Chapter 7
Endometriosis and Ovarian Cancer

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7.1 Introduction

Recent studies have provided much evidence to support the theory that endometriosis is actually a neoplasm and that affected cells can undergo malignant change. Women with endometriosis have a higher risk of certain types of ovarian cancer than the general female population [1]. Approximately 2.5 % of ovarian endometriosis turns malignant, but this may be an underestimation [2]. Studies have shown that Type 1 ovarian cancers such as clear cell carcinoma (CCC) and endometrioid adenocarcinoma (EAC) are associated with endometriosis [3]. Together, these carcinomas have been termed endometriosis-associated ovarian cancer (EAOC). The prevalence of endometriosis in ovarian cancer includes 39 % for clear cell carcinoma, 21 % for endometrioid carcinoma, and 3 % for serous and mucinous carcinoma [4].

Endometriosis and EAOC share a possible similar origin and etiology, and have defective immuno surveillance. Both the conditions are estrogen dependent and their growth is promoted by increased levels of estrogen and decreased levels of progesterone. They are both stimulated by steroid hormones and have common pathogenic mechanisms such as inflammation, persistent oxidative stress, hormonal alterations, retrograde menstruation, familial predisposition, and genetic alterations.

7.2 Sampson's Theory of Malignant Transformation

There are several theories as to how endometriosis develops, but the most widely Accepted is Sampsons's theory. The possibility of malignant transformation of endometriosis to EAOC was also first suggested by Sampson in 1925 [5]. The theory states that malignant transformation of endometrial cysts, which is believed to be a

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major factor concerning EAOC, must arise from pre-existing benign endometrial tissue that has not invaded from another unrelated source [6]. The benign and the carcinomatous tissue must be present in the same ovary and the tissue should resemble endometrial stroma and have epithelial glands [6]. This theory is supported by numerous studies that have found endometriosis in more than 50 % of clear cell and endometrioid cancers but in less than 10 % of serous cancers [4, 7–9].

7.3 Ovarian Cancers Associated with Endometriosis

Malignant transformation of endometriosis occurs most commonly in the ovaries, less commonly in rectovaginal septum, vagina and colon and more rarely in the abdominal wall [10]. Studies have reported that endometriosis involves, multiple genes and environmental factors that also contribute to its malignant transformation [11]. Pathological studies have found a sequence of steps in the transformation of normal endometriotic cyst epithelium to atypical endometriosis leading to invasive cancer. Tanase et al. reported a case in which the patient's disease advanced from a benign endometriotic cyst to atypical endometriosis and finally to endometrioid adenocarcinoma within 10 years and suggested that cases of atypical endometriosis need to be followed up diligently for long periods because of the possibility of malignant transformation [12].

7.4 Genetic Alterations Common in Endometriosis and EAOC

A number of factors have been associated with the malignant transformation of endometriosis into EAOC: oncogenic activation, deletion or loss of function of tumor suppressor genes, loss of heterozygosity (LOH) at numerous chromosomes, and OS [13]. Different cell system (cycle) components such as cyclins and cyclin dependent kinases (Cdk) may affect the pathogenesis of EAOC. Various techniques such as fluorescent in situ hybridization (FISH), comparative genomic hybridization (CGH), and conventional genomics were used to determine the extent of genomic mutations in women with endometriosis or EAOC (Table 7.1).

Accumulating evidence suggests that various epigenetic aberrations exist in endometriosis like in ovarian cancer. Some genes like HOXA10 and progesterone receptor B (PR-B) are hypermethylated (down-regulated) and estrogen receptor beta (ER-β), steroidogenic factor-1 (SF-1) and aromatase is hypomethylated (over-expressed) in eutopic endometrium (epigenendo). Growing evidence shows that microRNAs that play a key role in regulating gene expression and deregulated in cancer, are also involved in endometriosis such as ER-α, ER-β, PR and transforming growth factor β (TGF-β).

