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Endometriosis and endometriosis associated ovarian cancer

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Abstract
Endometriosis is defined by the presence of endometrial tissues outside of the endometrial cavity. It is a benign condition and even though it's pathogenesis is not yet fully understood different theories, such as the Coelomic theory and the theory of Mullerian rest, have been proposed as possible explanations for the development of this pathology. Evidence suggests that women diagnosed with endometriosis presents an increased risk for developing ovarian cancers. Therefore, this review will explore the pathogensis of endometriosis, explore its association with the development of ovarian cancers and identify treatment methods for managing lesions following malignant transformation.

Keywords: Endometriosis, ovarian cancer, endometriosis associated ovarian cancer, ovarian clear cell carcinoma, endometrioid carcinoma

1. Introduction
Endometriosis is defined by the presence of endometrial glands and stroma outside the endometrial cavity. It is associated with pelvic pain, dysmenorrhea and female infertility [1]. Despite the fact that endometriosis is considered a benign condition, due to its normal histology, studies have shown that this disease is associated with increased risk for specific histotypes of ovarian carcinoma (endometrioid and clear cell ovarian cancer) [2, 3]. A combination of different factors may cumulatively lead to the malignant transformations in women diagnosed with endometriosis. Interplay of inflammatory mediators, hormonal interactions and endometriosis induced changes within the pelvis may all ultimately lead to the development of malignancies. The presence of increase oestrogen may also influence malignant transformations [4, 5]. This literature review will therefore discuss the following 1) the pathogenesis of endometriosis, 2) the association between endometriosis and development of ovarian cancer and 3) potential treatment methods for managing ovarian lesions following malignant traansformations.

2. Pathogenesis of Endometriosis
Affecting 3–15% of premenopausal women, 3–5% of postmenopausal women [6], 25%-80% of infertile women and 40%-80% of women with pelvic pain [7], endometriosis is an oestrogen-dependent condition defined by the presence and growth of endometrial-type mucosa outside the uterine cavity. Ectopic endometrial tissue may be present around pelvic organs such as the ovaries, in addition to other organs including the colon and bladder. Endometriosis is mainly associated with inflammation, severe chronic pain, and infertility [8]. The diagnosis of endometriosis requires the presence of at least two of the following features: 1) endometrial epithelial cells, 2) epithelium, 3) endometrial stromal cells 4) and signs of bleeding from endometrium-like tissue [9, 10]. Endometriosis accounts for three anatomical subtypes [11, 12]: 1) superficial peritoneal disease subtype defined by superficial implants, haemorrhagic lesions or white scarring, 2) ovarian disease subtype defined by superficial lesions on the surface of the ovary, or the presence of endometriosis cysts inside the ovary commonly called endometriomas and 3) deep infiltrating disease subtype defined by lesions greater than 5 mm and the presence of formed connective tissue around the endometriosis stroma. Women diagnosed with endometriosis commonly report having pain and fertility issues. It is theorized that these two main symptoms are related to the pathogenesis of the disease which involves the influence of hormonal and immunological factors that leads to inflammation [13]. As a result of these discoveries, several concepts are now being explored to explain the pathogenesis of endometriosis.

The implantation theory describes retrograde menstruation as a possible initiating factor for the development of endometriosis [14]. Retrograde menstruation involves the backward flow of menstrual contents, including endometrial tissue, through patent fallopian tubes into the peritoneal cavity [15]. It is believed that this retrograde flow occurs initially at birth; however, deposited endometrial tissues are not activated until puberty when the ovaries begin to produce sex hormones [16]. Abnormalities that may promote this occurrence include: congenital malformations of the female reproductive tract, the production of thick cervical mucus and the presence of a tight internal uterine cervix os[17]. Evidence supports this theory as a higher prevalence of endometriosis has been observed in adolescent females presenting with congenital outflow tract obstruction [18] and the presence of outflow tract obstruction has been demonstrated to be associated with intra-peritoneal endometriotic lesions [19]. Following retrograde flow of menstrual contents into the peritoneal cavity, other processes must follow in order for endometriosis to finally occur. This may involve the failure of the immune system to detect and eliminate ectopic tissues, the attachment of ectopic tissues to the peritoneum or the development of local nerve and blood supply which supports survival [17].

