EJGO European Journal of Gynaecological Oncology

Prevalence of endometriosis in epithelial ovarian cancer. Analysis of the associated clinical features and study on molecular mechanisms involved in the possible causality

F. Machado-Linde[1], M.L. Sánchez-Ferrer[1], P. Cascales[2], A. Torroba[3], R. Orozco[1], Y. Silva Sánchez[1], A. Nieto[1], G. Fiol[4]

[1]Department of Gynecology and Obstetrics, University Hospital Virgin Arrixaca, Murcia
[2]Department of General Surgery, University Hospital Virgin Arrixaca, Murcia
[3]Department of Pathology, University Hospital Virgin Arrixaca, Murcia
[4]Department of Gynecology and Obstetrics, Hospital Torrecardenas, Almeria (Spain)

Summary

Purpose of investigation: To determine the prevalence of endometriosis in patients with epithelial ovarian cancer and explore the differences between women with endometrioid and clear-cell histologic subtypes with and without associated endometriosis. *Materials and Methods:* The medical charts of 496 patients with epithelial ovarian cancer at the Hospital Virgin de la Arrixaca (Murcia, Spain) between 1971 and 2010 were reviewed. *Results:* Endometriosis was present in 27 (5.4%) of the 496 cases ($p < 0001$), and was associated with the endometrioid histotype in 13/45 cases (29%) and with the clear cell histotype in 7/22 (32%). The prevalence of an association with endometriosis according to histologic type was 28.8% (13/45) for endometrioid carcinoma and 31.8% (7/22) for clear-cell carcinoma. *Conclusion:* Both endometrioid and clear-cell ovarians tumours are associated with pelvic endometriosis. Patients with endometiosis associated ovarian cancer differ from non-endometiosis associated ovarian cancer in their clinical characteristics.

Key words: Endometriosis; Ovarian cancer.

Introduction

Endometriosis is an estrogen-dependent inflammatory disease defined by the presence and growth of foci in endometrial tissue (stroma and glands) outside the uterine cavity [1]. The most common anatomic site of endometriosis is the pelvic peritoneum and the ovarian surface, which leads to adhesions, chronic pelvic pain, and infertility [2]. The prevalence of endometriosis is 7% to 15% among women of childbearing potential, but as high as 25% to 30% in infertile women and up to 40% to 70% in women with chronic pelvic pain [3]. The exact etiopathology is unknown. The theory most widely accepted is Sampson's classic theory on menstrual reflux through the fallopian tubes [4]. Although considered a benign disease, endometriosis presents some characteristics that resemble malignant neoplasms, such as the development of local and distant sites and the invasion of other target organs [5]. Additionally, several studies have consistently shown that endometriosis is associated with a higher risk of epithelial ovarian cancer [6-12]. This association is predominantly related to the clear-cell and endometrioid histologic subtypes of ovarian cancer [13]. However, not all authors confirm the association of endometriosis with ovarian cancer [14]. This study focused on the prevalence of endometriosis in patients who underwent surgery for ovarian cancer at the present hospital between 1971 and 2010.

Material and Methods

The study reviewed the anatomic pathology (AP) reports and medical histories of all patients operated for ovarian cancer ($n = 496$) from 1971 to 2010 in the Obstetrics and Gynecology Department of the Hospital Clínico Universitario Virgin de la Arrixaca (Murcia, Spain). Patients with ovarian tumor of low malignant potential were excluded from this study. The ovarian cancers were histologically classified according to the World Health Organization classification of ovarian tumors [15]. Concomitant endometriosis was determined by a review of the AP reports and the presence of glandular epithelium accompanied by endometrial stroma as described in the reports. The association of ovarian cancer and endometriosis was defined according category C by Van Gorp *et al.* [16]: *C)* ovarian cancer with concomitant endometriosis at any site in the pelvis: endometriosis in both ovaries, in the contralateral ovary, extragonadal, or unspecified lateralization or lesion site. The following variables were also collected from the patients' medical history: age, parity, menopausal status at the time of surgery, and disease stage. Tumors were staged according to the International Federation of Gynecology and Obstetric (FIGO) criteria [17]. Patients were grouped into two categories according to surgical staging: early stage (FIGO Stages I

