

**ORIGINAL ARTICLE**

**Predictive risk factors for occurrence of Tubo-ovarian abscess (TOA) in patients with ovarian endometriosis (OE), a prospective comparative study**

**Short title: Tubo-ovarian abscess in patients with ovarian endometriosis**

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## Abstract

Objective: to assess demographical and clinical criteria of patients with TOAs to evaluate predictive risk factors of occurrence of OE-TOA.

Patients and methods: in the current case control comparative study; 200 patients with OE were included and were divided into the first group (the case) (composed of 80 patients with OE-TOA) and the second group (the control) (composed of 120 patients with OE but no TOA). Then we compared between both groups regarding all parameters.

Results: There is statistically significant relation between occurrence of combined OE and TOA and spontaneous rupture of ovarian cyst ( $p=0.026$ ), history of PID ( $p=0.26$ ) and presence of DM ( $P=0.32$ ). Spontaneous rupture of ovarian cyst and history of PID are significantly associated with combined OE and TOA.

Lower genital tract infections were diagnosed in 8 (66.7%) of patients in the first group (OE-TOAs) and were diagnosed in only 4 (33.3%) patients with OE without TOAs ( $p = 0.042$ ).

History of spontaneous rupture of OE cyst and PID independently increase risk of TOA+ OE by 2.819 and 2.547 folds respectively

Conclusions: we found that predictive risk factors of OE-TOA were; rupture of OE cysts spontaneously in addition to lower genital tract infections, low immunity and neglected pelvic inflammatory diseases.

Keywords: Tubo-ovarian abscess, ovarian endometriosis, risk factors

## Introduction

Pelvic inflammatory diseases (PIDs) are group of infections of the uterus, fallopian tubes and the ovaries [1].

PIDs clinical importance was studied due to their sequels that include infertility, persistent pelvic pain and ectopic pregnancy. Additionally, inadequate treatment of PIDs might be complicated by; pyosalpinx and tubo-ovarian abscesses (TOAs) which are severe complications that were reported in 15–34% of patients with PIDs [2, 3]. It was previously hypothesized that PID and TOA have more liability to occur in severe degrees in patients with endometriosis more than in those without endometriosis [4]. Pelvic peritoneal endometriosis is an important cause of marked pelvic pain [5]. Endometriosis is as a disabling condition which worsen social, sexuality and mental health that might be caused by acute immunological reactions within the microenvironment of endometriosis lesions [6]. Smoking could increase endometriosis risk mainly in infertile nulliparae patients [7]. Moreover, when TOAs were associated with ovarian endometriosis (OE-TOA), it occurs in a severe and even life-threatening form [8].

Macrophages are classified into pro-inflammatory M1 and M2 which induce immunotolerance and angiogenesis. Both were significantly higher in endometriosis [9].

There are many reported risk factors for PIDs and TOAs as; young age of the patient, uterine instrumentation, sexually transmitted infections, multiple sexual partners, hysterosalpingography, and in vitro fertilization (IVF) [10, 11]. AntiMullerian hormone (AMH) levels have a significant accuracy in pregnancy prediction in patients with ovarian endometriosis [12]. The role of neurotrophins in eutopic endometrium from endometriosis-patients was investigated and no differences were found between patients with and without endometriosis with regards to the neurite outgrowth of sensory ganglia [13]. Pelvic nerve-sparing surgery is effective in improving intestinal symptoms after performing radical surgery for endometriosis which needed segmental intestinal resection [14].

However, there is a need for more comprehensive studies that assessed the risk factors for OE-TOA [15].

Aims of the present study were; to assess demographical and clinical criteria of patients with TOAs, to evaluate incidence of occurrence of TOAs in patients with ovarian endometriosis, to evaluate predictive risk factors of occurrence of OE-TOA and finally to correlate between TOAs patients with and without endometriosis to allow early diagnosis, prevention, and adequate treatment.