Another theory that has been developed to explain the pathogenesis of endometriosis is the Coelomic theory which involves the change or transformation of peritoneal tissue to ectopic endometrial tissue [20]. There are different factors that may influence these changes and endocrine disrupting chemicals (EDCs) have been proposed to play a potential role. It is also believed that endogenous agents such as hormonal or immunological factors may serve as inductive stimuli that ultimately support the changes or differentiation of normal peritoneal cells into endometrial cells[21,22]. Furthermore, according to the theory of Mullerian rests, residual cells originating from the embryonic Mullerian duct, migrate and maintain their ability to develop into endometriotic lesions in the presence of hormones such as oestrogen[23]. It has been postulated that extra-uterine stem/progenitor cells such as cells from the bone marrow, may also play a role in the pathogenesis of endometriosis through the differentiation into endometrial tissue [24].

Endometriosis is now being observed as a pelvic inflammatory condition. In women diagnosed with this disease, examination of the peritoneal fluid demonstrates an alarming increase in the presence of activated macrophages and alterations in cytokine/chemokine profiles [25]. Cytokines or chemokines that are found to be increased in the peritoneal fluid of women suffering from endometriosis include: 1) macrophage migration inhibitory factor, 2) tumour necrosis factor (TNF) -α 3) interleukin (IL) -1β, 4) IL-6, 5) IL-8 and 6) monocyte chemoattractant protein-1 (MCP-1). The reasons for this observation are yet to be determined [26]. The peritoneum of women diagnosed with endometriosis usually has high levels of prostaglandins which may account for the pathophysiology of the disease and its common presentation (pain and infertility). It is observed that the macrophages found in the peritoneum of endometriosis patients, possess higher levels of cyclo-oxygenase-2 (COX-2) and produce higher concentrations of prostaglandins as compared to macrophages found in healthy subjects. TNF-α stimulates endometrial cells to produce prostaglandin $F_{2\alpha}$ (PG $F_{2\alpha}$) and prostaglandin E_2 (PGE_2). COX-2, which is activated by IL-1β, induces the production of PGE_2 and this in turn stimulates steroidogenic acute regulatory (StAR) protein and aromatase. Oestrogen establishes a positive feedback loop through its up-regulation of PGE2 synthesis thus increasing the bioavailability of estradiol. This phenomenon explains the interconnection between oestrogen dependence and inflammation observed in endometriosis [20].

Furthermore, the protein hormone adiponectin has been explored for its potential role in the development of endometriosis. It regulates a variety of metabolic processes in the body such as the catabolism of glucose and fatty acids. Adipose tissues secrete adiponectin and it has been noted that the serum and peritoneal fluid of women suffering from endometriosis exhibit decreased levels of this protein hormone. Cultured endometrial stromal cells demonstrated a decrease in the secretion of IL-6, IL-8, and MCP-1 in the presence of adiponectin. This result shows the anti-inflammatory effects of this protein hormone on endometrial stromal cells, a protective effect which is not present in patients suffering from endometriosis [27].

3. Association between Endometriosis and the development of Ovarian Cancers

A meta-analysis done by Kim *et al.* to assess the impact of endometriosis on the risk and prognosis of ovarian cancer, concluded that there is a significant association between this pathology and the risk for developing ovarian cancers [28]. To date, the precise mechanism for malignant transformations of endometriosis is not fully known; however, different factors have been investigated for the role that they may play in this process [29].

Oxidative stress, possibly associated with genetic abnormalities, is an important mechanism commonly observed when investigating the association between endometriosis and the development of ovarian cancers [30]. The development of epithelial ovarian cancer (EOC) is commonly associated with defects in β-catenin and P16, phosphatase and tensin homolog deleted on chromosome 10 (PTEN) gene suggesting an association with oestrogen [31, 30]. Clear cell carcinoma (CCC) is associated with the expression of fewer oestrogen receptors [30]. Oxidative stress, promoted by the presence of iron in the fluid of endometriotic cysts, potentially results in genetic mutations. Repeated haemorrhage in endometriosis promotes iron-mediated oxidation. This combined with the expression of fewer oestrogen receptors, are proposed as a possible causes for the development of CCC in patients diagnosed with endometriosis [32].

The development of endometriosis-associated clear cell carcinoma (EACCC) is strongly associated with AID1A (a tumour suppressor gene, encoding (BRG-associated factor 250a) BAF250a protein) mutations whereas mutations in PTEN, KRas and β-catenin genes are more commonly observed with the development of endometriosis-associated endometrioid carcinoma (EAEC) [30]. Research has shown that the expression of the ARID1A- encoded protein is reduced in ovarian CCC. In addition, decreased ARID1A gene function is observed in endometriotic lesions which are found within close proximity to the site of the primary lesion [33]. Mutations in this gene has been identified in 41-57% of ovarian CCC and 15-20% of benign ovarian cysts and is it proposed that patients presenting with ARID1A mutations in benign endometriosis should be viewed as high risk for developing malignancies. Evidence suggests an association between ARID1A mutations and loss of expression of BAF250a. Loss of BAF250a combined with changes in γH2AX, pAKT activation and induction of pathways for apoptosis are observed as initial molecular events that occur in the development of EAOC [34]. ARID1A mutations with the loss of BAF250a protein expression has been identified as the most common occurrence in the development of CCC and

endometrioid carcinoma (EC) [35].

