



Comparison of Clinico-Pathological Features Between Epithelial Ovarian Cancer Patients With and Without Endometriosis: A Cross-Sectional Study

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Abstract

Objectives: Women with endometriosis have a high risk of developing ovarian carcinoma that may occur due to endometriosis lesions. There is few research have so far focused on the clinical factors in patients with endometriosis-associated ovarian cancer (EAOC). Accordingly, this study aimed at comparing the demographic and obstetric characteristics between ovarian cancer with and without endometriosis

Materials and Methods: This cross-sectional study was conducted on 20 EAOC patients and 140 non-EAOC individuals who had gone under surgery from 2011-17 at Al-Zahra hospital. Clinico-pathological characteristics of the two groups including first group only had malignant epithelial ovarian tumor (non-EAOC) and second group had both malignant epithelial ovarian tumor and endometriosis (EAOC). P value less than 0.05 was considered statistically significant.

Results: EAOC cases were significantly younger ($P=0.002$) and had lower number of pregnancy ($P=0.002$), parity ($P=0.004$), and term pregnancy ($P=0.005$) than non-EAOC patients. A large proportion of EAOC cases had clear cell and endometrioid histopathology in comparison to non-EAOC individuals ($P<0.001$) and most of the tumors in these cases were unilateral ($P=0.01$).

Conclusions: We found that age, parity, gravidity, and term pregnancy as well as laterality and histopathologic type of epithelial ovarian cancers vary in EAOC and non-EAOC individuals. Further research is required to identify these differences.

Keywords: Endometriosis, Ovarian epithelial cancer, Carcinoma.

Introduction

Endometriosis as a common gynecologic benign condition involves around 5%-10% of women in reproductive age. Endometriosis has been known as a tissue similar to endometrial tissue outside the uterine cavity. Through inflammation, endometriosis causes symptoms such as dysmenorrhea, dyspareunia, chronic pelvic pain and infertility. Ovarian endometriosis (endometrioma) where an ectopic endometrial tissue bleeds inside the ovary, causes hematoma restricted to the ovarian tissue (1,2). Although endometrioma is a benign disease, it may increase the risk of epithelial ovarian cancers especially in people with long-term endometriosis (3,4). The cause of these malignant changes in the cysts is iron production in the cystic fluid of endometrioma and oxidative stress that can lead to genetic mutation (5).

Based on the previous studies, atypical endometriosis has been introduced as a progressive lesion for endometriosis-associated ovarian cancer (EAOC) (6). Its co-occurrence with clear cell and endometrioid ovarian cancer has been reported at 54% and 42% respectively (7, 8).

Endometriosis is mostly related to specific ovarian

cancer histologic types like endometrioid, clear cell and low grade serous (9-12). Research has proved the presence of ovarian carcinoma in 5%-10% of individuals with endometriosis while some studies have reported malignant changes through atypical endometriosis in 0.7-1.6% of the patients (13).

Endometriosis-associated ovarian carcinomas are mostly have low stage and grade, which occur in individuals often before menopause age and at younger ages with low parity. These lesions are mainly unilateral and have a better survival rate than non-endometriosis-associated types (14-19). It was shown that ovarian clear cell adenocarcinoma (CCC) cases with concomitant ovarian endometriosis have a poorer prognosis compared with endometriosis-negative CCC cases (20).

Given the high prevalence of endometrioma in reproductive age women especially infertile women, and since the small size of such cysts will decrease the ovarian reserve in the case of surgical intervention, endometrioma is generally treated conservatively by fertility specialists. To date there is no firm clinico-pathologic association between endometriosis and concurrent epithelial ovarian



Key Messages

- ▶ Endometriosis can be a risk factor for epithelial ovarian cancer.
- ▶ Gynecologists should be alert in the management of ovarian endometrioma.

cancers; therefore, we tried to examine the concurrent endometrioma with ovarian tumors and determine the odds of developing EAOC in terms of demographic and obstetric characteristics to draw the attention of gynecologists, especially fertility specialists to the importance of endometriosis and meticulous surveillance of these patients.

