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Review Article

Endometriosis, Ovarian Cancer and Mrp4, Is There A Truth Correlation?

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ABSTRACT
Endometriosis is a hormonal and immune system disease in which cells similar to endometrium grow outside the uterine cavity. Etiopathogenesis is not well known yet, "retrograde menstruation" is the most accepted theory, after migrating, PGE2 promotes adhesion and invasion of the endometrium on other tissues. Prostaglandins are produced from arachidonic acid through the path of COX 1 and 2 that are inhibited by aspirin and other NSAIDs. A molecular difference between eutopic and ectopic endometrium is the over expression of the multidrug resistance–associated protein 4 (MRP4) in endometriosis. MRP4 plays a role in modulating some drugs, like aspirin and some drugs used for chemotherapy of ovarian cancer. At the same time, studies have been published on aspirin resistance and because of MRP4 is over expressed in human endometriotic cells (23), we think that it modulates the action of both some NSAIDs and aspirin even in the endometrium, so the COX1 and 2, are not modulated, as well as PGE2, which remains high in such cells.The aim of this review is to propose a possible correlation between MRP4 and resistance to drugs used in chemotherapy for ovarian cancer, including cancers developed from endometriotic implants.
Our findings seem to support our idea of the possible correlation between MRP4 and resistance to drugs used in chemotherapy for ovarian cancer, including cancers developed from endometriosis implants.
So, it would be appropriate to assess whether the use of NSAIDs for endometriosis, might cause a resistance to chemotherapy, for possible development of ovarian cancer from endometrioma, to make it possible, in the future, to treat better patients with endometriosis and avoid a possible development of resistance to chemotherapy drugs because of NSAIDs.
Keywords: endometriosis, MRP4, ovarian cancer, NSAIDs

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INTRODUCTION
Endometriosis is an estrogen-dependent inflammatory disease (1). It is defined by the presence of a tissue similar to uterine endometrium that is located in places other than physiologically appropriate, uterine endometrial cavity, most commonly in the pelvic cavity, like the miometrial thickness, ovary, tubes, intestine, bladder, ureter, Douglas's cavity, uro-rectal septum, and many other sites which are distant, like lungs.(2). The lesion in the ovary is called endometrioma.
The most frequent symptoms are: chronic pelvic pain, dysmenorrhea, dyspareunia, and subfertility or infertility, these symptoms negatively affect the daily activities of women with endometriosis, and for this reason, patients use either aspirin or other no steroidal anti-inflammatory drugs NSAIDs (3).

Being one of the most common benign gynecological conditions,itaffects as many as 10–15% of premenopausal women (4), endometriosis is a debilitating disease with detrimental effects on social, occupational and psychological functioning.

Laparoscopy is the only diagnostic test that can reliably rule out endometriosis. Risk factors generally relate to exposure to menstruation: early menarche, late menopause, nulliparity and first pregnancy late in life increase the risk whereas the use of oral contraceptives reduce such risk.

Etiopathogenesis is not well known yet, there are three different hypothesis:

The "retrograde menstruation" theory, Sampson proposed that fragments of menstrual endometrium move towards the fallopian tubes and then become implanted on peritoneal surfaces and persist there (5).

The "coelomic metaplasia hypothesis", which proposes that the genesis of endometriotic lesions within the peritoneal cavity is the differentiation of mesothelial cells into endometrium-like tissue (6).

The "metastatic or embolic endometriosis", argues that menstrual tissue from the endometrial cavity travels to other sites through veins or lymphatic vessels (7).

"Retrograde menstruation" is the most accepted theory, and migrating, endometrium adheres and invades other tissues.

Different studies indicate that growth factors, cytokines, and prostaglandins promote the establishment and maintenance of endometriosis (8-9-10).

In fact, endometriosis and endometrium have molecular differences such as the overproduction of estrogen, prostaglandins, and cytokines in endometriotic tissue (11-12-13).

