Gynecology and Minimally Invasive Therapy 6 (2017) 152–156

Contents lists available at ScienceDirect

Gynecology and Minimally Invasive Therapy

journal homepage: www.e-gmit.com

Review article

Clinical implication for endometriosis associated with ovarian cancer

Pao-Ling Torng*

Department of Obstetrics and Gynecology, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 30 April 2017
Received in revised form
5 August 2017
Accepted 7 August 2017
Available online 30 August 2017

Keywords:
Endometriosis
Epithelial ovarian cancer
Malignant transformation

ABSTRACT

We reviewed current literature regarding the association of endometriosis and epithelial ovarian cancer based on epidemiology studies, molecular researches and clinical observations. Our methods include a review of literature research of MEDLINE, PubMed, Cochrane Library of Systematic Reviews and reference search in selected papers. The life time risk of epithelial ovarian cancer in women with endometriosis is low, yet there might be a cluster of individuals who have higher risk of developing epithelial ovarian cancer from endometriosis. Endometriosis associated ovarian cancer (EAOC) is predominant in particular histological subtypes of epithelial ovarian carcinoma and are related to some specific molecular aberrations. Clinical observations showed age as an important variable to the development of EAOC. Rapid growth of tumor and solid components in sonography are key features to detect malignant transformation of endometriosis. Evidence is not clear about prophylactic oophorectomy in preventing EAOC in patients with endometriosis. This review provided rationale data for identifying, monitoring, counseling and management of women with endometriosis who are potentially high risk for malignant transformation.

Introduction

Endometriosis is a common gynecologic disease. The estimated frequency among women of reproductive age is 6–10%,[1] and is particular frequent among women with pelvic pain and infertility.[2] It is characterized by endometrial-like tissue outside the uterus, primarily on the pelvic peritoneum, ovaries, and rectovaginal septum, and in rare cases on the diaphragm, pleura, and pericardium.[2]

Endometriosis occurred concomitantly with ovarian cancer, denoted as endometriosis associated ovarian cancer (EAOC), has been documented since the first description of such a condition by Sampson in 1925.[3] Evidence of malignant transformation of endometriosis was approved by demonstrating direct origin of carcinoma from an endometriotic focus.[3] Multiple pathways could have involved in malignant transformation of endometriosis. Endometriosis shares several molecular characteristics with invasive cancer, such as inflammation, tissue invasion, angiogenesis, dysfunction of immune cells, increased local estrogen production, apoptosis, and pro-survival features.[4] Iron-induced oxidative stress derived from repeated hemorrhage due to menstruation was believed to be the major pathway in the malignant transformation of endometriosis.[5,6]

We reviewed literature research of MEDLINE, PubMed, Cochrane Library of Systematic Reviews and reference search in selected papers that related to malignant transformation of endometriosis, focusing on epidemiology studies, molecular researches and clinical observations in EAOC. The objective of this review is to collect data associated with such disease and for selective patient surveillance and management.

Prevalence of ovarian cancer in women with endometriosis

Many epidemiologic studies supported a link between endometriosis and invasive epithelial ovarian cancer based on high prevalence and incidence of epithelial ovarian cancer and endometriosis. A meta-analysis on 28 studies showed that the standardized incidence ratio (SIR, defined as observed cases/expected cases after adjusted for age) for epithelial ovarian cancer in women with surgical or histological diagnosed endometriosis was 1.43–8.95; and the odds ratio (OR, defined as the ratio of disease odds given exposure status) was 1.34. The prevalence (defined as

Conflicts of interest declaration: The author has no conflicts of interest relevant to this article.