Table 7.1 Genetic alternations in endometriosis compared to EAOC

Genetic alteration seen in endometriosis	Genetic alteration seen in EAOC
PTEN Deletion: Present in endometrial cyst (Sato N et al.)	*PTEN Deletion*: Present in 40 % of CCC of ovary (Tan D S and S. Kaye)
HNF-1 β upregulation: Seen during oxidative stress conditions (Shigetomi et al.)	*HNF-1 β upregulation*: Over expression seen in CCC of ovary (Kobayashi, H et al.)
KRAS activation: Seen in endometriosis adjacent to ovarian cancer (Otsuka et al.)	*KRAS activation*: Overexpression present in EAOC (Dinulesc et al.)
ER β expression: Expression of ER-β was significantly higher in ectopic endometriotic stromal cells (Xue et al.)	*ER β expression*: SRAP causes decreases ER-β expression in CCC (Lin K et al.) Upregulation of ER-β in EAOC (Lai et al.)
ARID1A/BAF250 loss: Present in atypical endometriosis (Wiegan et al.)	*ARID1A/BAF250 loss*: Loss of BAF250 in 73 % of OCC and 50 % of endometrioid with ARID1A mutation (Wiegan et al.)

Number of cell signaling pathways and gene mutations are involved in the pathogenesis of malignant transformation of endometriosis into endometrioid and clear cell carcinoma. Gene mutations include loss of ARID1A/BAF 250a expression, KRAS activation, inactivation of PTEN [14]. Increased SRAP [15], changes in ER-beta expression, upregulation of HNF-1b [16] microsatellite instability [17]. Mutations of CTNNB1 are seen in 16–53.3 % of cases of endometrioid adenocarcinoma. Mutations in PIK3CA are present in 20–40 % of cases of clear cell carcinoma of the ovary [3] (Table 7.1).

7.5 Mechanistic Pathways Underlying Conversion of Ovarian Endometriosis to EAOC

Oxidative stress is known to be involved in a number of pathological conditions, including atherosclerosis, neurodegeneration, cancer and aging. It is also associated with endometriosis and its conversion to EAOC. It causes genetic alterations by inducing stress responsive genes. Some of the genetic alterations include DNA hypo-methylation, telomere shortening, chromosomal aberration, microsatellite instability.

High quantities of iron found within the endometriotic cysts play a vital role in the transformation of endometriosis to EAOC. Free iron due to retrograde menstruation in endometriosis causes persistent oxidative stress and modification of proteins and lipids in the cells, generating free radicals and hypoxia. This leads to extensive DNA damage [18], loss of heterozygosity, and decreased DNA repair contributing to carcinogenesis [19] (Fig. 7.1).

Recent studies have shown HNF-1β overexpression in endometriosis, including both the inflammatory and atypical lesions and within the foci of endometriotic cells. Over expression of hepatocyte nuclear factor-1 (HNF-1 beta) contributes to

the formation of clear cell carcinoma under stressful conditions such as oxidative stress. Oxidative stress causes hypo-methylation, which may lead to HNF-1 beta activation and genomic instability, which are evident in clear cell carcinoma of ovary [16] (Fig. 7.1).

Yamada et al. [20] proposed three major processes by which iron induces oxidative stress in endometriosis leading to EAOC (Fig. 7.1).

1. Oxidative stress causes DNA modifications like chromatin remodeling, histone modification, and gene product activation/inactivation contributing to the initiation of EAOC.
2. Iron-induced oxidative stress activates detoxification and anti-apoptotic pathways through the over expression of HNF-1β, which is involved in the promotion of clear cell carcinoma of the ovary.
3. Iron-induced generation of ROS creates an environment that supports the formation of new blood vessels, growth, invasion, and migration of cancer cells through an estrogen-dependent (EAC) or estrogen-independent mechanism (CCC) [20].

SRAP (Steroid Receptor Activator Protein) is a protein that enhances estrogen receptor-beta expression. The activation of estrogen receptor-beta increases endometrial cellular apoptosis, because it augments pro-apoptotic gene expression. Methylation of DNA suppresses pro-apoptotic gene activity by altering the chromatin structure and plays a role in the pathogenesis of ovarian cancer. Lin et al. observed decreasing levels of estrogen receptor beta expression when endometriosis of the ovary progress to atypical endometriosis, which then leads to ovarian clear cell carcinoma [15, 21] (Fig. 7.2). Previous studies have reported decreased levels of ER-beta m-RNA expression in estrogen dependent tumors like breast, ovarian and prostate cancers which highlights on the evidence that loss of ER-beta expression may be involved in carcinogenesis [21]. Lin k et al. [15], in their study speculated that during the malignant transformation of endometriosis to clear cell carcinoma, SRAP (Steroid Receptor Activator Protein) acts as a co-repressor, hypermethylates the promoter region of ER-beta (Estrogen Receptor-beta), suppressing gene activity and contributing to clear cell carcinoma of the ovary.