Prostaglandin E2 (PGE2) promotes adhesion, migration, invasion, proliferation, and survival of several types of cells, like the adhesion of human endometriotic epithelial cells 12Z and stromal cells 22B to collagen I, vibronectin, fibronectin, collagen IV, and laminin in a substrate- and epithelial-stromal cell-specific manner of the peritoneal extracellular matrix (ECM) (14).

Prostaglandins are produced from arachidonic acid through the path of cyclooxygenases 1 and 2, that are inhibited by aspirin and other NSAIDs. Some studies demonstrate that COX-2/PGE2 promote the pathophysiology and pathogenesis of endometriosis in humans (15).Therefore these drugs are useful for the treatment of pain and for the inhibition of both COX 1 and 2.

Another molecular difference between eutopic and ectopic endometrium is the overexpression of the multidrug resistance–associated protein 4 (MRP4) in endometriosis.

Multidrug resistance protein 4 (MRP4/ABCC4) is a plasma membrane transporter capable of the ATP-dependent efflux of a range of anionic compounds from cells (16).

MRP4 is especially elevated in peritoneal endometriosis, and it could be regulated by lipoxin A (LXA) (17).

Some studies indicated that several members of the multidrug resistance-associated protein (MRP) family mediate the transport of prostanoids. Particularly, A. Furugen, in his study, investigated the contribution of MRPs,including MRP1, MRP2, and MRP4, to the release process of the prostanoids from human lung adenocarcinoma epithelial A549 cells. Their results suggest that MRPs including MRP4 contribute to the release process of prostanoids in A549 cells (18).

MRP4 plays also a role in modulating some drugs (19).

Aspirin is a substrate for MRP4 and can be extruded from platelet through its transportation (20).

Other studies showed that MRP4 is involved in resistance to some drugs used for chemotherapy of ovarian cancer (21).

At the same time, studies have been published on aspirin resistance and because of MRP4 is over expressed in human endometriotic cells (22), we think that it modulates the action of both some NSAIDs and aspirin even in the endometrium, so the COX1 and 2, are not modulated, as well as PGE2, which remains high in such cells.

The aim of this review is to propose a possible correlation between MRP4 and resistance to drugs used in chemotherapy for ovarian cancer, including cancers developed from endometriotic implants.

There are several studies on the topics briefly described in the introduction: endometriosis and ovarian cancer, the role of prostaglandins and cyclooxygenases 1 and 2 in the pathophysiology and pathogenesis of endometriosis in humans, the role of aspirin and other NSAIDs for the therapy of endometriosis, the role of MRP4 in endometriosis and in drug resistance.

1- Endometriosis and ovarian cancer:

Endometriosis has recently received much attention as an important origin of cancer, especially in the ovary, that is the most common

site for endometriosis (23). Kobayashi's group has reported that the possible incidence of malignant transformation of ovarian endometriotic cysts is 0.7% (24).

Several investigators have suggested that endometriosis is a pre-cancer disease, in which endometrial ectopic cells may be cells with cancer-like characteristics that differentiate into neoplastic cells (25-26).

Ovarian cancers are classified according to the microscopic appearance of their structures (histology or histopathology). Histology dictates many aspects of clinical treatment, management, and prognosis. Ovarian cancers are histologically divided into four different classes:

Epithelial carcinoma is the most common type of ovarian cancer. It includes serous tumor, mucinous tumor, endometrioid tumor, clear cell adenocarcinoma, transitional cells carcinoma and others.

Sex cord stromal tumor.

Germ cell tumor.

Secondary ovarian cancer.

Although among various histological types of ovarian carcinoma, clear cell and endometrioid adenocarcinomas are known to arise frequently in ovarian endometriotic cysts (27).

Little is known about molecular basis of malignant change, Yamaguchi's group has disclosed that a high-iron microenvironment exists in ovarian endometriotic cysts, and that this may be related to clear cell carcinogenesis that is characterized by the expression of specific genes (28).

Many authors have studied the correlation between endometriosis and ovarian cancer.

L.A. Laman et al. (1965), was one of the first to describe the association between endometriosis and ovarian cancers. He published a work in which he describes endometriosis and the possible correlation with ovarian cancer and then he presents five clinical cases of carcinoma apparently developing in endometrial cysts of the ovary (29).