Revised manuscript accepted for publication November 14, 2013

Table 1. — *Frequency (in percentage) of ovarian cancer cases with endometriosis according to histologic subtype and selected characteristics in Murcia, Spain from 1971 to 2010.*

Factors		OCE	C6CAE	CCNAE	EAE	ENAE	OAE
	Patients n=496	27 (5.4%)	7 (25.9%)	15 (68.1%)	13 (48.1%)	32 (71.1%)	7 (25.9%)
Age (mean ± standard deviation)	51 (±13)	51 (±13.9)	55.1 (±11)	55 (±12.9)	53.8 (±15.9)	50.9 (±11.5)	41.5 (±8.7)
FIGO, Stage I/II			83%	53%	75%	42.3%	28%
Postmenopausal		55.5%	85.7%	78.6%	53.8%	37.5%	28.6%
Nulliparous			42.8%	26.6%	30.8%	24.2%	42.9%

Abbreviations: OCE: ovarian cancer associated to endometriosis; CCAE: clear cell associated to endometriosis; CCNAE: clear cell not associated to endometriosis; EAE: Endometrioid associated to endometriosis; ENAE: Endometrioid not associated to endometriosis; OAE: another (histologic subtype) associated to endometriosis.

and II) or advanced stage (Stages III and IV). The authors performed a descriptive study, in which numeric variables were described as mean ± SD. The qualitative variables are summarized as frequencies and percentages. For the comparative studies, the authors used the Pearson chi-squared test to analyze associations between qualitative variables and the Student *t* test for comparisons of means. Statistical significance was set at $p < 0.05$. SPSS 18.0 was used for the statistical analysis.

Results

A total of 496 cases of ovarian cancer were treated at the present hospital over 39 years; endometrioid and clear-cell histologic subtypes were identified in 45 (9.%) and 22 patients (4.4%), respectively. An association between ovarian cancer and endometriosis was found in 27 cases (5.4%) ($p < 0.001$). Among the 45 patients with endometrioid carcinoma, association with endometriosis was found in 13 (28.8%), which accounted for 2.6% of all ovarian cancers in the series and 48.1% ($p < 0.079$) of all ovarian cancers associated with endometriosis. Regarding clear-cell carcinoma, the presence of endometriotic tissue was observed in 7/22 cases (31.8%), specifically in 1.4% of all cancers and 25.9% ($p < 0.627$) of cancers associated with endometriosis, respectively. The other 7/27 (25.9%) cases of ovarian cancer associated with endometriosis presented different histologic types with no clear predominance.

The mean age of the series ($n = 496$) was 51.4 (±11.9) years. Patients with ovarian cancer associated with endometriosis presented a mean age of 51 (±13.9) years. In patients with endometrioid carcinoma, the mean age was 50.9 (±11.5) years in those without endometriosis and 53.8 (±15.9) years in those with endometriosis associated with their cancer. In the clear-cell subtype, the mean age was 55.1 (±11) years when endometriosis was present and 55 (±12.9) years in cases without endometriosis. In the group of "other histologic types" associated with endometriosis, the mean age was 41.5 (±8.7) years. Among patients with ovarian cancer associated with endometriosis, 55.5% were menopausal. In patients with endometrioid carcinoma, 53.8% of those associated with endometriosis were menopausal compared to 37.5% without endometriosis. In clear-cell carcinoma, 85.7% of patients with endometriosis and 78.6% of those without endometriosis were menopausal. Nulliparous patients accounted for 24.2% of patients with endometrioid carcinoma but no endometriosis and 30.8% of patients with endometrioid carcinoma and endometriosis. In clear-cell carcinoma patients, 26.6% of those without endometriosis had no offspring, compared to 42.8% in those with endometriosis. Lastly, 42.3% (11/26, unknown stage in six cases) of patients with endometrioid carcinoma not associated with endometriosis presented an early stage of the disease (FIGO Stage I/II) versus 75% (9/12, unknown stage in one case) of cases associated with endometriosis. In patients with clear-cell carcinoma, 53% (7/13; unknown stage in two cases) presented early stage when the cancer was not associated with endometriosis compared to 83% (5/6; unknown stage in one case) when associated with endometriosis. A total of 2/7 (28%) patients diagnosed with other tumors associated with endometriosis presented early stage (Table 1 summarizes the results).