Estrogen receptor-beta is a tumor suppressor gene and therefore reduces the growth of tumor cells. It reduces the expression of genes involved in the cell cycle such as cyclin D. It decreases the proportion of cells in the S phase of the cell cycle, which is the synthesis phase where the replication of DNA occurs. However, Estrogen receptor beta increases the proportion of cells in the G2-M Phase, which is the cell cycle check point where DNA damage is assessed before the cell enters the mitotic phase. ER-β indirectly acts on ER-α and hence, inhibits cell proliferation. Whenever there is a decrease in ER-β expression, there is reversal of all these mechanisms and cell proliferation increases, leading to carcinoma [22] (Figs. 7.3, 7.4 and 7.5).

Endometriosis and endometrioid ovarian carcinoma cells are estrogen dependent and predominantly positive for estrogen receptor beta unlike clear cell carcinoma, which has low ER expression. Endometriotic stromal cells have higher levels of ER-beta expression due to deficient methylation. These increased ER-beta levels

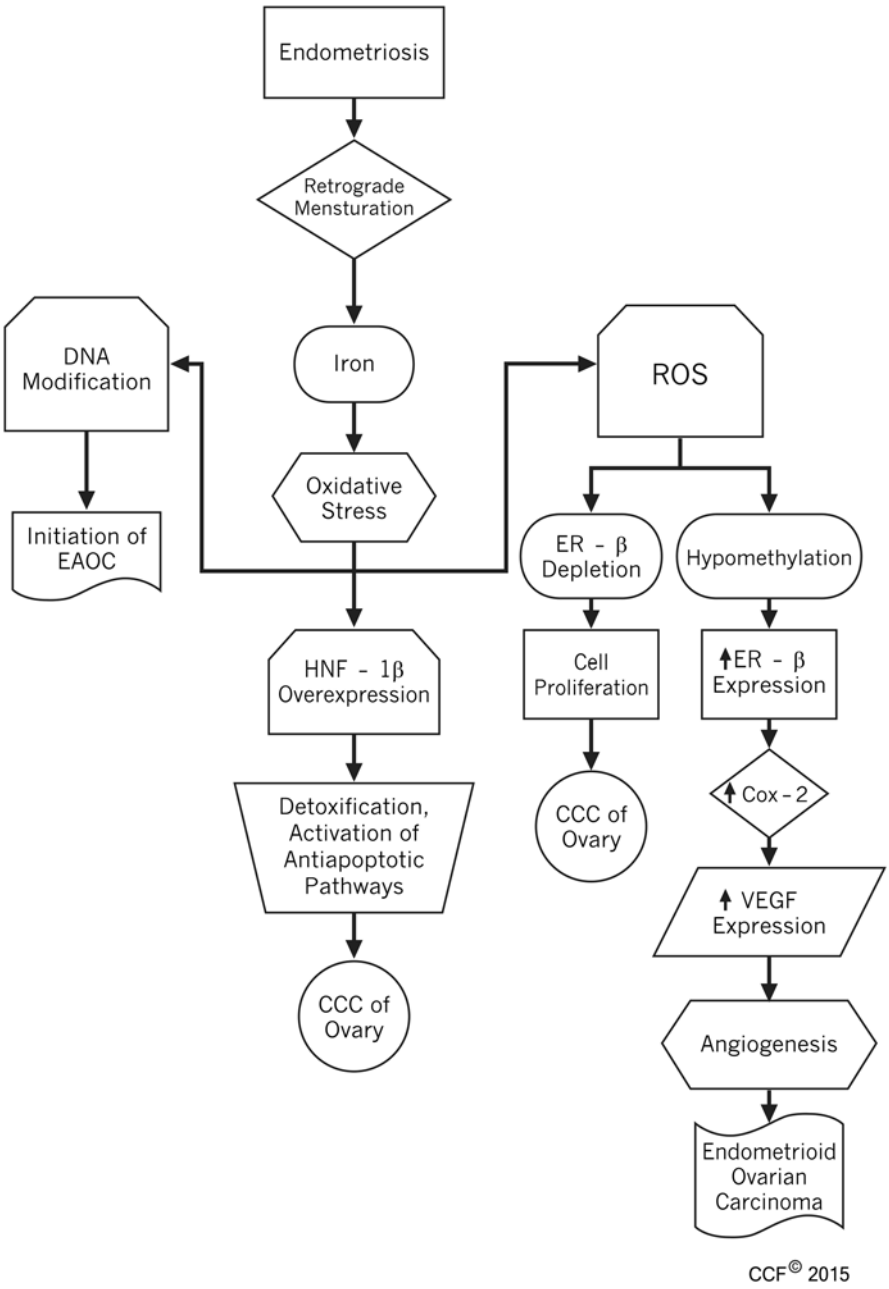

Fig. 7.1 Role of oxidative stress in malignant transformation of endometriosis to EAOC. *EAOC* endometriosis-associated ovarian cancer, *HNF* hepatocyte nuclear factor, *VEGF* vascular endothelial growth factor, *CCC* clear cell carcinoma, *ER* estrogen receptor

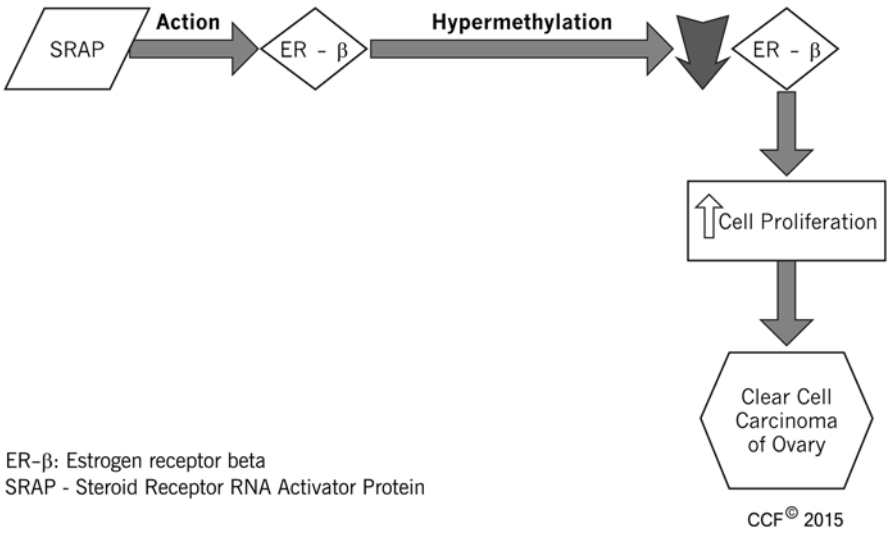

Fig. 7.2 Pathogenic mechanism leading to clear cell carcinoma of the ovary-increased SRAP action on ER-beta expression