The mechanism of DNA methylation has been observed for the role that it may play in the development of ovarian cancers in endometriosis. Some major genes that have been identified through research include genes that are inactivated through hyper-methylation including: 1) Runt-related transcription factor 3 (RUNX3), 2) human mutL homolog 1 (hMLH1), 3) E-cadherin (CDH1),4) Ras-association domain family of gene 2 (RASSF2), 5) PTEN and genes activated by hypo-methylation such as: 1) long interspersed nuclear element-1 (LINE-1) and syncytin-1 [36]. Inactivation of RUNX3 through methylation is observed as an early molecular event in the development of EAOC [37] and it has been reported that higher frequencies of RUNX3 methylation and inactivation occur in patients suffering from endometriosis [38]. Hyper-methylation and inactivation of RUNX3 play a pivotal role in the development of malignant transformation in endometriosis. Hyper-methylation of RUNX3 affects both normal and abnormal endometrial tissues [30]. hMLH1 corrects errors in DNA that may occur during replication. An absence in the expression of hMLH1 protein, due to promoter methylation and inactivation, has been demonstrated to play critical roles in the malignant transformation of ovarian endometrium [39].

Despite the potential risk for malignant transformation that presents with the presence of endometriosis, eivdence suggests that steps can be taken to reduce this risk in women presenting with this pathology [40, 41]. Evidence suggests that performing a hysterectomy while preserving the ovaries may help to prevent the development of ovarian cancers in women. Report from Dixon-Suen *et al.* on a study carried out on 837 942 women from Western Australia, demonstrated that in women diagnosed with endometriosis or fibroids, a hysterectomy significantly reduced their overall risks for developing ovarian cancers (HR = 0.17, 95% CI = 0.12-0.24, and HR = 0.27, 95% CI = 0.20-0.36, respectively) [42]. Furthermore, in some cases of endometriosis, cystectomies may also aid in preventing cancer development [43]. In addition, hormonal influences and reproductive factors, may also play potential roles in delaying or reducing malignant transformation in women diagnosed with endometriosis. Modugno *et al.* assessed the odds ratios of ovarian cancers in association with the use of oral contraceptives, childbearing, performance of a hysterectomy and tubal ligation in women presenting with or without a history of endometriosis. This study reported that the use of oral contraceptives, childbearing and undergoing tubal ligation or a hysterectomy similarly decreased the risk for developing ovarian cancers in women presenting with or without a diagnosis of endometriosis [44].

4. Management of Endometriosis-Associated Ovarian Cancer

Once malignant transformation occurs and ovarian cancers develop, the primary management is surgery. Surgery is important for staging and debulking of tumours and can provide a cure for lesions that have not yet metastasized. The extent of the surgery required depends on the stage at which the cancer is detected and its potential for malignant transformation [45, 46]. In late stage presentations and stage II cancers, chemotherapy treatment is recommended following surgical resection of the malignancy [47]. There still remains a need for the development of targeted therapies with the sole purpose of addressing the common genetic mutations of EAOC [43]. Therefore, different forms of therapy have been studied for their potential application in the treatment of EAOC.

Steps have alredy been taken to demonstrate the beneficial effects of immunotherapy in the management of EAOC. Clinical trials exploring the use of immunotherapy for the management of ovarian cancers have already been undertaken. Hamanishi *et al.* investigated the safety and antitumor activity of nivolumab (an anti-PD-1 antibody that functions to inhibit PD-1 signalling) in patients presenting with platinum-resistant ovarian cancer and concluded that the use of nivolumab was found to be relatively safe and clinically effective; therefore, this intervention measure definitely warrants future attention. This study, which investigated 20 patients of interest, reported the occurrence of adverse events in two study participants and a 45% disease control rate[48]. Matulonis *et al*. examined two cohorts of study participants with advanced recurrent ovarian cancer (ROC) and demonstrated that there was some degree of response (16%) to the use of pembrolizumab as a single agent in patients with ROC [49]. In patients suffering from CCC the IL-6/JAK/STAT pathway is observed to be active and IL-6 may be used as an independent factor for predicting poor prognoses in CCC patients [50]. A retrospective cohort study which enrolled 192 participants identified as having stage I CCC concluded that in addition to sub-stage classification, the degree of IL-6 expression can also serve as an excellent prognostic factor for CCC discovered at stage I and that the use of IL-6 molecular stratification may be useful in maximizing therapeutic methods and improving survival rates in these population of patients [51]. From these findings the inhibition of this IL-6/JAK/STAT pathway may promote improvement in treatment methods, and it has already been demonstrated from animal studies that the use of anti-IL6 antibody in CCC potentially yields better prognoses [52]. *PIK3CA* mutations are demonstrated in 33-40% of patients diagnosed with CCC [53]. Mutations in this gene activate the PI3K/AKT/mTOR pathway. The use of inhibitors directly targeting the PI3K/AKT/mTOR pathway may yield favourable results for the management of CCC [54, 55]. It has also been suggested that the use of Poly ADP-ribose polymerase (PARP) may serve potential benefits for the treatment of CCC when *BRCA1/BRCA2* mutations are present [56].