* Department of Obstetrics and Gynecology, National Taiwan University Hospital, No. 7, Chung Shan South Road, Taipei 10002, Taiwan. Fax: +886 2 886 223114965.
E-mail address: pltorng@ntu.edu.tw.

http://dx.doi.org/10.1016/j.gmit.2017.08.003

cases/person-time of observation) of epithelial ovarian cancer in women with endometriosis was 2.0–17.0%, and the prevalence of endometriosis in women with epithelial ovarian cancer was 3.4–52.6%.[7] The wide ranges of reported incidence and prevalence of epithelial ovarian cancer in women with endometriosis is due to high heterogeneity in meta-analysis. In addition, different criteria used to diagnose endometriosis could result with great difference in the incidence rate (IR, defined as number of new cases per population at risk in a given time period per 10,000 person-year) of epithelial ovarian cancer in women with endometriosis. In a cohort study from the National Health Insurance Research Database (NHIRD) of Taiwan and the Registry for Catastrophic Illness Patients that included 239,385 women, the reported IR of epithelial ovarian cancer in women with endometriosis were 1.90 in women with recalled endometriosis to 18.70 in women with tissue-proved ovarian endometriosis, as compared to those women without endometriosis (0.77–0.89). Consequently, these IRs contributed to a range of crude hazard ratio (HR, defined as instantaneous risk over the study time period) of epithelial ovarian cancer in women with endometriosis as 2.59–24.04.[8]

Endometriosis associated ovarian cancer (EAOC) does not exist as a homogenous group of malignancies, but as several histological subtypes. Based on recalled self-reported endometriosis, a pooled analysis of 13 case–control studies of ovarian cancer that included 13,226 controls and 7911 women with invasive ovarian cancer showed that endometriosis was highly associated with clear cell (odds ratio, OR 3·05), low-grade serous (OR 2·11), and endometrioid ovarian cancers (OR 2·04).[9] No association was noted between endometriosis and risk of mucinous or high-grade serous ovarian cancer, or borderline tumors of either subtype (serous and mucinous).[9] A study from Danish National Patient Register and Danish Cancer Register that included 45,790 women with endometriosis based on clinical diagnosis of endometriosis also reported that the SIR of EAOC was 1.34; and SIR for endometrioid and clear cell carcinoma were 1.64 and 3.64, respectively.[10] In another meta-analysis on 20 case–control and 15 cohort studies that included 444,255 patients with self-reported and histological endometriosis, the RR of endometrioid carcinoma was 1.759 and the RR of clear cell carcinomas was 2.606 in EAOC, whereas serous carcinoma was less frequent (RR, 0.733); and there was no difference in the risk of mucinous carcinoma between EAOC and non-EAOC (RR, 0.805).[11] In the study of National Health Insurance Research Database (NHIRD) of Taiwan that included 5945 women with surgico-pathological diagnosed endometriosis compared with multivariable-matched 23,780 controls, the IR of epithelial ovarian cancer was 11.64, contributing to HR of 4.48; and the HR in clear cell carcinoma subtypes was 7.36.[12]

All these epidemiological studies observed the close association of endometriosis with particular histological of EAOC, i.e. endometrioid and clear cell carcinoma, especially when the diagnosis of endometriosis was more evidence based, such as through surgical-pathological diagnosis.

Pathogenetic similarities between endometriosis and EAOC

Several gene mutations have been identified concurrently in endometriosis lesions and in the EAOC tumors. Many studies have focused on assessing LOH at 10q23.3 (such as loss of heterozygosity (LOH) and mutations leading to functional inactivation of the PTEN tumor suppressor gene, located on chromosome 10q23.3) and MSI (leading to the functional inactivation of the PTEN gene) in EAOC. Sato et al reported LOH at the 10q23.3 locus in 56.5% of solitary endometrial cysts, 42.1% of endometrioid carcinoma and 27.3% of clear cell carcinoma, suggesting that inactivation of genes at 10q23.3 might be involved in these lesions.[13] Furthermore, Ali-Fehmi et al reported LOH at D10S608 in 4.3% of endometriosis lesions and 23.5% of EAOC.[14] Ali-Fehmi et al also reported MSI in 82.6% of endometriosis, 75% of atypical endometriosis and 53% of epithelial ovarian cancer (in 4 of 5, 80% clear cell carcinomas, 3 of the 7, 42.8% endometrioid carcinomas, and 4 of 8, 50% serous papillary carcinomas).[14] These results highlight that endometriosis and atypical endometriosis might act as precursor lesions that have the potential to progress into EAOC.