Materials and Methods

Setting Study

This cross-sectional, descriptive-comparative study draws on the files of individuals who had undergone surgery at Al-Zahra hospital of Tabriz University of Medical Sciences from 2011-2017 years due to malignant epithelial ovarian tumors.

Data Sources and Measurement

Cases with pathology results of epithelial ovarian cancers of the serous, mucinous, clear cell, undifferentiated, Brenner, and endometrioid types were included in the study with no age limits.

Participants

Individuals with malignant germ cell, sex cord, and metastatic tumors and patients with history of ovarian cancer were excluded. Qualified cases were divided into two groups: the first group only had malignant epithelial ovarian tumor (non-EAOC). The second group had both malignant epithelial ovarian tumor and endometriosis (EAOC).

Quantitative Variables/ Bias and Sample Size

An information collection form was developed to record some clinical information such as age, history of infertility, duration of infertility, history and duration of oral contraceptive (OCP) consumption, history of taking fertility aids, and family history of ovarian cancer, parity, gravidity, abortion, term pregnancy. Furthermore, pathologic information including tumor size, histopathology, concurrent endometrial hyperplasia and cancer, and the side of the involved ovary with tumor and endometriosis was collected for each participant.

Data Analysis

Clinical and histopathologic data were analyzed in the SPSS version 17.0 using descriptive statistics (frequency, percentage, mean and standard deviation). To compare the qualitative variables, chi-square test or Fisher's exact test was used and for quantitative variables, independent

t test or Mann-Whitney U test and calculation of odds ratio (OR) with a 95% confidence interval (CI) were used. Significance level was $P < 0.05$.

Results

Of the 190 ovarian cancer cases who had underwent surgery from 2011 to 2017, 30 individuals were excluded from the study because of metastatic and non-epithelial ovarian cancer and 160 individuals with epithelial ovarian cancer were studied. Of these, 20 were EAOC and 140 were non-EAOC cases (Figure 1).

Clinical characteristics of the two groups are shown in the (Table 1). The mean age of the EAOC cases was lower than the non-EAOC ones ($P = 0.002$). The gravida of a large number of the EAOC individuals was less than 3 ($P = 0.002$) and the odds ratio of developing EAOC in women with gravida less than 3 was 4.3 times greater than in the other groups (OR=4.3, 95% CI=1.6-11). The number of term pregnancies <3 in the EAOC group was higher than in the non-EAOC group ($P = 0.005$) (OR=3.9, 95% CI=1.4-10.9). About parity in the EAOC group, the number of over-5-month pregnancies ≥ 3 was lower than in the non-EAOC group ($P = 0.004$) (OR=4, 95% CI=1.4-11). OCP consumption in the EAOC group was significantly higher than in the non-EAOC group ($P = 0.013$). However, no difference was found between the two groups in terms of the number of abortion, history of infertility and using fertility aids, duration of OCP consumption, presence of hyperplasia or endometrial cancer, presence of atypical endometriosis, and family history of ovarian cancer. Pathological characteristics of the participants are shown in (Table 2). The histopathologic types of cancers were different between the two groups. A high percentage of the EAOC individuals had clear cell and endometrioid types of epithelial ovarian cancer while in the non-EAOC group, the serous type was the most frequent histopathologic type ($P < 0.001$). In 50% of the EAOC cases, right ovarian endometriosis was higher than left ovary ($P < 0.001$). In these women, the side of tumor-affected ovary was more in the right part and in 16 (80%) EAOC individuals, endometriosis was observed on the

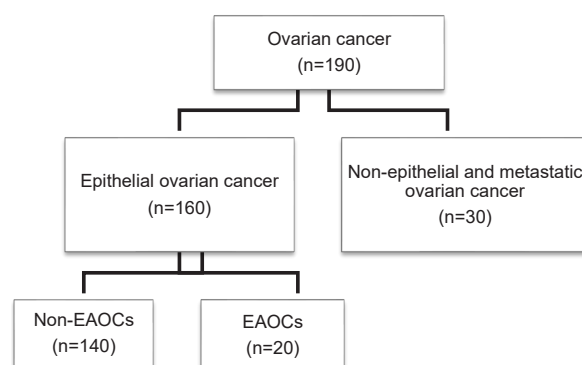


Figure 1. Flow Diagram of the Study.