A large percentage of women diagnosed with CCC expresses the angiogenic factor, VEGF *(*Vascular endothelial growth factor) [54, 57]. Antibodies to VEGF are used for treating ovarian cancers and has also been recommended for the treatment of EAOC [58, 59, 60]. It is theorized that the use of anti-VEGF antibodies along with other related drug therapies, may yield excellent results for the future treatment of EAOC [43]. The inhibition of VEGF receptors are also potentially excellent therapy strategies for treating ovarian cancers. Sorafenib inhibits VEGF and RAF kinase which both act on the *RTKs* and the PAF/MEK/ERK pathway to initiate tumour angiogenesis[61]. Matei *et al*. assessed the efficacy and tolerability of sorafenib in patients experiencing ROC or primary peritoneal carcinomatosis. In this study 71 patients met the eligibility criteria for inclusion. It was demonstrated from this investigation that sorafenib exhibited some degree of antitumor activities, however, there were cases of significant toxicity- rashes (n = 7), hand-foot syndrome (n = 9), metabolic (n = 10), GI (n = 3), cardiovascular (n = 2), and pulmonary (n = 2**)** [62]. Chekerov *et al*. investigated the use of sorafenib in combination with topotecan used for continued maintenance therapy for treating platinum-refractory ovarian cancer. This study concluded that the use of sorafenib combined with topotecan and as continued maintenance therapy potentially provides significant clinical benefits by improving survival rates in women presenting with platinum-resistance ovarian cancer [63].

The tumour microenvironment (TME) is greatly influenced by

tumour-associated macrophages (TAMs) and research has already been undertaken to investigate the use of therapies that target TAM in the treatment of ovarian cancer [64]. TAM treatment strategies may inhibit the recruitment of macrophages, decrease the survival of TAM, enhance the ability of M1 macrophages to kill and destroy tumours and suppress the activities of M2 macrophages, thus inhibiting tumour promoting activities [65, 66].

5. Discussion

Evidence suggests that women diagnosed with endometriosis exhibit an increased risk for developing ovarian cancers especially clear cell and endometrioid cancers. It is also observed that women presenting with a long-standing history of endometriosis carry an even greater risk for developing these cancers [67, 68]. Brinton *et al.* carried out a study to determine the extent of association between endometriosis or uterine leiomyomas and the development of cancers and insinuated that the presence of endometriotic lesions potentially influence the development of ovarian cancers, particularly CCC and EC. It was demonstrated from this study that following a period of five years or more with a diagnosis of endometriosis, the relative risks (RRs) for developing EC were RR= 2.53; 95% CI, 1.19-5.38 and for developing CCC were RR=3.37; 95% CI, 1.24-9.14 [8]. Elsewhere, it has been reported that women who carry a diagnosis of endometriosis carry a risk that is 2 to 3 times greater for developing ovarian cancers [69]. Kim *et al.* assessed the effects of endometriosis- associated genetic variation on the risk for developing ovarian cancers reported a link between endometriosis- associated genetic variation and the development of ovarian cancers, particularly high-grade serous and CCC [28]. A meta-analysis which included 20 case-control and 15 cohort studies with a total of 444255 participants reported an increased risk for developing ovarian cancers in women diagnosed with endometriosis [70].

Based on evidence from the literature, EAOC most likely develops when the woman approaches her late 40s. It is however observed that if malignant trasnformation was not present before menopause, transformation following menopause is less likely [71, 72]. One study carried out in Japan by Kobayash *et al.* concluded that the presence of ovarian endometrioma increases the risk for developing ovarian cancers. This study enrolled 6398 women who had a diagnosis of ovarian endometrioma. After observing this cohort for 17 years, it was noted that the presence of ovarian endometrioma increased the risk for ovarian cancer development, as 46 cases of ovarian cancers were observed (SIR = 8.95, 95% CI = 4.12-15.3). This study also demonstrated that the risk for occurrence of ovarian cancers was higher in women who received a diagnosis of ovarian endometrioma at an older age [73].