Discussion

The incidence of endometriosis in ovarian cancer in the present series was 5.4% ($p < 0.0001$), a figure within the range reported by other authors (4%-29%) [18]. These findings are difficult to interpret because the actual incidence of endometriosis is unknown. The true incidence is generally agreed to be around 10% of women of childbearing potential [3] and, therefore, the association of endometriosis with ovarian cancer would be in a similar range to that of the general population. In the present series, as in most published series, the histologic types of epithelial ovarian cancer most commonly associated with endometriosis were endometrioid carcinoma (48%) and clear-cell carcinoma (25.9%) [19, 20]. The association with certain histologic types is the most relevant evidence in establishing a causality relationship between ovarian cancer and endometriosis. Although this may seem to be proven, there are two important aspects to consider before this evidence is applied to daily clinical practice in patients with endometriosis. Firstly, the endometrioid and clear-cell histologic types of ovarian cancer are rare, in the

present series accounting for 4.4% and 9% of total cases. When related to the total sample, association with endometriosis was even more rare: 2.6% of endometrioid type and 1.4% of clear-cell type of ovarian cancers treated in this series. Secondly, although some evidence already indicates that atypical endometriosis may be the precursor of these two histologic types of ovarian cancer, it is still not conclusive [21]. Some authors have identified a mutation of the ARID1A tumor-suppressor gene in endometrioid and clear-cell carcinoma samples and in adjacent endometrial tissues [22, 23]. These genetic alterations have also been observed in endometrioid tissues not associated with ovarian cancer, particularly in endometriosis [24]. However, confirmation that the endometrial tissue in which these molecular abnormalities develop is a premalignant lesion would require comparing them to samples from the same patients who develop ovarian cancer years later. Wiegand *et al.* [25] reported the case of a patient diagnosed with atypical endometriosis who showed reduced BAF250 expression and presented endometrioid carcinoma at the same site two years later, although the lesion was possibly already present and simply unnoticed. Ayhan *et al.* [26] recently reported that in 31 of 47 cases of endometrioid and clear-cell carcinoma associated with endometriosis, they found a decrease in ARID1A immunoreactivity in the carcinoma and epithelium of the endometriotic cyst adjacent to the carcinoma, but not in the epithelium of the cyst not adjacent to the tumor.

In the present series, the authors found no statistical differences between the endometrioid and clear-cell histologic types in the clinical parameters analyzed: age, menopausal status, and parity. However, they observed that the percentage of nulliparous women was higher among patients with ovarian cancer associated with endometriosis (for both clear-cell and endometrioid subhistologic types) than among those with no associated endometriosis. These data are consistent with those published by other authors. Nevertheless, it is not clear if sterility or endometriosis is the true risk factor, because endometriosis is itself a cause of sterility [27, 28]. A case-control study by Nagle *et al.* [29] compared endometrioid and clear-cell carcinoma, but not in relation to endometriosis association, and found a higher risk for both histologic types in patients with endometriosis and a lower risk in patients with at least one term pregnancy. Therefore, it is unclear if this lower parity-related risk can be attributed to the protective effect of pregnancy on ovarian cancer or if the presence of endometriosis, known to cause sterility, raises the risk [30, 31]. Similar to reports published by other authors [27, 32], patients with endometrioid carcinoma were somewhat younger than those who presented clear-cell carcinoma, a difference that was more pronounced in endometrioid carcinoma associated with endometriosis in the present study. In terms of menopausal status, both Nagle *et al.* [29] and the present studies found a high number of menopausal patients, but the authors observed that the percentage was higher when both histologic types were associated with endometriosis (53% vs, 37.5% in endometrioid and 85% vs. 78% in clear-cell). Orezzoli *et al.* [33] studied clear-cell carcinoma based on an association with endometriosis and observed a higher percentage of menopausal and nulliparous patients among patients with clear-cell carcinoma associated with endometriosis, compared to those not associated with endometriosis.