Loss of BAF250a expression and ARIDIA mutation were frequently and specifically reported in histological subtypes of endometrioid and clear cell carcinoma of EAOC. BAF250a is encoded by ARID1A and has been believed to confer specificity in regulation of gene expression. By immunohistochemical staining, loss of BAF250a expression was reported in 22% (13/59) of endometrioid carcinomas, 47% (17/36) of clear cell carcinoma, 44% (8/18) of contiguous endometriosis, and 8% (3/66) of benign endometriotic ovarian cysts.[15] By whole transcriptomes sequencing, ARID1A mutations were found in 46% (55/119) of ovarian clear cell carcinomas, 30% (10/33) of endometrioid carcinomas, but none of the serous carcinoma.[16] Both ARID1A mutations and loss of BAF250a expression were identified in the tumor and contiguous atypical endometriosis but not in distant endometriotic lesions.[16] These results suggest the close correlation between ARD1A and BAF250a in the pathogenesis of EAOC.

ARID1A and PIK3CA mutations were particularly important in the clear cell carcinoma subtype of EAOC. Using Whole-genome and targeted deep sequencing, concurrent ARID1A and PIK3CA mutations were found in ovarian clear cell carcinoma and in tumor-adjacent and distant endometriotic lesions, regardless of any cytological atypia.[17] In a study that included 23 clear cell carcinomas with synchronous putative precursor lesions (i.e. endometriosis adjacent to carcinoma, with or without cytological atypia), PIK3CA gene mutations were detected in 43% (10/23) of ovarian clear cell carcinomas and in 90% (9/10) of the coexisting endometriotic epithelium, adjacent to the clear cell carcinoma.[18] Using immunohistochemical analysis, loss of ARID1A and PIK3CA were frequently found in 130 cases of ovarian clear cell carcinoma (56.2% and 45.0%, respectively). Loss of ARID1A was particular frequent (76.9%, 20/26) in clear cell carcinoma with concurrent endometriosis. PIK3CA expression was reported not related to clinical features or survival of clear cell carcinoma. But loss of ARID1A, along with low-level HNF-1β expression, was common in patients at cancer recurrence and was correlated with late-stage and worse survival outcome.[19] Another study that included 35 pure-type (73.9% with endometriosis) and 11 mixed-type clear cell carcinoma (45.5% with endometriosis) showed that both ARID1A and p53 were mutually altered in pure-type clear cell carcinoma by immunohistochemical analysis. Altered expression of p53 in these clear cell carcinomas was associated with significant worse prognosis than that of ARID1A ($P < 0.001$).[20] These studies suggested that PIK3CA gene mutation could be a putative precursor for clear cell carcinoma in EAOC; while ARID1A in associated with other genetic mutation (two-hit hypothesis), is a later event in the malignant transformation of endometriosis that leads to disease.

Endometrioid adenocarcinoma showed a distinct molecular profile from clear cell carcinoma. CTNNB1 encodes b-catenin, which plays a pivotal role in the Wnt/b-catenin signaling pathway. CTNNB1 mutations are highly characteristic of ovarian endometrioid carcinoma as they have not been detected in other types of ovarian carcinoma. Mutations in exon 3 of the β-catenin gene were identified in 60% (21/35) of endometrioid carcinoma. The mutations were also detected in the coexisting non-atypical (52.4%) and atypical (73.3%) endometriosis, and the single-nucleotide substitutions were identical in most cases. In contrast, the mutations were not identified in any of the clear cell carcinomas and their

coexisting endometriosis.[21] Using an animal model, Wu et al demonstrated that inactivation of Pten and β-catenin pathways in the murine surface epithelium resulted in adenocarcinomas formation with similar morphology as human ovarian endometrioid carcinoma.[22] These results suggest the clinical significance of Pten and β-catenin in endometrioid adenocarcinoma and the possible role in the malignant transformation of endometriosis to endometrioid carcinoma.