#### Methods

The current prospective comparative study is performed in Gynecology and obstetrics department, Faculty of Medicine, Zagazig University after taking an approval from the local ethical committee and written informed consents from all patients.

We included all cases with clinical, radiological and pathological evidence of endometriosis with or without TOAs who were surgically operated by laparotomy or laparoscopy in the period from March 2016 till March 2021.

Inclusion criteria of the study:

The surgical indications for all patients were presence of an adnexal mass (greater than four cm in size).

Criteria of inclusion of patients in the first group (the case) were; detected pus during surgery then pathological confirmation of the presence of OE-TOA by detecting endometrial glands/ stroma or hemosiderin laden macrophages in the detected tubo-ovarian cyst, in addition to detection of heavy infiltrate of neutrophils in the capsule of the ovarian cyst and the tube.

Criteria of inclusion of patients in the second group (the control) were; no detected pus during surgery and pathological confirmation of the presence of only OE cysts without the presence of TOAs.

The exclusion criteria were: (1) Malignant tumor of any pelvic organs; (2) suppurative appendicitis with or without appendicular abscesses; (3) patients with incomplete or with lost data.

After application of inclusion criteria 200 patients with OE were included and were divided into the first group (the case) (composed of 80 patients with OE-TOA) and the second group (the control) (composed of 120 patients with OE but no TOA).

We collected all demographic and clinical data of all patients in addition to collection of possible predictive risk factors for OE-TOA. The collected data includes age, marital status, parity, primary or secondary infertility, past history of PID or ectopic pregnancy and history of previous OE cysts removal. We collected data about any previous performed surgery within 15 days as appendectomy, cesarean delivery or uterine cavity surgery within 15 days. We recorded the presence of lower genital tract infection or spontaneous rupture of OE cysts, dysmenorrhea, and any co-existent medical disease as diabetes mellitus or hypertension in addition to monitoring levels of carbohydrate antigen 125 (CA125).

We treated all patients with one of the following 2 antibiotic regimens according to Centers for Disease Control (CDC) guidelines: 1) IV doxycycline 100 mg every 12 h, IV cefoxitin 2 g every 6 h 2) IV clindamycin 900 mg every 8 h and gentamycin 1.5 mg/kg [9].

In case of lack of clinical improvement of the patient in addition to failure of medical treatment response within 48-72h surgery was performed.

Then we divided all included patients into two groups according to clinical and pathologic findings; the first group includes patients with histopathologically confirmed OE-TOAs and those with only OE without TOAs then we compared between both groups regarding all parameters.

Ethical approval to perform the manuscript was taken from local ethical committee of Faculty of medicine Zagazig University.

This manuscript conform the Enhancing the QUALity and Transparency Of health Research (EQUATOR) network guidelines.

Statistical analyses were performed with SPSS version 17 (SPSS Inc., Chicago, IL, USA). We used Kolmogorov-Smirnov and Shapiro-Wilk tests for assessment of normality of data.

We detected mean  $\pm$  standard deviation (SD) for evaluating normally distributed data. We used independent samples *t*-test, Mann-Whitney U test and Kruskal- Wallis tests for comparing the groups according variables distribution. We used Chi-squared test for comparing categorical variables. Binary regression analysis was used to measure odds of risk factor in producing TOAs. Statistical significance was set at  $P < 0.05$  for all tests.

## Results

A total of 200 women were evaluated in this study. Among these women, 80 were diagnosed with OE-TOA and 120 patients were diagnosed with OE without TOAs.

The collected demographic data of both groups were found and compared in table 1.