L.A. Laman et al. (1966), published another work with a review of literature and 7 clinical cases of carcinoma of the ovary, which developed within endometrial cysts, with consideration of the types of carcinomas and relations to other Mullerian epithelium. He discussed the difficulty in discerning associated endometriosis in extensive carcinoma and the finding of associated endometriosis in ovarian carcinomas (30).

M. Erzen et al. (1998), made a study to investigate the occurrence of ovarian cancer arising in ovarian endometriosis diagnosed in their laboratory, and the relation of the disease to the patient's age. Their results reported that the occurrence of ovarian cancer arising in ovarian endometriosis was most influenced by the patient's age, the extent of sampling and the consistency of histologic reports about the presence of endometriosis in ovarian adenocarcinoma (31).

S.W. Baxter et al. (2001), have investigated the hereditable genetics factors that contribute to the development of endometriosis, which is a putative precursor of the endometrioid and clear cell histological subtypes of ovarian cancer; they particularly studied the null genetic polymorphism in the gene encoding the glutathione S-transferases, GST, class mu (GSTM1) enzyme, that has been reported to be significantly elevated in patients with endometriosis and may represent an endometriosis susceptibility allele. (32).

T. Akahane et al. (2005), made a study where they determined the immunohistochemical expression of steroid hormone receptors and cancer-related genes in ovarian clear-cell carcinoma (OCCA)and ovarian endometrioid carcinomaOEMC specimens containing endometriosis and atypical endometriosis (33).

A. Kontoravdis et al. (2007), made a retrospective analysis to determine the prevalence of ovarian cancer and endometrial polyps in women with moderate and severe ovarian endometriosis. Their results showed that ovarian endometriosis may be associated with an increased incidence of both ovarian cancer and endometrial polyps, so they think that careful evaluation for coexistent pathology should be undertaken in women with symptoms (34).

M.S. Abrao et al. (2009), in his review article, wrote an update on the diagnostic, clinical and therapeutic knowledge and management of bowel implants of endometrial tissue, as well as on the relation to neoplastic processes, which aims to clarify their benign nature or possible potential for malignancy (35).

M. Mandai et al. (2009), made a review, where they analyzed molecular biology, pathology, and clinical management of ovarian cancer in endometriosis, and their conclusion is that the effective management of endometriosis remains a desirable goal for the prevention of endometriosis-associated ovarian cancerEAOC (36).

I.M. Matalliotakis et al. (2010), made a study, whose aim was to investigate the family risk of ovarian, colon and prostate cancer in women

with endometriosis, and their data suggest a familial association of endometriosis with those types of cancers (37).

A. Pacchiarotti et al. (2011) carried on a study, whose aim was to test the expression of the oct-4 and c-kit, both markers of stem cells, in the ectopic endometrial tissue of endometriotic lesions of women with severe endometriosis. Their findings show that ectopic epithelial cells express oct-4 and c-kit and this suggests that the ectopic endometrium in endometriosis has a stem cell origin and could explain the possible progression to ovarian cancer (38).

M.A. Merritt et al. (2012), made a case–control study to evaluate risk factors whose associations differ among subgroups of invasive epithelial ovarian cancer (EOC) defined by the dualistic model (type I/II). Type I tumors (low-grade serous, low-grade endometrioid, clear cell and mucinous carcinomas) are thought to arise in a stepwise manner from a precursor lesion, generally exhibits lower rates of cell proliferation and a gradual increase in chromosomal instability, tend to have a better prognosis and harbor a variety of somatic mutations. On the contrary, type II tumors (high-grade serous carcinoma, high-grade endometrioid as well as malignant, mixed mesodermal tumors and undifferentiated carcinomas) tend to develop rapidly, metastasize early and are usually associated with a poor prognosis. Their results suggest that a history of endometriosis increased the risk for a type I tumor while strong protective factors for type I tumors included parity and having a previous tubal ligation or hysterectomy, and the risk for type II tumors, increase with older age and a higher number of ovulatory cycles (39).