By new technology, full-genome screening has recently been performed to identify more EAOC related genes. Using pooled genetic analysis focused on selected endometriosis associated single-nucleotide polymorphisms (SNPs) in 15,361 ovarian cancer cases and 30,815 controls, endometriosis-related genetic variation was identified in ovarian high-grade serous, in addition to the clear cell histotypes.[23] Another study that focused on endometriosis datasets (3194 cases and 7060 controls) and ovarian cancer dataset (10,065 cases and 21,663 controls) supported the previous epidemiological reports that clear cell carcinoma (0.51, 95% CI = 0.18–0.84), endometrioid and low-grade serous carcinomas (0.48, 95% CI = 0.07–0.89 and 0.40, 95% CI = 0.05–0.75, respectively) were strongly genetic correlated with endometriosis.[24] Based on these genetic alterations and the identification of more shared genetic susceptibility loci in EAOC, the underlying molecular pathways related to EAOC could then be established in the future.

Risk factor for malignant transformation in endometriosis

Increasing age is a major risk factor associated with EAOC. Using NHIRD database of Taiwan, IR of EAOC increased consistently with increasing age; ranging from 4.99 per 10,000 person-years in women <30 years to 35.81 in women ≥50 years, contributing to a progressive increased risk of epithelial ovarian cancer (crude HRs ranging from 2.80 to 6.74 and adjusted HRs ranging from 3.34 to 9.63) compared to age-matched women without endometriosis. Women at ≥50 years with endometriosis had significantly higher risks of epithelial ovarian cancer than the age-matched women without endometriosis (adjusted HR 9.63) and the young women at <30 years with endometriosis (adjusted HR 4.97).[12] The time interval between the diagnoses of endometriosis with the later development of EAOC was controversial. Risk of epithelial ovarian cancer was reported to increase even after 5–10 years after endometriosis in women whose endometriosis was diagnosed by self-reported recall data.[9] However, study from Taiwan NHIRD showed that the occurrence of epithelial ovarian cancer was not affected by exposure time of endometriosis in women whose endometriosis was diagnosed by chart records or surgical confirmation.[25]

Endometriosis shares many risk/protective factors with epithelial ovarian cancer, such as early menarche, incessant ovulation or menstruation due to either early menarche, late menopause, infertility, or nulliparity, tubal ligation, hysterectomy, multiple pregnancies, breast feeding, use of oral contraceptives, and recreational physical activity.[1,26,27] A risk factor scores that included Jewish ethnicity, less than 1 year of oral contraceptive use, nulliparity, no breastfeeding, no tubal ligation, painful periods or endometriosis, polycystic ovary syndrome or obesity, and talc use has been identified associated with higher life time risk of developing epithelial ovarian cancer. The life time risk for ovarian cancer in a woman at age 40 years was calculated as 1.2% with a 0–1 score to 6.6% with a score of 5 or higher.[28]

Endometriosis frequently appeared in patients with infertility. The association of infertility with epithelial ovarian cancer has been investigated. A nationwide historic cohort study that included sub-fertile women who were infertile due to male factor or idiopathic reason was reported. By comparing women who had endometriosis based on self-report, medical records, and/or pathology confirmed database (n = 3657) with women without endometriosis (n = 5247), HR of all ovarian malignancies (epithelial ovarian cancer and borderline ovarian tumor, BOT) in women with endometriosis was 8.2. The HR associated with endometriosis was 12.4 for epithelial ovarian cancer and 5.5 for BOT.[29] But when women with pathological diagnosed endometriosis were excluded from the database, HRs dropped to 3.0 for all ovarian tumors, 4.3 for ovarian cancer and 1.9 for BOT. The subsequent calculated HR did not show much difference form the general population, suggesting that infertility by itself is not the risk factor for EAOC.[29] Another cohort study that included Australia whole population linked hospital and registry data of 21,646 women treated for infertility showed no evidence of epithelial ovarian cancer risk following IVF in women who give birth. But women diagnosed with endometriosis who remained nulliparous had a three-fold increase in the rate of epithelial ovarian cancer.[30] This suggests endometriosis in nulliparous women, but not the procedure of controlled ovarian stimulation, might be associated with a higher risk of EAOC.