In the present series, patients with endometrioid carcinoma presented less advanced (Stages I/II) disease compared to patients diagnosed with clear-cell carcinoma. These findings are similar to other publications that report a more somber prognosis for clear-cell carcinoma [34]. Thus, the present authors observed that the percentage of patients in early stage was higher in both histologic types when concomitant with endometriosis. Other authors also reported a better prognosis for cancer associated with endometriosis [29, 35].

In a Swedish cohort study, Melin *et al.* [36] studied the repercussions of endometriosis on the prognosis of various malignant diseases. They reported greater survival among patients with endometriosis, particularly in patients with breast or ovarian cancer; however, the presence of endometriosis casts a shadow over the prognosis of patients with melanoma. Nonetheless, the repercussions of endometriosis coexistence with ovarian cancer on prognosis are still debated. Cuff *et al.* [28] studied clear-cell and endometriod carcinomas, but found no significant relationship between disease-free survival and the presence of endometriosis. In this regard, Katagiri *et al.* [37] considered the finding of the ARID1A gene mutation in clear-cell carcinoma to be a negative prognostic factor, as its presence determines a higher rate of resistance to platinum-based chemotherapy and a shorter disease-free period. Furthermore, as the present authors have stated, some findings [22, 24] reveal an important correlation between the ARID1A mutation and endometrioid and clear-cell ovarian carcinomas and between these two types of carcinomas and atypical endometriosis. Consequently, the current findings are controversial. The presence of the ARID1A gene mutation may be related to poorer response to treatment in clear-cell carcinoma [35] or to a more promising prognosis in clear-cell and endometrioid carcinomas associated with endometriosis [33]. Other authors have found no endometriosis-related differences in the prognosis of these ovarian cancer histiotypes [32].

Conclusion

In conclusion, although the present study was descriptive and retrospective and, therefore, had all the limitations common to these types of studies, the series confirms a significant association between endometrioid or clear-cell ovarian cancer and endometriosis. Despite this, there is currently no evidence to suggest a change in the treatment of endometriosis in clinic practice.

References

[1] Bulun S.E.: "Endometriosis". *N. Engl. J. Med.*, 2009, *360*, 268.

[2] Jenkins S., Olive D.L., Haney A.F.: "Endometriosis: pathogenic implications of the anatomic distribution". *Obstet. Gynecol.*, 1986, *67*, 335.

[3] Missmer S.A., Cramer D.W.: "The epidemiology of endometriosis". Obstet. Gynecol. *Clin. North Am.*, 2003, *30*, 1.

[4] Sampson J.A.: "Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity". *Am. J. Obstet. Gynecol.*, 1927, *14*, 422.

[5] Garry R.: "Endometriosis: an invasive disease". *Gynecol. Endosc.*, 2001, *10*, 79.

[6] Rossing M.A., Cushing-Haugen K.L., Wicklund K.G., Doherty J.A., Weiss N.S.: "Risk of epithelial ovarian cancer in relation to benign ovarian conditions and ovarian surgery". *Cancer Causes Control*, 2008, *19*, 1357.

[7] Brinton L.A., Gridley G., Persson I., Baron J., Bergqvist A.: "Cancer risk after a hospital discharge diagnosis of endometriosis". *Am. J. Obstet. Gynecol.*, 1997, *176*, 572.