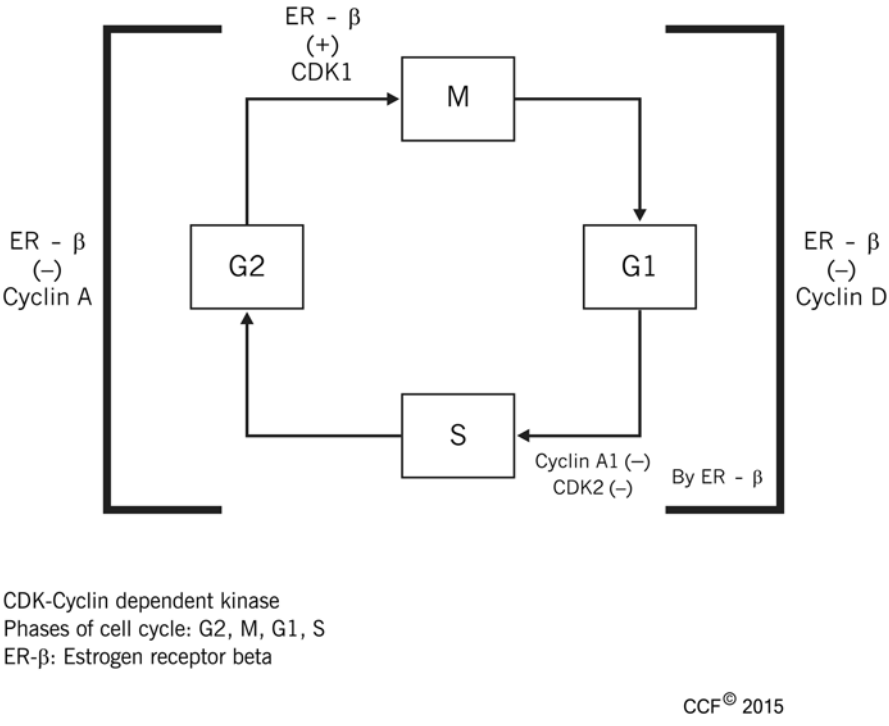

Fig. 7.3 ER-β action on cell cycle

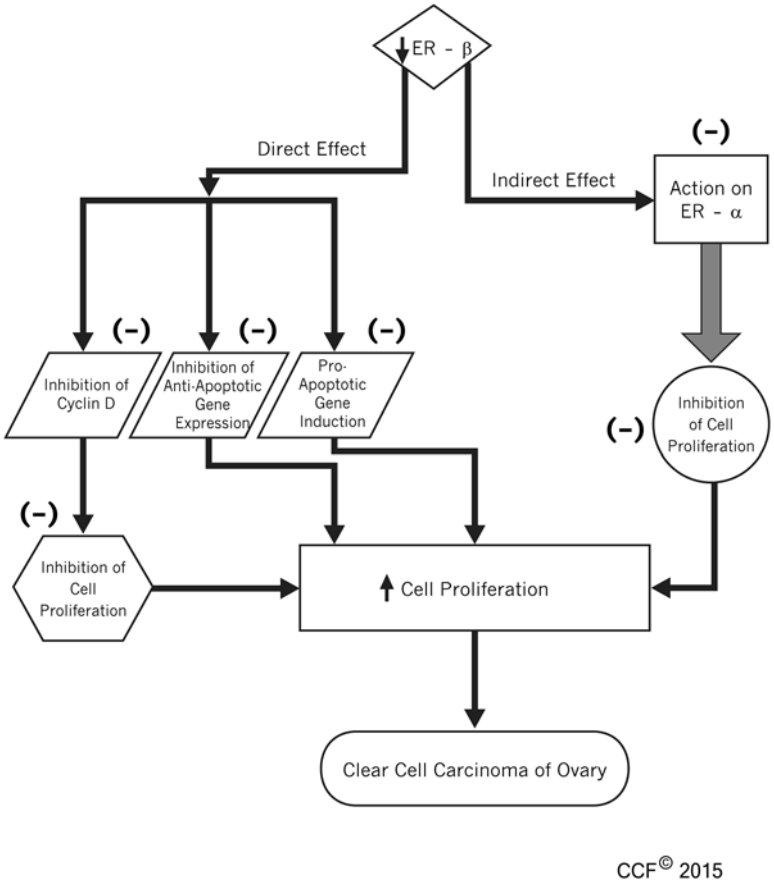

Fig. 7.4 Impact of ER-β expression in the pathogenesis of clear cell carcinoma of ovary

increase cyclooxygenase 2 [cox-2] and decrease progesterone receptor (PR) and ER alpha. Interaction with the estrogen receptor enhances the transcription of genes and promotes the synthesis of specific RNAs and proteins. Increased COX-2 levels are linked to endometriosis and also early malignant transformation (Fig. 7.5).

7.5.1 PI3K/AKT-Pathway

The PI3K (phosphatidylinositol 3-kinase) pathway is a significant pathway in the development of many cancers including breast, colon, and ovarian. PI3K has three classes among which class 1A is mostly involved in the development of cancer.