Survival outcome of EAOC

The impact of endometriosis on the survival of patients with epithelial ovarian cancer is unknown. In meta-analysis, patients with EAOC were more commonly diagnosed at nulliparity, and at stage I–II and grade 1 disease (RRs, 1.327, 1.959 and 1.319).[11] A study that included 139 patients with epithelial ovarian cancer (49 with endometriosis and 90 without endometriosis) showed that patients with EAOC were younger, and more likely confined to the pelvis (54% vs. 9%) and at lower grade (51% vs. 29%) at diagnosis compared with patients with non-EAOC.[31] Current reports on the survival outcome of EAOC were basically comparing the survival differences between EAOC and non-EAOC patients. In a meta-analysis on 20 case–control and 15 cohort studies that included 444,255 patients reported that there were no differences in progression free survival (PFS) (HR, 1.023), but a slightly better overall survival (OS) by crude analyses (HR, 0.778) in EAOC than non-EAOC.[11] A study that included 139 patients with grade and staged matched epithelial ovarian cancer (49 with endometriosis and 90 without endometriosis), EAOC showed improved PFS and OS (HR = 0.20; 0.18 respectively) compared to non-EAOC patients. However, endometriosis showed no independent prognostic significance.[31] When focusing on histological subtypes, a study included 67 patients with endometriosis associated clear cell carcinoma and endometrioid carcinoma (in which 45 arising in endometriosis) demonstrated better PFS but not OS compared to 134 age and stage matched patients with papillary serous carcinoma.[32] Contradictory, another study of 73 patients with only clear and mixed endometrioid-clear cell ovarian cancer (in which 46 arising in endometriosis) showed that endometriosis was not associate with a lower stage tumor or to predict prognosis.[33] By concise summary, these results suggested that histological subtype, other than endometriosis, is a key determine factor to survival outcome in patients with EAOC.

EAOC was also frequently associated with endometrial cancer. SIR of type 1 endometrial cancer in EAOC was 1.54 in the study of Danish National Patient Register and Danish Cancer Register.[10] Synchronous endometrial cancer was reported to be 23.8–33.3% in EAOC with evidence of malignant transformation in patients with clear cell carcinoma and endometrioid carcinoma associated with endometriosis.[32] However, such association was uncommon[32] or not seen[33] in EAOC patients with clear cell carcinoma, suggesting that endometrioid carcinoma was the major EAOC with synchronous endometrial cancer.

Clinical implication

Age is a key factor related to EAOC. Based on a case–control study that included 42 women with ovarian cancer arising in the background of endometriosis and 96 women with benign endometrioma, age was reported to be a significant predictor for malignant transformation of endometriosis. OR of EAOC was 2.17 for every increase of 5 years ($P = 0.003$). An age of 49 years or greater had an 80.6% sensitivity (95% CI: 62.5–92.5%) and an 82.9% specificity (95% CI: 67.9–92.8%) for malignancy.[34]

Sonography is commonly used to identify the nature of ovarian tumors. In the study that included 73 patients with clear and mixed endometrioid-clear cell tumors that were either associated or strictly arising from endometriosis, most tumors were found to be unilateral involved and were cystic without the presence of ascites.[14] When compared EAOC with benign endometrioma, EAOC was larger (14 cm vs. 7.5 cm), more often multilocular (45.7% vs. 12.2%), and contained solid components (77.1% vs. 14.5%). Solid component on imaging showed an independent OR of 23.7 for malignancy.[34] Kuo et al reported a 63.6% of solid components, demonstrated as "inward mass within ovarian cyst" in a retrospective study to review images from patients with unexpected EAOC that were operated as endometrioma.[35] Taniguchi et al reported the appearance of mural nodules within the endometriomas by image study in all EAOC cases. They found size not correlated with EAOC, but rapid growth of the endometrioma (doubled in size 6 months prior to the diagnosis of malignant transformation) in 30/33 of their patients and should be used as an indicator for malignant transformation.[36]

