited immune reactivity to HNF1β but not to oestrogen receptors. The right ovarian tumour was identified as a grade 1 endometrioid carcinoma that had developed from endometriosis and contained a chocolate-like component. This tumour exhibited immunological reactivity to the oestrogen receptor.

As seen in these cases and other reports, a patient with EAOC typically presents with a palpable pelvic lump, abdominal fullness and pain, lack of appetite, and generalized malaise. In addition, frequent micturition and weight loss tend to occur in some patients.

Investigations

Endometriosis itself is already challenging to diagnose since signs and symptoms may vary, and since there are no good diagnostic blood biomarkers [79]. An increase in the CA-125 biomarker is not a specific indicator as it can indicate the presence of other gynaecological conditions, including other ovarian cancers or inflammation. Its correlation with EAOCs was studied, and the results are debatable. In some instances, serum human epididymis secretory protein E4 (HE4) levels can be used to differentiate endometriosis from ovarian and endometrial malignancies [80].

Transvaginal ultrasonography and pelvic examination have low specificity and sensitivity for detecting ovarian cancer Yet, transvaginal sonography remains one of the most useful diagnostic modalities in diagnosing endometrioma and suspicious ovarian tumours [39]. There are currently no biomarkers available that can identify women who are at risk for EAOC. However, ongoing research aims to discover these markers, which might lead to focused screening of these individuals [49].

Management

Management of Endometriosis

Women with symptomatic or atypical endometriosis should undergo surgical removal of their lesions. Indeed, surgery with histological confirmation of ectopic endometrial tissue remains the gold standard for diagnosis [81]. In addition, those with atypical endometriosis should be advised about the possibility of recurrence and the modest risk of progression to EAOC [31].

Women who have atypical endometriosis or EAOC are advised to seek further management from a gynaecologic oncologist. Obesity-related weight loss and hormonal therapy for endometriosis might help reduce the risk of cancer in women by decreasing circulating oestrogen levels. However, there is no evidence to suggest that hormone therapy for endometriosis can reduce the risk of these cancers [31].

The implications of the potential connection between endometriosis and ovarian cancer are significant, particularly for women experiencing pelvic pain and seeking to preserve their fertility. Endometriosis can cause chronic pelvic pain and is a leading cause of infertility. Women with endometriosis may undergo various treatments, including hormonal therapy and surgery, to manage their symptoms and preserve fertility. However, the potential increased risk of ovarian cancer adds another layer of complexity to the management of endometriosis [82].

Fertility preservation is a major concern for women with endometriosis, especially those who require surgery to manage their symptoms. The potential link between endometriosis and ovarian cancer further emphasizes the importance of considering fertility preservation options, such as oocyte freezing, for women with endometriosis [83].

Diet and Endometriosis

Understanding the correlation between diet and endometriosis can provide crucial insights, especially for couples who are looking to preserve their fertility prior to undergoing fertility-sparing surgery and oocyte freezing.

When it comes to quality of life (QoL), the impact of diet cannot be understated. Endometriosis can cause chronic pelvic pain, fatigue, and infertility—all of which can significantly affect a couple's emotional well-being and their ability to conceive. By adhering to a diet that potentially minimizes the symptoms and progression of the disease, couples can improve their QoL and better prepare for fertility-preserving interventions [84].

Comparatively, other gynaecological malignancies, such as endometrial cancer, also showcase a link with diet. For instance, diets high in saturated fats, cholesterol, and refined carbohydrates are associated with an increased risk of endometrial cancer. The relationship between diet and these gynaecological conditions highlights the importance of dietary habits in managing and preventing diseases that can impact fertility and overall health [73,85].

Preventive Management of Patients who are at Risk EAOC

Although new advancements to discover biomarkers of EAOC risk are still being explored, it is essential to emphasize current interventions that are known to reduce the incidence of EAOC. For example, regular intake of the oral contraceptive pill for five years was found to reduce CCC and EC risk by 20%–30% [2].

Tubal ligation is as effective as oral contraception in decreasing the likelihood of EAOCs and can lower the risk of endometrioid and clear cell carcinoma by almost 50% [86]. Tubal occlusion is also a good consideration for women seeking permanent contraception since the fallopian tube is the likely path for crucial elements leading to the genesis and proliferation of endometriosis. However, more research is required to assess the impact of risk-lowering bilateral salpingo-oophorectomy in preventing EAOCs [2].