Since the presence of endometriosis may be assocaited with an increased risk for malignant transformation, it is important that patients diagnosed with this pathology be closely monitored for this potential development. This can be achieved through the use of biological markers that can be used for the early identification of individuals that exhibit an increased risk for developing ovarian malignancies. Biomarkers are important as they can be used for early identification of high-risk cases and thus allow for the application of early intervention methods that may help in reducing the occurrence of EAOC, in addition to giving patients better prognoses [44]. Other methods that can be applied for the early identification of patients that carry increased risks for malignant transformations include the detection tumour DNA levels in the circulation or possibly screening for the presence of various mutations specific for different types of ovarian cancers. These advancements help clinicians in better diagnosing, treating and predicting disease outcomes [74, 75].

6. Conclusion

In conclusion, it is quite evident that there is some association between endometriosis and the development of ovarian cancers most commonly, CCC and EC. The exact mechanism for malignant transformation is not yet fully understood; however, different genes, proteins and receptors have been investigated for the role they may play in this process. The use of different surgical interventions like fallopian tube ligation and cystectomies in addition to the use of oral contraceptives may serve to delay or prevent malignant transformations in women diagnosed with endometriosis. Surgical intervention for tumour staging and debulking followed by chemotherapy treatment, depending on the stage of the disease, remain the main methods for successfully treating EAOC; however, other strategies are now being investigated for their potential effectiveness in treating this pathology.

Declaration of Interest

The authors of this paper declare no conflict of interest.

7. References

1. Kobayashi H. Potential scenarios leading to ovarian cancer arising from endometriosis. Redox Rep 2016;21(3):119-26.
2. Sampson JA. Endometrial carcinoma of the ovary arising in endometrial tissue in that organ. American Journal of Obstetrics & Gynecology 1925;9(1):111-4.
3. Melin A, Sparén P, Bergqvist A. The risk of cancer and the role of parity among women with endometriosis. Hum Reprod 2007;22(11):3021-6.
4. Zanetta GM, Webb MJ, Li H, Keeney GL. Hyperestrogenism: a relevant risk factor for the development of cancer from endometriosis. Gynecol Oncol. 2000;79(1):18-22.
5. Ness RB. Endometriosis and ovarian cancer: Thoughts on shared pathophysiology. American Journal of Obstetrics & Gynecology 2003;189(1):280-94.
6. Del Carmen MG, Smith Sehdev AE, Fader AN, Zahurak ML, Richardson M, Fruehauf JP, *et al*. Endometriosis-associated ovarian carcinoma: differential expression of vascular endothelial growth factor and estrogen/progesterone receptors. Cancer 2003;98(8):1658-63.
7. Nezhat F, Datta MS, Hanson V, Pejovic T, Nezhat C, Nezhat C. The relationship of endometriosis and ovarian malignancy: a review. Fertil Steril. 2008;90(5):1559-70.
8. Hickey M, Ballard K, Farquhar C. Endometriosis. BMJ. 2014;348:g1752.
9. Al H, IK, PS. Invasive and noninvasive methods for the diagnosis of endometriosis [Internet]. Clinical obstetrics and gynecology. Clin Obstet Gynecol 2010, 53. [cited 2020 Sep 29]. Available from: https://pubmed.ncbi.nlm.nih.gov/20436318/
10. Bulun SE, Yilmaz BD, Sison C, Miyazaki K, Bernardi L, Liu S *et al*. Endometriosis. Endocrine Reviews 2019;40(4):1048.
11. Koninckx PR, Ussia A, Adamyan L, Wattiez A, Donnez J. Deep endometriosis: definition, diagnosis, and treatment. Fertil Steril 2012;98(3):564-71.
12. Anglesio MS, Yong PJ. Endometriosis-associated Ovarian Cancers. Clin Obstet Gynecol 2017;60(4):711-27.