Serum CA-125 levels is a poor screening modality for EAOC. Kadan reported that CA-125 was higher in patients with EAOC compared to benign endometrioma, but did not reach statistical significance (mean 204.9 vs. 66.9 U/mL, $P = 0.1$).[34] Taniguchi et al following up 33 patients with initial endometriosis that subsequent developed into EAOC and reported that CA-125 level was not correlated with malignant transformation.[36] And contradictory, CA-125 levels were found lower in patients with EAOC compared with patients with non-EAOC (mean: 122.9 vs 1377.5 U/mL, $P < 0.001$), and patients with EAOC were more likely to display normal CA-125 level ($P < 0.001$).[37]

In summary, patients who are nulliparous, who are diagnosed at older age and with long term endometriosis should pay special attention to the possibility of malignant transformation. More awareness should be focus on unilateral, larger and multilocular cyst with solid components that showed rapid growth.

Future directions

It is now widely accepted that salpingectomy while performing hysterectomy could reduce risk of later development of type II epithelial ovarian cancer, such as serous carcinoma.[38] However, prophylactic oophorectomy to prevent later development of epithelial ovarian cancer is not conclusive. In the past, women near the age of menopause commonly received prophylactic bilateral salpingo-oophorectomy during hysterectomy for benign gynecological disease. From 2001 through 2006, 47% oophorectomy were performed in 144,877 women at the aged 18 years or older undergoing hysterectomies for benign gynecologic conditions in New York.[39] This number decrease over time. By 2013–2014, histologically normal ovaries were removed in nearly 1 of every 4 women at age <51 years undergoing hysterectomy for benign indications in United State.[40] Nowadays, surgical indications associated with oophorectomy with normal resultant pathology were: family history of cancer (OR, 3.09), endometrial hyperplasia (OR, 2.36), endometriosis (OR, 2.01), and cervical dysplasia (OR, 1.91).[40] However, hysterectomy with or without salpingo-oophorectomy has no statistical significance concerning with preventing the risk of epithelial ovarian cancer in women with infertility.[30] The benefits of prophylactic oophorectomy in women who are at high risk of EAOC, such as women with older age, long term endometriosis, required more surveys.

Conclusion

Women with endometriosis showed a higher risk of developing EAOC, especially in cases with surgical or pathologically proved endometriosis. EAOCs are more likely to be associated with endometrioid and clear cell carcinoma. Based on molecular studies, CTNNB1 and ARID1A mutations were particularly related to these two histological types of EAOC. Risk of malignant transformation is higher in women at older age. Cautious should be paid in cases with rapid growth of endometrioma and with solid components. In such cases, more aggressive surgery such as oophorectomy or prophylactic oophorectomy during hysterectomy might be better than waiting for spontaneous regression of endometrioma after menopause.