Patients age ranges from 19 to 59 years with mean age 41.4 years and mean BMI was 24.92 kg/m<sup>2</sup>. About 77% were married, out of them, 19% had previous CS and 34% of them were infertile. Forty percent of the studied patients had OE-TOA. Diabetes and hypertension occurred in

6% and 5% of patients respectively. Concerning past history, 7%, 5%, 4.5%, 7.5%, 6.5%, 7.5% and 6% had history of previous appendectomy, uterine surgery within previous 15 days, IVF, PID, spontaneous rupture of OE, menstrual irregularities, and lower UTI. Table 2

There is statistically non-significant relation between combined OE and TOA and either age of patients, BMI, gravity, parity, marital status, ectopic pregnancy, surgical history, past history of removal of OE cysts, previous appendectomy, previous cesarean delivery or previous uterine cavity surgery.

There is statistically significant relation between occurrence of combined OE and TOA and spontaneous rupture of ovarian cyst ( $p=0.26$ ), history of PID ( $p=0.26$ ) and presence of DM ( $P=0.32$ ). Spontaneous rupture of ovarian cyst and history of PID are significantly associated with combined OE and TOA.

There is statistically non-significant relation between combined OE and TOA and either infertility, previous CS, menstrual irregularities, hypertension, history of ovarian cyst removal, previous appendectomy, history of uterine surgery. Table 3

The number of patients in the first group (OE-TOAs) using IUDs was more than that in the other group (OE) only without TOAs ( $p = 0.042$ ).

Lower genital tract infections were diagnosed in 8 (66.7%) of patients in the first group (OE-TOAs) and were diagnosed in only 4 (33.3%) patients with OE without TOAs ( $p = 0.042$ ).

In multivariate analysis we showed that the most significant predictive risk factors for OE-TOAs are; infections in the lower genital tract, OE cysts spontaneous rupture and concomitant DM.

Treatment options include hysterectomy in addition to adnexectomy through laparotomy was performed for all post-menopausal patients and for some patients older than 40 years.

Adnexectomy without total hysterectomy or ovarian cystectomy was performed in the remaining patients (68.6%) through laparoscopy (17.8%) or laparotomy (0.8%).

Binary logistic regression analysis of factors associated with combined OE+TAH among the studied patients: Table 4

History of spontaneous rupture of OE cyst and PID independently increase risk of TAH+ OE by 2.819 and 2.547 folds respectively

#### Discussion

OE is a relatively common gynecological disorder but OE complicated by formation of secondary TOAs is relatively uncommon pathological finding that was reported to ranged from 2.15% in 1981 to 2.3% in 1997 [17, 18]. Of the 5,595 patients with OE in this study, 44 (0.79%) were diagnosed with OE-TOA. The incidence in Gao et al., [2] was markedly lower than that was reported in previous studies.

Despite rarity of such disorder but it is considered a serious and even fatal disease sometimes fatal [1].

With advancement in using broad-spectrum antibiotics therapy, TOAs incidence and fatality decreased but about 12.5-35% of females complained of PID were still in a need for surgical intervention [19].

It was found that patients with OE are more susceptible to TOA [18], as according to recent reports, endometriosis was found to be a risk factor for TOAs occurrences [20, 21].

It was hypothesized that the initiating factor in TOA formation is invasion of the epithelium of fallopian tube by an organism that damaged the tissues causing necrosis thus abscess formation. There are several incriminated risk factors for TOAs other than OE as the sexual habits, old age and lower immunity [20, 21].

Mechanisms of occurrence of TOAs due to OE are ;(1) OE is considered an immunodeficiency condition which impairs the ability of the immune system to remove and overcome infections, thus leads to TOA (2) The capsule of endometriotic ovarian cyst is thin which allow easy penetration of the bacteria (3) blood content of the OE is a perfect media for bacterial invasion and growth [22]. (4) The "bacterial contamination hypothesis" which states that occurrence of intrauterine bacterial colonization is higher in females with endometriosis [23].