[8] Ness R.B., Cramer D.W., Goodman M.T., Kjaer S.K., Mallin K., Mosgaard B.J., *et al.*: "Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies". *Am. J. Epidemiol.*, 2002, *155*, 217.

[9] Wu A.H., Pearce C.L., Tseng C.C., Templeman C., Pike M.C.: "Markers of inflammation and risk of ovarian cancer in Los Angeles County". *Int. J. Cancer*, 2009, *124*, 1409.

[10] Melin A., Sparén P., Persson I., Bergqvist A.: "Endometriosis and the risk of cancer with special emphasis on ovarian cancer". *Hum. Reprod.*, 2006, *21*, 1237.

[11] Borgfeldt C., Andolf E.: "Cancer risk after hospital discharge diagnosis of benign ovarian cysts and endometriosis". *Acta Obstet. Gynecol. Scand.*, 2004, *83*, 395.

[12] Brinton L.A., Sakoda L.C., Sherman M.E., Frederiksen K., Kjaer S.K., Graubard B.I., *et al.*: "Relationship of benign gynecologic diseases to subsequent risk of ovarian and uterine tumors". *Cancer Epidemiol. Biomarkers Prev.*, 2005, *14*, 2929.

[13] Ness R.B.: "Endometriosis and ovarian cancer: thoughts on shared pathophysiology". *Am. J. Obstet. Gynecol.*, 2003, *189*, 280.

[14] Olson J.E., Cerhan J.R., Janney C.A., Anderson K.E., Vachon C.M., Sellers T.A.: "Postmenopausal cancer risk after self-reported endometriosis diagnosis in the Iowa Women's Health Study". Cancer, 2002, *94*, 1612.

[15] Scully R.E.: "Histological typing of ovarian tumors". 2nd ed. New York: Springer-Verlag, 1999.

[16] Van Gorp T., Amant F., Neven P., Vergote I., Moerman P.: "Endometriosis and the development of malignant tumours of the pelvis. A review of literature". *Best Pract. Res. Clin. Obstet. Gynecol.*, 2004, *18*, 349.

[17] FIGO Committee on Gynecologic Oncology: "Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia". *Int. J. Gynaecol. Obstet.*, 2009, *105*, 3.

[18] Somigliana E., Vigano' P., Parazzini F., Stoppelli S., Giambattista E., Vercellini P.: "Association between endometriosis and cancer: a comprehensive review and a critical analysis of clinical and epidemiological evidence". *Gynecol. Oncol.*, 2006, *101*, 331.

[19] Viganò P., Somigliana E., Parazzini F., Vercellini P.: "Bias versus causality: interpreting recent evidence of association between endometriosis and ovarian cancer". *Fertil. Steril.*, 2007, *88*, 588.

[20] Pearce C.L., Templeman C., Rossing M.A., Lee A., Near A.M., Webb P.M. *et al.*: "Ovarian Cancer Association Consortium. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies". *Lancet Oncol.*, 2012, *13*, 385.

[21] Munksgaard P.S., Blaakaer J.: "The association between endometriosis and ovarian cancer: a review of histological, genetic and molecular alterations". *Gynecol. Oncol.*, 2012, *124*, 164.

[22] Wiegand K.C., Shah S.P., Al-Agha O.M., Zhao Y., Tse K., Zeng T., Senz J., *et al.*: "ARID1A mutations in endometriosis-associated ovarian carcinomas. N Engl J Med 2010; 363: 1532-43.

[23] Samartzis E.P., Samartzis N., Noske A., Fedier A., Caduff R., Dedes K.J., *et al*.: "Loss of ARID1A/ BAF250a-expression in endometriosis: a biomarker for risk of carcinogenic transformation?" *Mod. Pathol.*, 2012, *25*, 885.