References

1. Eskenazi B, Warner ML. Epidemiology of endometriosis. *Obstet Gynecol Clin North Am*. 1997;24:235–258.
2. Giudice LC. Clinical practice. Endometriosis. *N Engl J Med*. 2010;362:2389–2398.
3. Sampson JA. Endometrial carcinoma of ovary arising in endometrial tissue in that organ. *Arch Surg*. 1925;10:1–72.
4. Guo SW. Link of endometriosis with ovarian cancer. *Fertil Steril*. 2015;104:813–830.
5. Higashiura Y, Kajihara H, Shigetomi H, Kobayashi H. Identification of multiple pathways involved in the malignant transformation of endometriosis (Review). *Oncol Lett*. 2012;4:3–9.
6. Vercellini P, Crosignani P, Somigliana E, et al. The 'incessant menstruation' hypothesis: a mechanistic ovarian cancer model with implications for prevention. *Hum Reprod*. 2011;26:2262–2273.
7. Heidemann LN, Hartwell D, Heidemann CH, Jochumsen KM. The relation between endometriosis and ovarian cancer – a review. *Acta Obstet Gynecol Scand*. 2014;93:20–31.
8. Lee WL, Chang WH, Wang KC, et al. The risk of epithelial ovarian cancer of women with endometriosis may be varied greatly if diagnostic criteria are different: a nationwide population-based cohort study. *Medicine*. 2015;94:e1633.
9. Pearce CL, Templeman C, Rossing MA, et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. *Lancet Oncol*. 2012;13:385–394.
10. Mogensen JB, Kjær SK, Mellemkjær L, Jensen A. Endometriosis and risks for ovarian, endometrial and breast cancers: a nationwide cohort study. *Gynecol Oncol*. 2016;143:87–92.
11. 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;110:1878–1890.
12. Wang KC, Chang WH, Lee WL, et al. An increased risk of epithelial ovarian cancer in Taiwanese women with a new surgico-pathological diagnosis of endometriosis. *BMC Cancer*. 2014;14:831.
13. Sato N, Tsunoda H, Nishida M, et al. Loss of heterozygosity on 10q23.3 and mutation of the tumor suppressor Gene PTEN in benign endometrial cyst of the ovary: possible sequence progression from benign endometrial cyst to endometrioid carcinoma and clear cell carcinoma of the ovary. *Cancer Res*. 2000;60:7052–7056.
14. Ali-Fehmi R, Khalifeh I, Bandyopadhyay S, et al. Patterns of loss of heterozygosity at 10q23.3 and microsatellite instability in endometriosis, atypical endometriosis, and ovarian carcinoma arising in association with endometriosis. *Int J Gynecol Pathol*. 2006;25:223–229.
15. 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. *Gynaecol Obstet*. 2015;130:27–30.
16. Wiegand KC, Shah SP, Al-Agha OM, et al. ARID1A mutations in endometriosis-associated ovarian carcinomas. *N Engl J Med*. 2010;363:1532–1543.
17. Anglesio MS, Bashashati A, Wang YK, et al. Multifocal endometriotic lesions associated with cancer are clonal and carry a high mutation burden. *J Pathol*. 2015;236:201–209.
18. Yamamoto S, Tsuda H, Takano M, Iwaya K, Tamai S, Matsubara O. PIK3CA mutation is an early event in the development of endometriosis-associated ovarian clear cell adenocarcinoma. *J Pathol*. 2011;225:189–194.
19. Ye S, Yang J, You Y, et al. Clinicopathologic significance of HNF-1β, AIRD1A, and PIK3CA expression in ovarian clear cell carcinoma: a tissue microarray study of 130 cases. *Medicine (Baltimore)*. 2016;95:e3003.