Table 1. Clinical Characteristics of the Participants

Characteristics	EAO (n=20)	Non-EAO (n=140)	P Value*
Age (y), Mean ± SD	46.5±5.9	55±13.1	0.002
Gravidity, n (%)			
<3	13 (65)	42 (30)	0.002
≥3	7 (35)	98 (70)	0.002
Parity, n (%)			
<3	14 (70)	51 (36.4)	0.004
≥3	6 (30)	89 (63.6)	0.005
Term Pregnancy, n (%)			
<3	14 (70)	52 (37.1)	0.005
≥3	6 (30)	88 (62.9)	0.005
Abortion, n (%)			
<1	16 (80)	96 (68.6)	0.2
≥1	4 (20)	44 (31.4)	0.3
Infertility, n (%)	0 (0)	14 (10)	0.13
OCP users, n (%)	10 (50)	33 (23.6)	0.013
Familial history of ovarian cancer, n (%)	1 (5)	3 (2.1)	1
Endometrial cancer, n (%)	1 (5)	4 (2.9)	1

* The data were analyzed by one-way ANOVA and Tukey post hoc test in SPSS version 17.0. Calculation of odds ratio (OR) with a 95% confidence interval were used and significance level was $P<0.05$.

Table 2. Pathological Characteristics of the Participants

Characteristics	EAO (n=20)	Non-EAO (n=140)	P Value*
Tumor grade, n (%)			
High grade	17 (85)	116 (82.9)	0.8
Low grade	3 (15)	24 (17.1)	0.72
Histologic type, n (%)			
Clear cell	5 (25)	7 (5)	<0.001
Endometrioid	7 (35)	6 (4.3)	<0.001
Serous	7 (35)	111 (79.3)	0.031
Mucinous	0 (0)	8 (5.7)	0 (0)
Mixed epithelial	1 (5)	0 (0)	0 (0)
Laterality of tumor n (%)			
Right	12 (60)	40 (28.6)	0.024
Left	5 (25)	37 (26.4)	0.9
Bilateral	3 (16)	63 (45)	0.021
Tumor size (cm), mean ± SD	12 ± 5.9	10.5 ± 5.5	0.26

* The data were analyzed by one-way ANOVA and Tukey post hoc test in SPSS version 17.0. Calculation of odds ratio (OR) with a 95% confidence interval were used and significance level was $P<0.05$.

same side of the cancer-afflicted ovary ($P<0.001$). Most of the EAO cases had unilateral tumors while the non-EAO cases mainly had bilateral tumors ($P=0.01$) (Table 2). However, no statistically significant difference was found in tumor size and grade between the two groups.

Discussion

Our finding showed that the odds ratio of extending EAO in women with gravida >3 compared to the other groups was remarkably increased. In addition, the mentioned group has higher pregnancies number than the non-EAO group. Moreover, our pathological characteristics results indicated that the percentage of the EAO individuals with clear cell and endometrioid types of epithelial ovarian cancer were significantly more than

the non-EAO group. For decades, studies have shown the relationship between endometriosis and ovarian cancer. One theory in this regard is that during menstruation, endometrial cells that enter the pelvic cavity retrogradely through the fallopian tubes cause the development of endometriosis there and ovarian cancer will develop over time because of mutation in cells of the formed tissue (17).

Clear cell and endometrioid histologic types are the less aggressive subtypes of epithelial ovarian cancers that have been shown in the literature and the present study to be associated with endometriosis. The possible theory behind this is that the mechanism and pathogenesis of the malignancy in these patients are different from those of individuals with non-endometriosis-associated tumors and these differences are the reason for predominance of

some histologic subtypes in these patients (10-12,14).