Management of EAOC

There are no clear guidelines for the management of patients with EAOC after initial staging and debulking surgery. Due to the rarity of the illness, therapies range from expectant care to adjuvant chemotherapy, radiation therapy, or a combined strategy, depending on the histologic type and stage of the disease [29].

Due to a lack of available data, EAOC is treated postoperatively using the conventional chemotherapy guidelines for epithelial ovarian cancer - surgery followed by chemotherapy (paclitaxel and carboplatin). Since these women tend to be younger and have a lower stage and grade, they may benefit from tailored therapy and follow-up [60]. To date, it is still unclear whether these women are being overtreated.

Standard platinum-based chemotherapy has a low impact on ovarian CCC [39]. The variance in response rates of 15%–45% between CCC and other types of ovarian cancer may be because CCC is more genetically stable and grows more slowly. Nowadays, platinum-based chemotherapy is the most effective treatment, although there are no better alternatives. Nonetheless, Nagai *et al*. [87] (2007) found that whole abdominal radiotherapy following surgery was more effective than chemotherapy alone in improving the prognosis of patients with stage IC-III CCC. Likewise, Hoskins *et al*. [88] (2012) found that patients with CCC who had radiotherapy and chemotherapy had better outcomes than those who had just solely received chemotherapy.

Combination chemotherapy was proven to reduce disease recurrence in early-stage CCC. In retrospective cohort studies [89,90], regimens primarily included carboplatin/paclitaxel or irinotecan/cisplatin for six cycles. This approach showed benefits for women diagnosed with stage 1C, but its effectiveness for stages 1A and 1B is uncertain, as it led to reduced recurrence rates without a change in overall survival. Chemotherapy resistance has been remarkably noticed in the advanced stages of CCC. In various clinical trials, it has been observed that women with advanced-stage CCC who received radiotherapy had improved survival rates and lower mortality rates, which could be due to their resistance to conventional chemotherapy treatments [29].

The preferred treatment for high-risk ovarian EC is debulking surgery, followed by chemotherapy based on platinum and taxane. This combination is more effective than using only one drug or different platinum combinations [91].

Ovarian cancer, like endometrial cancer, is oestrogen-sensitive. Endometrioid endometrial adenocarcinoma is stabilized by antiestrogenic therapies with either tamoxifen or progesterone, and targeted ER modulators may have a similar impact on ER-positive ovarian carcinomas, such as EC [37].

Aromatase converts androgens to oestrogens and is a primary source of oestrogen production [92]. Clinical trials have demonstrated that aromatase inhibitors can produce a therapeutic effect in approximately 35% of ovarian cancer cases that are sensitive to oestrogen and can maintain stable cancer rates ranging from 20% to 42% in patients with recurrent ovarian cancer [92,93]. In addition, many studies, including phase II trials with recurrent EC or chemotherapy-resistant EC, found that aromatase inhibitors reduced recurrence rates and improved survival. Long-term maintenance therapies involving adjuvant aromatase inhibitors and progesterone therapies have also demonstrated promising outcomes [91].

Infertility and Assisted Reproductive Technology (ART)

Infertility can have profound psychological implications for individuals and couples. It often leads to feelings of inadequacy, frustration, and grief, especially in societies where having children is highly valued. The process of trying to conceive, particularly when it involves more invasive surgical treatments, can be emotionally and physically exhausting [94].

Assisted Reproductive Technology (ART) is a valuable option for couples with fertility impairment, but it also plays a critical role for women diagnosed with cancer who are set to undergo chemotherapy. Chemotherapy, while effective in treating cancer, can have deleterious effects on fertility, potentially causing temporary or permanent ovarian failure [95].

In these cases, ART offers a pathway for fertility preservation for cancer patients. Before starting chemotherapy, women can undergo ovarian stimulation to produce multiple eggs, which can then be retrieved and frozen for future use. This process is known as oocyte cryopreservation. Alternatively, women may opt to undergo *in vitro* fertilization (IVF), where the retrieved eggs are fertilized with sperm in a laboratory before being cryopreserved as embryos. Another option available through ART is ovarian

tissue cryopreservation, where a piece of ovarian tissue is removed and frozen. After cancer treatment, the tissue can be reimplanted, and in some cases, it can regain its function, potentially allowing the woman to conceive naturally or through IVF [95,96].

ART methods provide women diagnosed with cancer a chance to preserve their fertility before undergoing treatments that may impair their ability to conceive. It empowers them to plan for their future family life, which can be of significant psychological support during a challenging period.