Gao Et Al., [2] observed an increase in risk factors of OE-TOA after lower genital tract infection due to impairment in the cervical mucosal barrier during infection, so infection could easily spread to other pelvic organs as tubes and ovaries which is a classic spread pattern [24]. It was found that the commonest incriminated organism for TOA was *Neisseria gonorrhoea* in addition to *Chlamydia trachomatis* [25, 26]. Recent study demonstrated that *Enterobacteriaceae* and *Streptococcus* are the most frequently detected organisms in TOAs-OE [27]. We showed in the present study that detection rate of lower genital tract microbial infection in the lower genital tract was higher in the cases than in controls, additionally, the most detected organisms were; *Escherichia coli* (50%), *Mycoplasma genitalium* (21.4%) and *Gardnerella vaginalis* (21.4%). These results were in line with results of Gao et Al., [2], confirming the need to a prompt evaluation, diagnosis and treatment of these infections with suitable antibiotics before occurrence of ascending infections.

We showed that rupture of endometriotic ovarian cyst was incriminated in increasing risks of OE-TOA and incidence of TOAs was more common in females with ruptured endometriotic cysts than females without rupture which was similar to results of Gao et Al., [2] but the exact mechanism was not clarified yet.

Possible explanations were previously demonstrated as; that the wall of the endometriotic cyst could easily rupture due bleeding inside it during menstruation which increased intra-cystic pressure [28], additionally after rupture of the cyst, pouring chocolate like material inside the abdominal cavity lead to peritonitis and abscess later on, moreover, cystic blood content is a suitable medium for flourishing bacterial infections [29].

If there was prompt initiation of treatment this will progress to more severe infections and TOAs.

Once clinical diagnosis of OE-TOA is established early surgical intervention by drainage in addition to intravenous antibiotics is needed [30].

TOAs were found to be a rare disease in postmenopausal females in comparison with females in the reproductive period [2]. It was previously found that incidence of TOAs in postmenopausal females ranged from 12% and 18% by researchers previously and was similar to our study (17.8%) [30, 31].

We showed that roles of endometriosis in causing TOAs were not only restricted to females in the reproductive period, but were found in post-menopausal females similarly results of Gao et al., [2]. Which could be explained by considering that endometriosis is a disease of dysregulation of both the endocrine and immune systems [32, 33].

### Conclusions

In the present study we showed an association between OE and TOAs in both females in the reproductive period and post-menopausal females and we found that predictive risk factors of OE-TOA were; rupture of ovarian endometriotic cysts spontaneously in addition to lower genital tract infections, low immunity and neglected pelvic inflammatory diseases.

We recommend giving prophylactic broad spectrum antibiotics to high risk and suspected patients to decrease rate of occurrence and complications of OE-TOA and improve patients prognosis, additionally we advise performing dramatic appropriate surgical drainage of diagnosed abscess.

### Points of strengths of the study

In the present prospective study, we highlighted the fact that suspecting TOAs showed be done in any case of OE which allowed early and better management for detected cases.

Limitations of the study include inclusion of a relatively few patient number due to performing the study in a single center.

### Compliance with Ethical Standards” section

#### Authors contribution:

Prof A. A Conceptualization, Data curation

Prof A. F. A. Project administration, Resources, Software, Supervision

Prof O. H. Validation, Visualization, Writing – original draft, Writing – review & editing.

Prof A.E. A Formal Analysis, Investigation, Methodology, Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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A written informed consent was obtained from all participants in the study.

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Ethical Approval was obtained from local ethical committee of Faculty of Medicine Zagazig University.