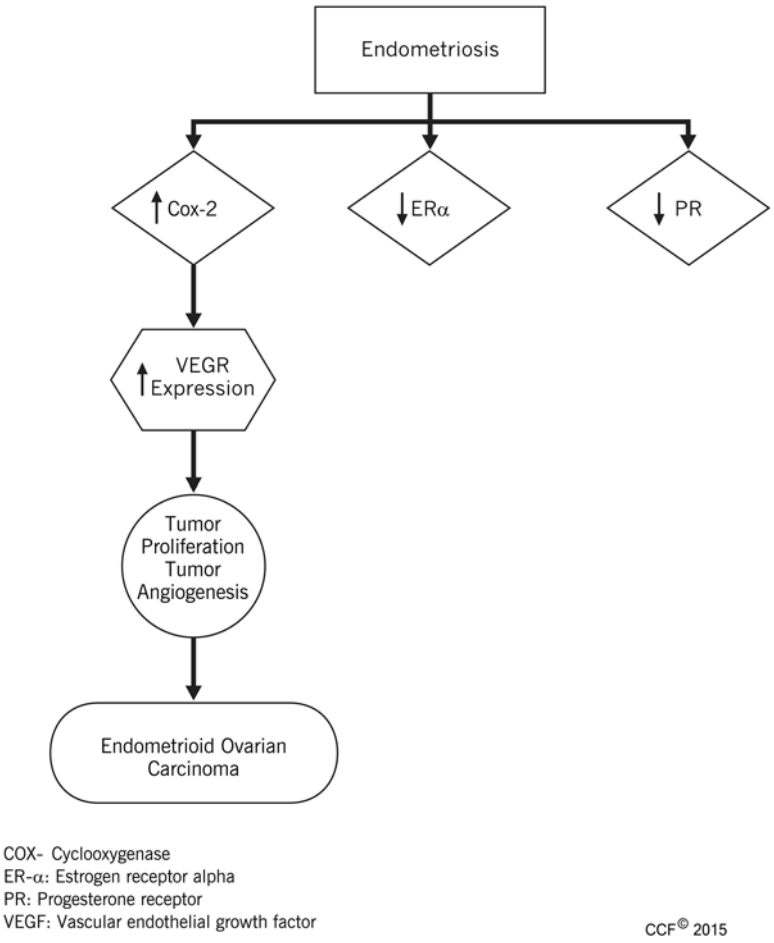

Fig. 7.5 Role of Cox-2 in the malignant transformation of endometriosis to endometriod carcinoma

The activation of PI3K/AKT pathway is more commonly achieved by activating its receptor tyrosine kinase (RTK). Genetic alterations such as mutation in tumor suppressor gene PTEN (Phosphatase and TENsin homolog) due to LOH (loss of heterozygosity) also activates the PI3K pathway, which contributes to the malignant transformation of endometriosis to EAOC [17]. Activation of phosphatidylinositol 3-kinase (PI3K) leads to activation of AKT, a serine-threonine protein kinase, which in turn activates mTOR (mammalian target of rapamycin), thus increases cell proliferation and reduces apoptosis leading to EAOC (Fig. 7.6).

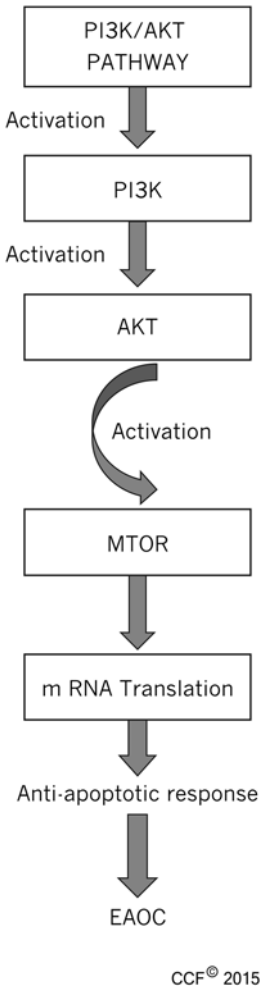

Fig. 7.6 P13/AKT pathway activation in EAOC. *PI3K* phosphatidylinositol 3-kinase, *MTOR* mammalian target of rapamycin

7.6 Preventive Measures and Screening Options

Although endometriosis increases the risk of ovarian cancer, the long-term risk can be reduced by hysterectomy without oophorectomy, oral contraceptives, aspirin and breast feeding [23]. All of these preventive measures suppress ovulation, which increases inflammation in the pelvic region [23]. Consequently, it has been shown that persistent inflammation leads to an increased risk of cancer.