Y. Chen et al. (2103), wrote a work whose aim was to report a case of malignant transformation from residual endometriosis following hysterectomy and bilateral salpingooophorectomy in a female patient with a positive family history of ovarian and colon cancer resulting from residual endometriosis (40).

J. Kotsopoulos et al. (2013), evaluated ovarian cancer risk factors in relation to dominant and non-dominant tumors, their results suggest that dominant tumors were more likely to be mucinous, endometrioid, or clear cell, whereas non-dominant tumors were more likely to be serous. Tubal ligation, two or more births, endometriosis, and age were more strongly associated with dominant rather than non-dominant tumors (41).

A missense single-nucleotide polymorphism (SNP) in the immune modulatory gene IL1A, rs1761, has been reported to be associated with increased susceptibility to endometriosis in two independent case-control studies in a Japanese population (42).

B. Charbonneau et al. (2013), reported that these missense SNP, rs17561, in the IL1A gene, is significantly associated also with clear cell, mucinous, and endometrioid ovarian cancer risk, the two tumors related with endoemtriosis (43).

L. N. Heidemann et al. (2014), carried on an electronic literature search in PubMed and he identified 1112 articles dealing with the relation between endometriosis and ovarian cancer, to assess the quality of the literature regarding the association between endometriosis and ovarian cancer and to estimate the extent of this relation. His results confirm that there is sufficient evidence to conclude that there is an increased risk of developing clear-cell and endometrioid epithelial ovarian cancer for women with histologically verified endometriosis (44).

Endometriosis is associated with an increased risk of ovarian cancer and few studies have also shown increased risk of breast cancer (45). It's also well known that BRCA1/2 mutations are linked to an increased risk of breast and ovarian cancers but their relation to endometriosis is unknown.

S. Aviel-Ronen et al. (2014), for this reason, carried on a study to examine the mutation rate of BRCA1/2 among women with surgically treated ovarian endometriosis. His results show that BRCA1/2 mutation rates in patients with endometriotic ovarian cysts and with non-endometriotic ovarian cysts are similar (46).

S. Ye et al. (2014), in his study, analyzed and compared the clinicopathological features and prognosis of ovarian clear cell carcinoma (CCC) with or without endometriosis in Chinese patients, their results show that patients with ovarian CCC and coexisting endometriosis had distinct clinicopathological features and better survival outcome. However, endometriosis did not confer a better survival (47).

D. Torres et al. (2014), presented the first case of a clear cell adenocarcinoma arising from foci of ectopic endometrial tissue in an adenomyoma of the broad ligament. It supports the association between endometriomas and clear cell adenocarcinoma. Therefore, patients with a significant history of endometriosis may benefit from close follow-up or definitive surgery (48).

B. Nakakita et al. (2014), described a case of cell carcinoma arising from a uterus-like mass located in the retroperitoneal space. The patient had a diagnosis of an ovarian endometriotic cyst for 14 years until ultrasonography and magnetic resonance imaging (MRI) demonstrated an enlargement of the cystic mass with a thickened irregular wall (49).

S.Suryawanshi et al. (2014), performed a comprehensive immune gene expression analysis of pelvic inflammation in endometriosis and endometriosis associated ovarian cancer (EAOC)(50).

Endometriosis and PGE2:

Some studies demonstrating that COX-2/PGE2 promote the pathophysiology and pathogenesis of endometriosis in humans (51).

E. Attar et al. (2006), in their review described some molecular aspects involved in endometriosis. They emphasize high estradiol (E2) in endometriotic lesions. Both genes steroidogenic acute regulatory protein (StAR) and aromatase are essential for E2 production. PGE2, that is produces from arachidonic acid through cyclo-oxygenase-2 (COX-2), is a potent stimulator of both genes StAR and aromatase and COX-2 in turn it is stimulated by E2, interleukin-1 (IL-1) and PGE2 itself in endometrial and endometriotic cells. Thus, there is a positive feedback loop that favors continuous formation of E2 and PGE2 in endometriosis (52).