13. Patel BG, Lenk EE, Lebovic DI, Shu Y, Yu J, Taylor RN. Pathogenesis of endometriosis: Interaction between Endocrine and inflammatory pathways. Best Pract Res Clin Obstet Gynaecol 2018;50:50-60.
14. Dastur AE, Tank PD. John A Sampson and the origins of Endometriosis. J Obstet Gynaecol India 2010;60(4):299-300.
15. Halme J, Hammond MG, Hulka JF, Raj SG, Talbert LM. Retrograde menstruation in healthy women and in patients with endometriosis. Obstet Gynecol 1984;64(2):151-4.
16. Brosens I, Benagiano G. Is neonatal uterine bleeding involved in the pathogenesis of endometriosis as a source of stem cells? Fertility and Sterility 2013;100(3):622-3.
17. Rolla E. Endometriosis: advances and controversies in classification, pathogenesis, diagnosis, and treatment. F1000Res [Internet]. 2019, [cited 2020 Aug 14];8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6480968/
18. Sanfilippo JS, Wakim NG, Schikler KN, Yussman MA. Endometriosis in association with uterine anomaly. Am J Obstet Gynecol 1986;154(1):39-43.
19. D'Hooghe TM, Bambra CS, Suleman MA, Dunselman GA, Evers HL, Koninckx PR. Development of a model of retrograde menstruation in baboons (Papio anubis). Fertil Steril 1994;62(3):635-8.
20. Burney RO, Giudice LC. Pathogenesis and Pathophysiology of Endometriosis. Fertil Steril [Internet]. 2012 Sep [cited 2020;98(3). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3836682/
21. Levander G, Normann P. The pathogenesis of endometriosis; an experimental study. Acta Obstet Gynecol Scand 1955;34(4):366-98.
22. Merrill JA. Endometrial induction of endometriosis across Millipore filters. Am J Obstet Gynecol. 1966;94(6):780-90.
23. Longo LD. Classic pages in obstetrics and gynecology. Aberrant portions of the müllerian duct found in an ovary: William Wood Russell Johns Hopkins Hospital Bulletin, vol. 10, pp. 8--10, 1899. Am J Obstet Gynecol. 1979;134(2):225-6.
24. Sasson IE, Taylor HS. Stem cells and the pathogenesis of endometriosis. Ann N Y Acad Sci. 2008;1127:106-15.
25. Rana N, Braun DP, House R, Gebel H, Rotman C, Dmowski WP. Basal and stimulated secretion of cytokines by peritoneal macrophages in women with endometriosis. Fertil Steril. 1996;65(5):925-30.
26. Cousins FL, O DF, Gargett CE. Endometrial stem/progenitor cells and their role in the pathogenesis of endometriosis. Best Pract Res Clin Obstet Gynaecol. 2018;50:27-38.
27. Osuga Y. Current concepts of the pathogenesis of endometriosis. Reprod Med Biol. 2010;9(1):1-7.
28. Kim HS, Kim TH, Chung HH, Song YS. Risk and prognosis of ovarian cancer in women with endometriosis: a meta-analysis. Br J Cancer. 2014;110(7):1878-90.
29. Xiao W, Awadallah A, Xin W. Loss of ARID1A/BAF250a expression in ovarian endometriosis and clear cell carcinoma. Int J Clin Exp Pathol 2012;5(7):642-50.
30. Brilhante AVM, Augusto KL, Portela MC, Sucupira LCG, Oliveira LAF, Pouchaim AJMV *et al*. Endometriosis and Ovarian Cancer: an Integrative Review (Endometriosis and Ovarian Cancer). Asian Pac J Cancer Prev 2017;18(1):11-6.
31. Matsumoto T, Yamazaki M, Takahashi H, Kajita S, Suzuki E, Tsuruta T *et al*. Distinct β-catenin and PIK3CA mutation profiles in endometriosis-associated ovarian endometrioid and clear cell carcinomas. Am J Clin Pathol 2015;144(3):452-63.