Couples often need to undergo *in vitro* fertilization (IVF) to achieve pregnancy following more invasive surgical treatments. However, IVF is not always successful, and multiple cycles may be needed, which can add to the emotional stress. The uncertainty of the outcome of IVF can create anxiety and depression in couples. The treatment is time-consuming and invasive, often requiring daily injections and frequent medical appointments. The cost of IVF can also be a significant source of stress, as it is expensive and not always covered by insurance [97].

Given the significant psychological implications of infertility and IVF, it is crucial for couples to have access to mental health support throughout their fertility journey. Counselling and support groups can provide valuable emotional support and coping strategies to help couples manage the stress and uncertainty of fertility treatments [98].

Prognosis

An ambiguous relationship exists between endometriosis and the prognosis of ovarian cancer. Indeed, ovarian cancer caused by endometriosis has several distinguishing features, such as endometroid or clear cell histology and a better prognosis [99]. However, remains unclear whether endometriosis is a prognostic factor for cancer survival. Noli *et al.* [100] (2013) found no conclusive link between endometriosis and prognosis. In contrast, del Carmen *et al.* [101] (2015) demonstrated that women with endometriosis had much higher survival than women with all other malignancies combined. This ambiguity might be attributed to the studies' small sample size and overdependence on self-reporting.

Furthermore, EAOC is often identified sooner than non-EAOC. However, it is unclear whether ovarian CCC and EC have a better prognosis when coupled with endometriosis than when not, because the earlier diagnosis may be attributed to the more abundant symptoms observed in endometriosis patients compared to the few symptoms reported in non-EAOC patients [102]. Clearly, additional research is required. Endometriosis status stratification might aid in revealing the role of endometriosis in prognosis [25].

Patients with ovarian CCC and EC at early stages and ovarian EC at advanced stages have favourable prognosis. However, patients with ovarian CCC at advanced stages have an earlier recurrence and an overall lower survival rate. Thus, many studies have implied that ovarian EC has a better overall prognosis than ovarian CCC [103,104].

Conclusion and Future Directions

Despite years of research, there are still more unknowns than knowns and this might be attributed to the complexity of endometriosis and ovarian cancer. While there is evidence suggesting a link between endometriosis and ovarian cancer, the evidence can be inconsistent at times.

Based on different epidemiological, histological, genetic, and biochemical studies, it appears that endometriosis may serve as a preliminary indication of ovarian cancers. While there is only concrete evidence of direct progression in a limited number of cases, the growing genetic associations between endometriosis and ovarian cancer are noteworthy. Furthermore, various genetic investigations suggest that endometriotic lesions may even display mutations in genes that are directly related to malignancies. However, the precise mechanism of this malignant transformation remains mainly theoretical and unexplored. As researchers continue to investigate the molecular mechanisms involved in endometriosis and EAOC, the crucial issue of identifying high-risk women with endometriosis for developing EAOC based on current knowledge remains unresolved.

To better describe the shift from endometriosis to atypia and neoplasia, molecular biomarkers must be identified to better understand the pathophysiology of the disease. Further to that, since EAOCs are so rare, reliable biomarkers for identifying high-risk women for targeted screening are yet to be found. In reality, at the moment, not a single reliable biomarker can be utilized to diagnose or treat patients. For a better understanding and management of endometriosis and EAOC, more research is required. Given that EAOC is a rare disease, this poses yet even more challenges when it comes to designing appropriate clinical trials.

Abbreviations

EAOC, endometriosis-associated ovarian cancer; CCC, clear cell carcinoma; EC, endometrioid carcinoma; FIGO, Federation of International of Gynaecologists and Obstetricians; Foxp3, forkhead box P3; Tregs, regulatory T lymphocytes; Hb, haemoglobin; ROS, reactive oxidative species; TNF-α, tumour necrosis factor-alpha; VEGF, vascular endothelial growth factor; COX-2, Cyclooxygenase 2; LOH, Loss of heterozygosity; miRNAs, MicroRNAs; HNF1β, hepatocyte nuclear factor 1-beta; ER, Oestrogen Receptor; ERα, Oestrogen Receptor alpha; ERβ, Oestrogen Receptor beta; MRI, magnetic resonance imaging; CA-125, Cancer antigen 125; HE4, human epididymis secretory protein E4.

Author Contributions

Both KL and JCA have made substantial contributions to conception and design. KL contributed to the analysis and interpretation of the data and was responsible for drafting the manuscript. JCA provided critical revisions to the article. Additionally, both KL and JCA gave final approval of this version to be published and agreed to be accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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