In particular, oral contraceptives are extremely effective because they counteract the pituitary gonadotropin hypothesis. The pituitary gonadotropin hypothesis states that the continuous presence of elevated luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in ovarian cysts stimulate trapped epithelial cells, cause inflammation and play a primary role in the malignant transformation of such

tissue to ovarian cancer [23]. Thus, oral contraceptives keep LH and FSH levels low through the negative feedback system involving the secretion of estrogen. If estrogen levels are high, as induced by oral contraceptives, then the hypothalamus, and, consequently, the pituitary gland, will secrete less LH and FSH, cutting off the gonadotropin supply necessary for epithelial cells trapped in ovarian cysts to grow. The best choice of oral contraception is one that combines both estrogen and progestin. This would suppress levels of both gonadotropins and eliminate the risk factors associated with unopposed estrogen [23].

Progesterone has been shown to counteract some of the biological effects of estrogen and increase endometrial cell apoptosis, thus making it preferable to estrogen-based medications. Oral contraceptives, of course, are not a viable treatment option for women who wish to become pregnant. In that case, other options must be explored. Nonetheless, oral contraception is a non-invasive treatment that may bring relief and reduce the risk of cancer in many women afflicted with endometriosis. A patient's risk for developing ovarian cancer is significantly reduced after hysterectomy without oophorectomy. One reason may be that the procedure removes the pathway connecting the lower and upper genital tract, preventing inflammants from reaching the ovaries [23]. Thus, removing the constant inflammation lowers the risk of ovarian cancer because the immune system is not activated, which prevents the tissues from entering an OS state, which in turn prevents the tissue from entering an OS state and causing DNA damage. However, unlike the treatment proposed with oral contraceptives, a hysterectomy is not an option for many women, including those of reproductive age who wish to preserve their fertility. Additionally, hysterectomy is an invasive and complicated medical procedure that carries a risk of infection and surgical and post-operative complications. Thus, a hysterectomy is a much more radical form of treatment as opposed to an oral contraceptive, and it therefore should only be considered in severe cases.

Another viable option for reducing the risk of ovarian cancer in women with endometriosis is treatment with non-steroidal anti-inflammatory drugs (NSAIDS) [24]. Because these drugs are anti-inflammatory, they have a dual advantage for patients—they not only help reduce the primary inflammation in the pelvic region initially caused by the endometriosis, but they also may prevent the carcinogenesis of epithelial tumors by inhibiting cyclooxygenase-2, which inhibits the aromatase enzyme, reducing estrogen levels [24]. Therefore, NSAID therapy is a realistic treatment option for endometriosis patients. It is a simple and low-cost treatment that can be taken daily. Similarly, NSAIDs appear to have beneficial effects on both inflammation and ovarian cancer. It is important to note that this treatment option does not suppress ovulation, making it an acceptable option for women of reproductive age.

Finally, breastfeeding has also been shown to decrease inflammation in patients with endometriosis and ultimately prevent ovarian cancer by reducing estradiol levels. Therefore, for women who have recently given birth and have been diagnosed with endometriosis, breast feeding is a viable option that can reduce both inflammation and the risk for developing ovarian cancer.

Because ovulation is a natural process that causes inflammation, suppressing it can control both inflammation and reduce the risk of ovarian cancer. However, it

should be remembered that in patients with endometriosis, the immune response is altered, leading to high levels of cytokines such as Interleukin 1, Interleukin 6 and TNF [23]. Thus, treatment becomes more *difficult*, and responses to treatment vary accordingly. The high levels of cytokines released in endometriosis patients are known to stimulate the proliferation of endometrial cells as they contain receptors for IL-6 and TNFα [25]. The presence of such cytokines also leads to persistent inflammation in the pelvic region. In fact, inflammatory cells have been found near ovarian tumors and are thought to help break down the extracellular matrix and allow tumors to invade, allowing ovarian cancer to metastasize [23].

Thus, the preventive care mentioned above would help women lower their risk for ovarian cancer mainly by suppressing ovulation. Treatment now centers on the idea that suppressing ovulation decreases the amount of inflammation, thus reducing the production of ROS and minimizing the immune system response. Together, this lowers the risk for ovarian cancer in patients with endometriosis, leading to an overall positive improvement in quality of life.