20. Matsuo Y, Tashiro H, Yanai H, Moriya T, Katabuchi H. Clinicopathological heterogeneity in ovarian clear cell adenocarcinoma: a study on individual therapy practice. *Med Mol Morphol*. 2015;48:146–154.
21. Matsumoto T, Yamazaki M, Takahashi H, et al. Distinct β-catenin and PIK3CA mutation profiles in endometriosis-associated ovarian endometrioid and clear cell carcinomas. *Am J Clin Pathol*. 2015;144:452–463.
22. Wu F, Hendrix-Lucas N, Kuick R, et al. Mouse model of human ovarian endometrioid adenocarcinoma based on somatic defects in the Wnt/b-catenin and PI3K/Pten signaling pathways. *Cancer Cell*. 2007;11:321–333.
23. Lee AW, Templeman C, Stram DA, et al. Evidence of a genetic link between endometriosis and ovarian cancer. *Fertil Steril*. 2016;105:35–43, e1–10.
24. Lu Y, Cuellar-Partida G, Painter JN, et al. Shared genetics underlying epidemiological association between endometriosis and ovarian cancer. *Hum Mol Genet*. 2015;24:5955–5964.
25. Chang WH, Wang KC, Lee WL, et al. Endometriosis and the subsequent risk of epithelial ovarian cancer. *Taiwan J Obstetrics Gynecol*. 2014;53:530–535.
26. Vercellini P, Eskenazi B, Consonni D, et al. Oral contraceptives and risk of endometriosis: a systematic review and meta-analysis. *Hum Reprod Update*. 2011;17:159–170.
27. Nnoaham KE, Webster P, Kumbang J, Kennedy SH, Zondervan KT. Is early age at menarche a risk factor for endometriosis? A systematic review and meta-analysis of case-control studies. *Fertil Steril*. 2012;98:702–712.e6.
28. Vitonis AR, Titus-Ernstoff L, Cramer DW. Assessing ovarian cancer risk when considering elective oophorectomy at the time of hysterectomy. *Obstet Gynecol*. 2011;117:1042–1050.
29. Buis CC, van Leeuwen FE, Mooij TM, Burger CW, OMEGA Project Group. Increased risk for ovarian cancer and borderline ovarian tumours in subfertile women with endometriosis. *Hum Reprod*. 2013;28:3358–3369.
30. Stewart LM, Holman CD, Aboagye-Sarfo P, Finn JC, Preen DB, Hart R. In vitro fertilization, endometriosis, nulliparity and ovarian cancer risk. *Gynecol Oncol*. 2013;128:260–264.
31. Dinkelspiel HE, Matrai C, Pauk S, et al. Does the presence of endometriosis affect prognosis of ovarian cancer? *Cancer invest*. 2016;34:148–154.
32. Davis M, Rauh-Hain JA, Andrade C, et al. Comparison of clinical outcomes of patients with clear cell and endometrioid ovarian cancer associated with endometriosis to papillary serous carcinoma of the ovary. *Gynecol Oncol*. 2014;132:760–766.
33. Scarfone G, Bergamini A, Noli S, et al. Characteristics of clear cell ovarian cancer arising from endometriosis: a two center cohort study. *Gynecol Oncol*. 2014;133:480–484.
34. Kadan Y, Fiascone S, McCourt C, et al. Predictive factors for the presence of malignant transformation of pelvic endometriosis. *Eur J Obstet Gynecol Reprod Biol*. 2015;185:23–27.
35. Kuo HH, Huang CY, Ueng SH, Huang KG, Lee CL, Yen CF. Unexpected epithelial ovarian cancers arising from presumed endometrioma: a 10-year retrospective analysis. *Taiwan J Obstet Gynecol*. 2017;56:55–61.
36. Taniguchi F, Harada T, Kobayashi H, Hayashi K, Momoeda M, Terakawa N. Clinical characteristics of patients in Japan with ovarian cancer presumably arising from ovarian endometrioma. *Gynecol Obstet Invest*. 2014;77:104–110.
37. Wang S, Qiu L, Lang JH, et al. Clinical analysis of ovarian epithelial carcinoma with coexisting pelvic endometriosis. *Am J Obstet Gynecol*. 2013;208:413.e1–413.e5.
38. Oliver Perez MR, Magriñá J, García AT, Jiménez Lopez JS. Prophylactic salpingectomy and prophylactic salpingoophorectomy for adnexal high-grade serous epithelial carcinoma: a reappraisal. *Surg Oncol*. 2015;24:335–344.
39. Novetsky AP, Boyd LR, Curtin JP. Trends in bilateral oophorectomy at the time of hysterectomy for benign disease. *Obstet Gynecol*. 2011;118:1280–1286.
40. Karp NE, Fenner DE, Burgunder-Zdravkovski L, Morgan DM. Removal of normal ovaries in women under age 51 at the time of hysterectomy. *Am J Obstet Gynecol*. 2015;213:716.e1–716.e6.