These histologic types of endometriosis-associated ovarian tumors often occur in young ages, which is also supported by the present findings; these types usually have lower grade and stage and better prognosis at the time of diagnosis (13-15). However, our results were not the same as to pathologic grade.

Similar to another study, endometriosis-associated tumors were generally unilateral in the present study. Researcher believe that the possible reason for unilaterality of these tumors and the young age of patients is that these tumors are diagnosed early due to their concurrence with endometriosis and related symptoms, while non-endometriosis-associated tumors are mostly asymptomatic (2). In this study, most of the EAOC patients had lower rates of gravidity, parity and term pregnancy than the non-EAOC patients. In a similar study with similar results about parity rate, it was assumed that this difference might be attributed to the different pathogenesis of such tumors (13). Although some studies on endometriosis-associated tumors have reported the increased risk of concurrent cancers especially endometrial cancer, we did not achieve the same results.

There is proof that OCP consumption for more than 5 years reduces the risk of ovarian cancer by 50% (19) and the theory proposed for such effect is that increased concentration of cervical mucus can prevent the entry of inflammatory factors that cause disturbance in protective cells against ovarian cancer (20). One meta-analysis that reported a 50% decrease in clear cell and endometrioid types of ovarian cancer through tubal ligation, confirms that theory (21). In the present study, despite the significant difference in OCP users between the two groups, no noticeable result was achieved as to the effect of OCP on prevention of EAOCs and non-EAOCs because the duration of OCP consumption was very short.

Limitations

Although the results of this study revealed the considerable difference of clinico-pathological features between epithelial ovarian cancer patients with and without endometriosis, we have encountered with some problems during the managing of the project that cannot be neglected. For instance, In spite of the proficient staff in disease diagnosis and patient care parts and the performing of strict methods with high quality measures followed by them, we have found that there was an inadequate data recording at the patient's reports. Furthermore, it seems that the patients' follow-up has not always been adequate and was shorter than the standard. However, more recently, based on our finding, we suggest that the epithelial ovarian cancer classification methods should be revisited and it is of importance to emphasize that epithelial ovarian cancer analysis in the Iranian Public Health Systems and in most of the hospitals need to change.

Conclusions

Endometriosis-associated ovarian tumors develop in young ages and have unique histologic subtypes. These tumors are usually unilateral and the rate of parity and pregnancy is lower in these patients. These differences are probably an indication of different mechanism and pathogenesis of malignancy development.

Suggestions

- Patients with endometriosis and especially endometrioma should receive closed follow-up so that in case of severity of clinical symptoms and sonographic changes such as change in size and development of parietal nodules, surgical decisions would be made instead of conservative treatments.
- Conducting more research with larger sample size on the impact of OCPs on reducing ovarian cancers especially of clear cell and endometrioid types in patients with endometriosis, and if confirmed, long-term OCP consumption could be used to reduce the possibility of developing associated ovarian cancers.
- Conducting cohort studies on patient survival and prognosis.
- Conducting more research on pathological and molecular pathways of EAOC development in order to find pathological pathways and thus prevent the development of ovarian cancers.

Authors' Contribution

MJS and NHS designed the study and conducted the research. HF, ADT, YP, PMG, MS, MV and VR monitored, evaluated, and analyzed the result of the study. Further, MJS, and SP reviewed the article. All authors approved the final manuscript and take responsibility for the integrity of the data.

Conflict of Interests

Authors have no conflict of interest.

Ethical Issues

This research was managed based on regulatory and ethics committee approval in Iran and the ethical approval of this research was obtained from the Ethics Committee of teaching Al-Zahra hospital in Tabriz University of Medical Sciences, Tabriz, Iran. Written informed consent for all living patients was obtained at Al-Zahra hospital in Tabriz University of Medical Sciences site. The experimental protocol conformed in accordance with the National Institutes of Health guide were approved by the Ethical Committee of Tabriz University of Medical Sciences, Tabriz, Iran (Permit Number: IR.TBZMED.REC.1397.292).

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