32. Scarfone G, Bergamini A, Noli S, Villa A, Cipriani S, Taccagni G *et al*. Characteristics of clear cell ovarian cancer arising from endometriosis: a two center cohort study. Gynecol Oncol 2014;133(3):480-4.
33. Worley MJ, Liu S, Hua Y, Kwok JS-L, Samuel A, Hou L, *et al*. Molecular changes in endometriosis-associated ovarian clear cell carcinoma. Eur J Cancer 2015;51(13):1831-42.
34. Chene G, Ouellet V, Rahimi K, Barres V, Provencher D, Mes-Masson AM. The ARID1A pathway in ovarian clear cell and endometrioid carcinoma, contiguous endometriosis, and benign endometriosis. Int J Gynaecol Obstet. 2015;130(1):27-30.
35. Wiegand KC, Shah SP, Al-Agha OM, Zhao Y, Tse K, Zeng T *et al*. ARID1A Mutations in Endometriosis-Associated Ovarian Carcinomas. New England Journal of Medicine. 2010;363(16):1532-43.
36. He J, Chang W, Feng C, Cui M, Xu T. Endometriosis Malignant Transformation: Epigenetics as a Probable Mechanism in Ovarian Tumorigenesis. Int J Genomics [Internet] 2018 [cited 2020 Aug 20];2018. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5892233/
37. Guo C, Ren F, Wang D, Li Y, Liu K, Liu S *et al*. RUNX3 is inactivated by promoter hypermethylation in malignant transformation of ovarian endometriosis. Oncology Reports. 2014;32(6):2580-8.
38. Suzuki M, Shigematsu H, Shames DS, Sunaga N, Takahashi T, Shivapurkar N, *et al*. DNA methylation-associated inactivation of TGFβ-related genes DRM/Gremlin, RUNX3, and HPP1 in human cancers. Br J Cancer. 2005;93(9):1029-37.
39. Ren F, Wang D, Jiang Y, Ren F. Epigenetic inactivation of hMLH1 in the malignant transformation of ovarian endometriosis. Arch Gynecol Obstet. 2012;285(1):215-21.
40. Cibula D, Widschwendter M, Májek O, Dusek L. Tubal ligation and the risk of ovarian cancer: review and meta-analysis. Hum Reprod Update. 2011;17(1):55-67.
41. Sieh W, Salvador S, McGuire V, Weber RP, Terry KL, Rossing MA, *et al*. Tubal ligation and risk of ovarian cancer subtypes: a pooled analysis of case-control studies. Int J Epidemiol 2013;42(2):579-89.
42. Dixon-Suen SC, Webb PM, Wilson LF, Tuesley K, Stewart LM, Jordan SJ. The Association Between Hysterectomy and Ovarian Cancer Risk: A Population-Based Record-Linkage Study. J Natl Cancer Inst 2019;111(10):1097-103.
43. Murakami K, Kotani Y, Nakai H, Matsumura N. Endometriosis-Associated Ovarian Cancer: The Origin and Targeted Therapy. Cancers 2020;12(6).
44. Modugno F, Ness RB, Allen GO, Schildkraut JM, Davis FG, Goodman MT. Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. Am J Obstet Gynecol 2004;191(3):733-40.
45. Liu JH, Zanotti KM. Management of the adnexal mass. Obstet Gynecol. 2011;117(6):1413-28.
46. Board PATE. Ovarian Epithelial, Fallopian Tube, and Primary Peritoneal Cancer Treatment (PDQ®) [Internet]. PDQ Cancer Information Summaries [Internet]. National Cancer Institute (US) 2020 [cited 2020 Sep 29]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK66007/
47. Doubeni CA, Doubeni AR, Myers AE. Diagnosis and Management of Ovarian Cancer. AFP. 2016;93(11):937-44.
48. Hamanishi J, Mandai M, Ikeda T, Minami M, Kawaguchi

