European Journal of Obstetrics & Gynecology and Reproductive Biology 185 (2015) 23–27

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Predictive factors for the presence of malignant transformation of pelvic endometriosis

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ARTICLE INFO

Article history:
Received 13 August 2014
Received in revised form 14 November 2014
Accepted 21 November 2014

Keywords:
Endometriosis
Endometrioma
Ovarian cancer
Risk factors

ABSTRACT

Objectives: To determine predictive factors for the presence of malignant transformation in ovarian endometriotic cysts.
Study design: This was an IRB approved, case control study analyzing patient data from 2004 to 2013. Pathology database records were searched to identify patients with benign endometrioma and ovarian carcinoma arising in the background of endometriosis. Inclusion criteria required each patient to have a preoperative diagnosis of adnexal mass and no other findings concerning for malignancy. Patient clinical records were queried for preoperative symptoms, serum CA125 levels and radiologic findings. Pathologic data were collected including histology, tumor grade and stage.
Results: A total of 138 patients met inclusion criteria; 42 women with ovarian cancer arising in the background of endometriosis and 96 women with benign endometrioma. Women diagnosed with ovarian cancer were significantly older than women with endometriosis (53.6 vs. 39.2 years). There was no difference in presence of symptoms between the two groups. Women with malignant tumors were found to have significantly larger cysts (14 cm vs. 7.5 cm; $p < 0.0001$) that were more often multilocular (45.7% vs. 12.2%; $p < 0.0001$), and contained solid components (77.1% vs. 14.5%; $p < 0.0001$). Among patients that were observed prior to surgery there was a significant difference in the change in size of the mass over time with 4.2 cm increase for cases vs. 1.0 cm increase for controls ($p = 0.02$). Multiple logistic regression analysis indicated that for every 5 years increase in age there was an adjusted OR of 2.17 ($p = 0.003$). 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, and solid component on imaging had an adjusted OR of 23.7 ($p < 0.0001$). Serum CA125 levels tended to be higher in patients with malignant tumors but did not reach statistical significance with a mean of 204.9 vs. 66.9 ($p = 0.1$).
Conclusions: Significant predictors for malignant transformation of endometriosis include cyst characteristics and age. Women above the age of 49 with multilocular cysts and solid components are at high risk for malignant transformation of endometriosis. Serum CA125 level is not a significant predictor of malignant transformation.

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Introduction

Endometriosis is a common gynecological condition estimated to affect 4–15% of women [1,2]. Cystic endometriotic implants in the ovary, known as endometriomas, pose a diagnostic and management dilemma for many asymptomatic patients and their physicians. While the majority of endometriomas never undergo malignant transformation, the elevated risk of ovarian cancer is well established. Endometriosis confers a significantly increased risk for clear cell, serous, and endometrioid ovarian adenocarcinoma in patients when compared to women without endometriosis [3].

The potential for malignant transformation of endometriomas has been cited as an indication for surgical resection, even in asymptomatic patients [4]. Surgical resection of endometriomas

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http://dx.doi.org/10.1016/j.ejogrb.2014.11.029
0301-2115/Published by Elsevier Ireland Ltd.

offers the benefit of a histologic diagnosis and the ability to cease ongoing medical therapy or cancer screening. However, universal surgical resection of endometriomas may unnecessarily expose many women to operative risks and decrease fertility rates [5].

Given the risks and benefits of surgical management, it is important to identify patients at high risk for malignant transformation of endometriomas. A recent prospective study following 6398 women with endometriomas described an ovarian cancer diagnosis in 46 women (0.72%) over a median follow-up period of 12.8 years. Tumor size $\geq$ 9 cm, postmenopausal status, and age $\geq$ 45 years were all identified as independent risk factors on multivariate analysis for the presence of ovarian cancer [6]. Other studies using both ultrasound and MRI modalities have confirmed increased likelihood of malignant transformation with advancing age and increasing endometrioma size as well as the presence of solid tissue, increased size of mural nodules, contrast enhancement on MRI, and papillary projections within an endometrioma [7,8].

In a case-control study evaluating the sensitivity and specificity of patient-reported symptoms in ovarian cancer, Goff found that pelvic/abdominal pain, increased abdominal size/bloating, and difficulty eating/feeling full were significantly associated with a diagnosis of ovarian cancer if patients experienced any of those symptoms >12 times per month but for <1 year. This index had a sensitivity of 56.7% for early-stage disease and 79.5% for late-stage disease [9].