However, ovulation suppression is not an option in women who are interested in maintaining their fertility or becoming pregnant. In these cases, antioxidant therapy may be considered. The goal is to regain a balance between ROS and antioxidant levels in the afflicted patient. This would help eliminate the detrimental effects of immune system by removing the main trigger—inflammation.

7.6.1 Screening

CA-125 is a highly sensitive biomarker for ovarian cancer, but its specificity is poor. Studies show that tissue expression of HE4 (human epididymis protein 4) is higher in malignant epithelial ovarian tumors than in benign ovarian tumors. In support to other studies [26–29], Huhtinen et al., found that levels of HE-4 in patients with ovarian and endometrial cancer were increased; this was not true in patients with endometriosis of the ovary. On the other hand, patients with ovarian endometriomas and advanced endometriosis had higher levels of serum CA-125. It has also been observed that concentrations of HE-4 increase with age whereas CA-125 levels do not [30]. The accuracy of using HE4 to distinguish ovarian cancer from other benign gynecological diseases such as endometriosis was found to be to be superior than serum CA125 [31]. Measuring both HE-4 and Serum CA-125 levels will provide a more reliable method of screening of patients with ovarian endometriosis and ovarian cancer and will help clinicians in differentiating the two conditions. It may also be useful during follow up to assess the malignant transformation of advanced endometriosis.

Among patients with an ultrasound-detected ovarian mass, increased levels of serum HE4 and CA125 would suggest the presence of ovarian cancer whereas higher levels of CA125 without elevated HE4 levels would suggest advanced endometriosis or ovarian endometrioma or other benign conditions. Also, normal serum levels of CA-125 and higher levels of HE-4 point towards the presence of either ovarian cancer or other type of cancer, such as endometrial cancer [30].

Studies have shown that plasma MiRNA profiling can be used as a biomarker to distinguish patients with endometriosis and ovarian cancer from normal healthy individuals [32, 33]. The golden standard for diagnosing endometriosis is laparoscopy. It allows direct visualization of lesions with histological confirmation. However, there is always a risk associated with surgery, so physicians prefer to use alternative methods. The most commonly used, non-invasive technique for screening (for both endometriosis and EAOC) is a combination of ultrasonography and laboratory testing for serum CA-125 [34]. While CA-125 has been used as a biological marker, it also has a high false positive rate among women [35]. Thus, HE4 can be used in conjunction with US and CA-125 [28, 29, 36]. It is important to note that this new marker is more sensitive to EAOC and the false positives associated with advanced stage endometriosis are considerably lower. Huhtinen et al. showed that the combination of CA 125 and HE4 was 94 % accurate in distinguishing women with cancer from those with endometriosis [30]. Together, CA-125, HE4 and US are commonly used to detect endometriosis without the need for laparoscopy. Doppler ultrasonography, trans-rectal ultrasonography, computerized tomography and magnetic resonance imaging (MRI) are the other noninvasive diagnostic approaches. MRI may be reliable for vaginal and extra pelvic localizations [37].

It has been also suggested that MRI is useful in showing malignant transformation within an endometrioma. The presence of one or more contrast material-enhanced mural nodules within a cystic mass, enlargement of the endometrioma and the disappearance of shading within the mass on T2 weighted images is suggestive of malignant transformation [38].

7.7 Key Points and Summary

In conclusion, numerous novel treatment options are beginning to be recognized and should be made available to women with endometriosis to decrease pelvic inflammation and reduce the risk of ovarian cancer. Possible preventative options are breast feeding in post-partum women and oral contraceptive pills for women who do not desire pregnancy. With the knowledge of the various pathways and pathologic mechanisms that underlie endometriosis and EAOC, novel biomarkers can possibly be identified for the early diagnosis of endometriosis. Physicians can use them to follow up patients with an established diagnosis of endometriosis to monitor the early events involved in the malignant transformation to EAOC and thereby prevent them from progressing to malignant disease. Combined screening with serum levels of CA-125, HE4 and US is recommended in current literature for possible noninvasive and specific diagnosis. As chronic inflammation is one of the most important underlying pathogenesis of endometriosis and its progression to EAOC, NSAIDs can be used. Further studies should evaluate whether anti-oxidant therapy can normalize levels of ROS and combat oxidative stress.

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