P.C. Chuang et al. (2006), described some molecular aspects of endometriosis. They demonstrated that PGE2 can directly induce FGF-9 expression via a novel signaling pathway involving EP3, PKC, and a member of the ETS domain-containing transcription factor superfamily in primary human endometriotic stromal cells. This is important because aberrant expression of FGF-9 also results in the evolution of many human diseases, such as cancers and endometriosis (53).

Cyclooxygenases 1 and 2 that are inhibited by aspirin and other NSAIDs therefore these drugs are useful for pain treatment and for COX 1 and 2 inhibition.

Endometriosis and MRP4:

Another molecular difference between eutopic and ectopic endometrium is the overexpression of the multidrug resistance–associated protein 4 (MRP4) in endometriosis.

S.K. Banu at al. (2008), in their study, determined the expression of COX-2 protein in ectopic and eutopic endometria in humans and the role of COX-2 in endometriotic cell survival, migration, and invasion in humans. Their results indicate that COX-2 protein is abundantly expressed in ectopic endometrium compared with eutopic endometrium. Consequently also PGE2 is high. Comparatively, expression of COX-2 protein is higher in eutopic endometria in women with endometriosis compared with women without endometriosis. They inhibited COX-2, and the results were the decrease of survival, migration, and invasion of endometriotic cells that are associated with decreased production of PGE. Their results support the emerging concept that COX-2/PGE2 promotes the pathophysiology and pathogenesis of endometriosis in humans (54).

J.H. Lee et al. (2013) made a similar study, where they showed that the inhibition of PTGER2 and PTGER4, in vitro, inhibits adhesion of human endometriotic epithelial cells 12Z and stromal cells 22B to collagen I, vibronectin, fibronectin, collagen IV, and laminin in a substrate and epithelial-stromal cell-specific manner of the peritoneal extracellular matrix (ECM) (55).

I. Gori et al. (2013), made a study to compare the expression of the prostaglandin (PG) E2 transporter multidrug resistance–associated protein 4 (MRP4) in eutopic and ectopic endometrial tissue from endometriosis patients with that of control subjects and to examine whether MRP4 is regulated by the anti-inflammatory lipid lipoxin A4 (LXA4) in endometriotic epithelial cells. They report for the first time that MRP4 is expressed in human endometrium, elevated in peritoneal endometriosis, and modulated by LXA4 in endometriotic epithelial cells (56).

MRP4 and aspirin resistance:

There are several studies on aspirin resistance, especially in modulating aspirin action on human platelets, and according to one of our studies also in human endometriotic epithelial cells.

T. Mattiello et al. (2011), carried on a study to investigate the role of multidrug resistance protein-4 (MRP4), in modulating aspirin action on human platelets cyclooxygenase (COX)-1. Their results suggest that Aspirin is a substrate for MRP4 and can be extruded from platelet through its transportation. Aspirin effect on COX-1 is little related to MRP4-mediated aspirin transport in healthy volunteers, but in coronary artery bypass graftingpatients with MRP4 over-expression, its pharmacological inhibition enhances aspirin action in an efficient way (57).

MRP4 and chemotherapy resistance:

Many authors have studied the role of mrp4 in the resistance of drugs used for chemotherapy in

ovarian cancer and other tumors.

P. Borst et al. (2000), described that MRP4 overexpression is associated with high-level resistance to the nucleoside analogues 9-(2-phosphonylmethoxyethyl) adenine and azidothymidine, both of which are used as antihuman immunodeficiency virus drugs. MRPs may, therefore, also have a role in resistance against nucleoside analogues used in cancer chemotherapy (58).

T. Oguri et al. (2001), made a study to investigate the roles played by the multidrug resistance- associated protein (MRP1) homologues MRP3 and MRP4 in resistance to platinum drugs. MRP4 expression has been investigated in cancer cell lines and drug-resistant cell lines, but, unlike MRP3, it has not been found to be overexpressed in any of the drug-resistant cell lines. Their report indicated that MRP4 did not contribute to drug resistance and found no induction of MRP4 by platinum drugs (59).