Serum biomarkers including cancer antigen 125 (CA125) and human epididymis protein 4 (HE4) are validated tools to assess the malignant potential of an adnexal mass. While CA125 is known to be elevated in benign gynecologic conditions such as endometriosis, adding HE4 and utilizing the Risk of Ovarian Malignancy Algorithm (ROMA) enhances the ability to distinguish benign from malignant lesions [10].

Based on these previous studies, it is clear that findings on diagnostic imaging, patient characteristics, and serum biomarkers can help identify patients at increased risk for malignant transformation of endometriomas. The development of a risk stratification system for malignant transformation of endometriomas may help clinicians in deciding which patients to operate on or refer to a gynecologic oncologist. The objective of our study was to use clinical, laboratory, and radiologic findings to determine predictors for the malignant transformation of endometriomas.

Materials and methods

This was an IRB approved retrospective case control study reviewing clinical and pathologic data from patients who underwent surgery at Women and Infants Hospital from 2004 to 2013. Patients who did not undergo surgery were not included in order to have definite histologic results for all included patients. Eligibility criteria included pre-operative diagnosis of ovarian cyst or pelvic mass. Patients with diagnosis of ovarian cancer and/or any other cancer before the surgery were excluded, as well as pre-operative findings of disease outside the adnexa, including moderate to large amounts of ascites. Ovarian cancer arising in the background of endometriosis was identified in 59 women of which 42 cases met inclusion criteria and were assigned to the ovarian cancer (OC) group (Fig. 1). Controls with a pathologic diagnosis of benign endometrioma were matched to cases from each corresponding year. Cases and controls were not matched by age in order to independently evaluate age as a predictor for malignant transformation. Data on HE4 levels were not included as the numbers were too few to analyze.

In the control cohort, 96 patients were eligible with sufficient data to comprise the benign endometriosis (BE) group. Clinical, laboratory and radiology data were collected from computer and paper charts. Due to different radiologic modalities among the patients imaging from any combination of ultrasound (US), computer tomography (CT) and magnetic resonance imaging (MRI) was included in the analysis. For the ovarian cancer patients, specific tumor related data were collected.

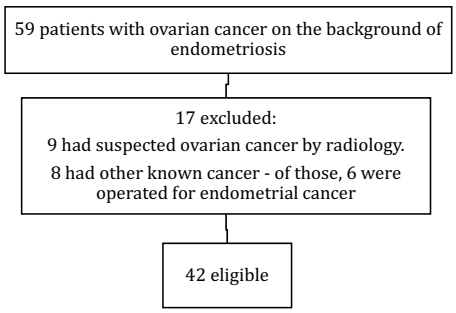

Fig. 1. Detailed description of patients that were screened for the OC group.

Data analysis was performed with STATA 10 (StataCorp, College Station, TX). Fisher's exact test, Student's *t*-test, or the Wilcoxon rank-sum test for comparison the two groups were employed for analysis. Multivariable logistic regression was used to evaluate potential independent predictors of ovarian cancer. Variables associated with cancer at $p \leq 0.1$ in univariate models were included in the multivariate analysis. Sensitivity and specificity for each variable and the combination of variable cut points were computed along with exact binomial 95% confidence intervals. Two-tailed *p*-values are presented; $p < 0.05$ is considered statistically significant.

Results

A total of 138 patients met inclusion criteria; 42 women with histology proven ovarian cancer arising in the background of endometriosis and 96 women with benign endometriotic cysts as controls. Patients' characteristics are summarized in Table 1. Patients with ovarian cancer were significantly older than patients with the benign endometriomas with increased number of patients that were postmenopausal compared to premenopausal. Tumor characteristics are summarized in Table 2. The majority of women (79%) were diagnosed with stage I disease with endometrioid and clear cell tumors comprising the majority of histologic subtypes (40.5% and 33.34%, respectively). Borderline tumors were diagnosed in eight patients. Complete surgical staging was performed in 81% of patients at the time of their initial surgery. Univariate analysis of the pre-operative

Table 1
Patient characteristics by group.

Variable	Case	Control	*p*-Value
Total	42	96	
Age (y)			
Mean (SD)	53.7 (9.5)	39.2 (9.0)	<0.0001
Median (range)	54 (24–78)	39 (21–64)	
BMI			
Mean (SD)	29.2 (8.4)	29.5 (8.4)	0.8
Median (range)	27.3 (19.2–64.3)	28.3 (15.1–61.9)	
Missing	0	8	
Menopause n (%)	(*n* = 34)	(*n* = 85)	<0.0001
Yes	16 (47.1)	6 (7.1)	
No	18 (52.9)	79 (92.9)	

Data are *n* (column %) unless otherwise noted. Missing data are not included in statistics.