A, Murayama T *et al*. Safety and Antitumor Activity of Anti–PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer. JCO. 2015;33(34):4015-22.
49. Matulonis UA, Shapira-Frommer R, Santin AD, Lisyanskaya AS, Pignata S, Vergote I *et al*. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. Ann Oncol. 2019;30(7):1080-7.
50. Kawabata A, Yanaihara N, Nagata C, Saito M, Noguchi D, Takenaka M *et al*. Prognostic impact of interleukin-6 expression in stage I ovarian clear cell carcinoma. Gynecol Oncol 2017;146(3):609-14.
51. Yanaihara N, Hirata Y, Yamaguchi N, Noguchi Y, Saito M, Nagata C *et al*. Antitumor effects of interleukin-6 (IL-6)/interleukin-6 receptor (IL-6R) signaling pathway inhibition in clear cell carcinoma of the ovary. Mol Carcinog 2016;55(5):832–41.
52. Chandler RL, Damrauer JS, Raab JR, Schisler JC, Wilkerson MD, Didion JP *et al*. Coexistent ARID1A-PIK3CA mutations promote ovarian clear-cell tumorigenesis through pro-tumorigenic inflammatory cytokine signaling. Nat Commun 2015;6:6118.
53. Kuo K-T, Mao T-L, Jones S, Veras E, Ayhan A, Wang T-L, *et al*. Frequent Activating Mutations of PIK3CA in Ovarian Clear Cell Carcinoma. Am J Pathol 2009;174(5):1597-601.
54. Mabuchi S, Kawase C, Altomare DA, Morishige K, Hayashi M, Sawada K, *et al*. Vascular endothelial growth factor is a promising therapeutic target for the treatment of clear cell carcinoma of the ovary. Mol Cancer Ther. 2010;9(8):2411-22.
55. Shibuya Y, Tokunaga H, Saito S, Shimokawa K, Katsuoka F, Bin L, *et al*. Identification of somatic genetic alterations in ovarian clear cell carcinoma with next generation sequencing. Genes, Chromosomes & Cancer 2018;57(2):51-60.
56. Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J *et al*. BRCA Mutation Frequency and Patterns of Treatment Response in BRCA Mutation–Positive Women With Ovarian Cancer: A Report From the Australian Ovarian Cancer Study Group. J Clin Oncol. 2012;30(21):2654-63.
57. Barreta A, Sarian LO, Ferracini AC, Costa LBE, Mazzola PG, de Angelo Andrade L, *et al*. Immunohistochemistry expression of targeted therapies biomarkers in ovarian clear cell and endometrioid carcinomas (type I) and endometriosis. Hum Pathol 2019;85:72-81.
58. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H *et al*. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011;365(26):2473-83.
59. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G *et al*. A Phase 3 Trial of Bevacizumab in Ovarian Cancer. New England Journal of Medicine 2011;365(26):2484-96.
60. Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A *et al*. OCEANS: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Chemotherapy With or Without Bevacizumab in Patients With Platinum-Sensitive Recurrent Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer. J Clin Oncol. 2012;30(17):2039–45.
61. Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H *et al*. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004;64(19):7099-109.
62. Matei D, Sill MW, Lankes HA, DeGeest K, Bristow RE, Mutch D *et al*. Activity of sorafenib in recurrent ovarian cancer and primary peritoneal carcinomatosis: a gynecologic oncology group trial. J Clin Oncol. 2011;29(1):69-75.
63. Chekerov R, Hilpert F, Mahner S, El-Balat A, Harter P, De Gregorio N *et al*. Sorafenib plus topotecan versus placebo plus topotecan for platinum-resistant ovarian cancer (TRIAS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2018;19(9):1247-58.
64. Yang Y, Yang Y, Yang J, Zhao X, Wei X. Tumor Microenvironment in Ovarian Cancer: Function and Therapeutic Strategy. Front Cell Dev Biol [Internet]. 2020 [cited 2020 Sep 30];8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7431690/
65. Tang X, Mo C, Wang Y, Wei D, Xiao H. Anti-tumour strategies aiming to target tumour-associated macrophages. Immunology 2013;138(2):93-104.
66. Cassetta L, Pollard JW. Targeting macrophages: therapeutic approaches in cancer. Nat Rev Drug Discov 2018;17(12):887-904.
67. Greene AD, Lang SA, Kendziorski JA, Sroga-Rios JM, Herzog TJ, Burns KA. Endometriosis: Where are We and Where are We Going? Reproduction 2016;152(3):R63-78.
68. Brinton LA, Sakoda LC, Sherman ME, Frederiksen K, Kjaer SK, Graubard BI, *et al*. Relationship of benign gynecologic diseases to subsequent risk of ovarian and uterine tumors. Cancer Epidemiol Biomarkers Prev. 2005;14(12):2929-35.
69. Novel insights on the malignant transformation of endometriosis into ovarian carcinoma [Internet]. ResearchGate. [cited 2020 Sep 29]. Available from: https://www.researchgate.net/publication/262928986_Novel_insights_on_the_malignant_transformation_of_endometriosis_into_ovarian_carcinoma
70. Lee AW, Templeman C, Stram DA, Beesley J, Tyrer J, Berchuck A, *et al*. Evidence of a genetic link between endometriosis and ovarian cancer. Fertility and Sterility. 2016;105(1):35-43.e10.
71. Melin A, Sparén P, Persson I, Bergqvist A. Endometriosis and the risk of cancer with special emphasis on ovarian cancer. Hum Reprod 2006;21(5):1237-42.
72. Aris A. Endometriosis-associated ovarian cancer: A ten-year cohort study of women living in the Estrie Region of Quebec, Canada. J Ovarian Res 2010;3:2.
73. Kobayashi H, Sumimoto K, Moniwa N, Imai M, Takakura K, Kuromaki T, *et al*. Risk of developing ovarian cancer among women with ovarian endometrioma: a cohort study in Shizuoka, Japan. Int J Gynecol Cancer 2007;17(1):37-43.
74. Dawson A, Fernandez ML, Anglesio M, Yong PJ, Carey MS. Endometriosis and endometriosis-associated cancers: new insights into the molecular mechanisms of ovarian cancer development. Ecancermedicalscience [Internet]. 2018 Jan 25 [cited 2020 Oct 5];12. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5813919/
75. Perakis S, Speicher MR. Emerging concepts in liquid biopsies. BMC Medicine 2017;15(1):75.