M. Leggas et al. (2004), have studied the role of mrp4 in anticancer therapy with topotecan agent for tumors used for the central nervous system (CNS), they have shown that Mrp4 restricts the penetration of anticancer agent topotecan in the brain. Furthermore, their findings illustrate that Mrp4 overexpression in tumor cells can limit drug penetration and confer topotecan resistance (60).

Q. Tian et al. (2005), made a study, to evaluate if MRP4 is involved in the chemotherapy resistance. Their results confirm that Human MRP4 gives a significant resistance to cyclophosphamide, CPT, CPT-11, SN-38, rubitecan, and 10-OH-CPT. CPT-11 and SN-38 are substrates for MRP4 (61).

C.L. Dai et al. (2009), made a study to characterize the in vitro and in vivo actions of FG020326, a newly synthesized triaryl-substituted imidazole derivative, to reverse MDR, because the effectiveness of chemotherapeutic treatment is usually limited by the overexpression of adenosine triphosphate binding cassette (ABC) transporters, which mediate multidrug resistance (MDR) by acting as efflux pumps to remove chemotherapeutic agents from MDR cancer cells. Thus, the inhibition of ABC transporters may represent a promising strategy to reverse MDR (62).

G.L. Beretta et al. (2010), made a study, to investigate the molecular bases of resistance to platinum (Pt) drugs. They showed that the overexpression of fully glycosylated MRP1 or MRP4 in tumor cell line of ovarian origin was associated with resistance to oxaliplatin and cisplatin and that the development of resistance to oxaliplatin results in up-regulation of MRPs, they support that patients with oxaliplatin-refractory ovarian carcinomas may benefit from non-Pt-based regimens which do not contain MRP1 and MRP4 substrates (63).

Y.H. Zhang et al. (2010), have studied mrp4 and cisplatin (DDP) resistant cell line (SGC7901/DDP) from a Chinese gastric cancer cell line (SGC7901), they showed that acquired resistance of gastric cancer cell to DDP is mediated by over-expression of MRP4 and could be reversed by silencing MRP4 (64).

M. Bagnoli et al. (2013), made a study to examine the prognostic role of transporters of the MRP family, and the results suggest that in epithelial ovarian cancer, MRP1 may be a marker for aggressiveness because its expression was associated with tumor grade and support that MRP4 may play an unfavorable role in disease outcome (65).

A. Gradilone et al. (2014), carried on a study, to describe a paradoxical effect of celecoxib at clinically relevant concentration in lung cancer cell lines, i.e., the induction of MRP-4 expression, their preliminary results, besides suggesting that the efficacy of celecoxib in combination with standard chemotherapy may be strictly dependent on the type of drug regimen used, recommend that celecoxib-dependent induction of MRP-4 should be always taken into consideration before planning drug choice in lung cancer patients, to exclude the administration of celecoxib in combination with drugs (irinotecan, topotecan), which are substrate for MRP-4 (66).

CONCLUSION

These results demonstrated various scientific evidence that correlate ovarian cancer, particularly the endometrioid and clear cell tumor with endometriosis.

Minor evidence shows that the endometriosis is related to prostaglandin E2 and consequently the cyclooxygenase, suggesting the importance of the role of NSAIDs, and shows that MRP4 is increased in endometriosis.

At the same time studies have been published on aspirin resistance and because MRP4 is over expressed in human endometriotic cells (67), we think that it modulates the action of some NSAIDs and aspirin even in the endometrium, so COX1 and 2, are not modulated, as well as PGE2, which remains high in such cells.

These findings seem to support our idea of the possible correlation between MRP4 and

resistance to drugs used in chemotherapy for ovarian cancer, including cancers developed from endometriotic implants.

So, it would be appropriate to assess whether the use of NSAIDs for endometriosis, might cause a resistance to chemotherapy, for possible development of ovarian cancer from endometrioma, to make it possible, in the future, to treat better patients with endometriosis and avoid a possible development of resistance to chemotherapy drugs because of NSAIDs.

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