[24] Yamamoto S., Tsuda H., Takano M., Tamai S., Matsubara O.: "PIK3CA mutations and loss of ARID1A protein expression are early events in the development of cystic ovarian clear cell adenocarcinoma". *Virchows Arch.*, 2012, *460*, 77.

[25] Wiegand K.C., Lee A.F., Al-Agha O.M., Chow C., Kalloger S.E., Scott D.W., *et al.*: "Loss of BAF250a (ARID1A) is frequent in high-grade endometrial carcinomas". *J. Pathol.*, 2011, *224*, 328.

[26] Ayhan A., Mao T.L., Seckin T., Wu C.H., Guan B., Ogawa H., *et al.*: "Loss of ARID1A expression is an early molecular event in tumor progression from ovarian endometriotic cyst to clear cell and endometrioid carcinoma". *Int. J. Gynecol. Cancer*, 2012, *22*, 1310.

[27] Brinton L.A., Melton L.J. 3rd., Malkasian G.D. Jr., Bond A., Hoover R.: "Cancer risk after evaluation for infertility". *Am. J. Epidemiol.*, 1989, *129*, 712.

[28] Ness R.B., Cramer D.W., Goodman M.T., Kjaer S.K., Mallin K., Mosgaard B.J., *et al.*: "Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies". *Am. J. Epidemiol.*, 2002, *155*, 217.

[29] Nagle C.M., Olsen C.M., Webb P.M., Jordan S.J., Whiteman D.C., Green A.C., *et al.*: "Endometrioid and clear cell ovarian cancers: a comparative analysis of risk factors". *Eur. J. Cancer*, 2008, *44*, 2477.

[30] de Ziegler D., Borghese B., Chapron C.: "Endometriosis and infertility: pathophysiology and management". *Lancet*, 2010, *376*, 730.

[31] Merritt M.A., De Pari M., Vitonis A.F., Titus L.J., Cramer D.W., Terry K.L.: "Reproductive characteristics in relation to ovarian cancer risk by histologic pathways". *Hum. Reprod.*, 2013, *28*, 1406. doi: 10.1093/humrep/des466. Epub 2013 Jan 12.

[32] Cuff J., Longacre T.A.: "Endometriosis does not confer improved prognosis in ovarian carcinoma of uniform cell type". *Am. J. Surg. Pathol.*, 2012, *36*, 688.

[33] Orezzoli J.P., Russell A.H., Oliva E., Del Carmen M.G., Eichhorn J., Fuller A.F.: "Prognostic implication of endometriosis in clear cell carcinoma of the ovary". *Gynecol. Oncol.*, 2008, *110*, 336.

[34] Chan J.K., Teoh D., Hu J.M., Shin J.Y., Osann K., Kapp D.S.: "Do clear cell ovarian carcinomas have poorer prognosis compared to other epithelial cell types? A study of 1411 clear cell ovarian cancers". *Gynecol. Oncol.,* 2008, *109*, 370.

[35] Kumar S., Munkarah A., Arabi H., Bandyopadhyay S., Semaan A., Hayek K., et al.: "Prognostic analysis of ovarian cancer associated with endometriosis". *Am. J. Obstet. Gynecol.*, 2011, *204*, 63.e1.

[36] Melin A., Lundholm C., Malki N., Swahn M.L., Sparen P., Bergqvist A.: "Endometriosis as a prognostic factor for cancer survival". *Int. J. Cancer*, 2011, *129*, 948.

[37] Katagiri A., Nakayama K., Rahman M.T., Katagiri H., Nakayama N., Ishikawa M., *et al.*: "Loss of ARID1A expression is related to shorter progression-free survival and chemoresistance in ovarian clear cell carcinoma". *Mod. Pathol.*, 2012, *25*, 282.

Address reprint requests to:
M.L. SÁNCHEZ FERRER, M.D.
Department of Gynecology and Obstetrics,
University Hospital Virgin Arrixaca
30120 Murcia (Spain)
e-mail: marisasanchezferrer1@gmail.com