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**Table 1. Baseline data of the studied patients.**

<b>Parameter</b>	<b>N=200</b>
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<b>Age:</b>	
Mean ± SD	41.4 ± 7.72
Range	19 – 59
<b>BMI:</b>	
Mean ± SD	24.92 ± 3.11
Range	20 – 30
<b>Gravity:</b>	
Median (IQR)	2 (1 – 3)
Range	0 – 5
Nulligravida	24 (12%)
<b>Parity</b>	
Median (IQR)	1 (1 – 2)
Range	0 – 5
Nullipara	24 (12%)
<b>Marital status:</b>	
Unmarried	47 (23.5%)
Married	153 (76.5%)
<b>Infertility:</b>	N=153 (%)
Absent	101 (66%)
Present	52 (34%)
<b>History of ovarian cyst removal:</b>	
Absent	175 (87.5%)
Present	25 (12.5%)
<b>Previous appendectomy:</b>	
Absent	186 (93.0%)
Present	14 (7.0%)
<b>Previous CS:</b>	N=105
Absent	85 (81.0%)
Present	20 (19.0%)
<b>History of uterine surgery within 15 days:</b>	
Absent	190 (95%)
Present	10 (5%)

<b>History of IVF:</b>	
Absent	191 (95.5%)
Present	9 (4.5%)
<b>History of PID:</b>	
Absent	185 (92.5%)
Present	15 (7.5%)
<b>Spontaneous rupture of OE cyst:</b>	
Absent	187 (93.5%)
Present	13 (6.5%)
<b>Menstrual irregularities:</b>	
Absent	185 (92.5%)
Present	15 (7.5%)
<b>Lower UTI:</b>	
Absent	188 (94%)
Present	12 (6%)
<b>DM:</b>	
Absent	188 (94%)
Present	12 (6%)
<b>Hypertension:</b>	
Absent	190 (95%)
Present	10 (5%)

**Table 2. Relation between occurrence of combined OE and TOA and demographic data.**

Parameter	Total N=200	Group		Test	
		OE+non-TOA	OE+TOA	t	p
		N=120 (%)	N=80 (%)		
<b>Age:</b>					
Mean ± SD	41.4 ± 7.72	40.34 ± 7.38	42.24 ± 8.11	-1.117	0.089
Range	19 – 59	40 – 59	19 – 43		
<b>BMI:</b>					
Mean ± SD	24.91 ± 3.11	24.92 ± 3.14	24.91 ± 3.08	0.009	0.993
Range	20 – 30	20 – 30	20 – 30		
<b>Gravity:</b>					
Median (IQR)	2 (1 – 3)	2 (1 – 3)	2 (1 – 3)	-0.109 <sup>¥</sup>	0.913
Range	0 – 5	0 – 5	0 – 5		
<b>Parity</b>					
Median (IQR)	1 (1 – 2)	1 (1 – 2)	1 (1 – 2)	-0.093 <sup>¥</sup>	0.926
Range	0 – 5	0 – 5	0 – 5		
<b>Marital status:</b>					
Unmarried	47 (23.5%)	32 (68.1%)	15 (31.9%)	1.673 <sup>∞</sup>	0.196
Married	153 (76.5%)	88 (57.5%)	65 (42.5%)		

<sup>¥</sup> Mann Whitney test    <sup>t</sup> independent sample t test    <sup>∞</sup> Chi square test

**Table 2. Relation between occurrence of combined OE and TOA and both medical and clinical characteristics.**

Parameter	Total N=200	Group		Test	
		OE+non-TOA	OE+TOA	t	p
		N=120 (%)	N=80 (%)		
<b>Infertility:</b>	N=153 (%)				
Absent	101 (66%)	56 (55.4%)	45 (44.6%)	0.522 <sup>∞</sup>	0.47
Present	52 (34%)	32 (61.5%)	20 (38.5%)		
<b>History of ovarian cyst removal:</b>					
Absent	175 (87.5%)	109 (62.3%)	66 (37.7%)	3.048 <sup>∞</sup>	0.081
Present	25 (12.5%)	11 (44.0%)	14 (56.0%)		
<b>Previous appendectomy:</b>					
Absent	186 (93.0%)	112 (60.2%)	74 (39.8%)	0.051 <sup>∞</sup>	0.821
Present	14 (7.0%)	8 (57.1%)	6 (42.9%)		
<b>Previous CS:</b>	N=105				
Absent	85 (81.0%)	51 (60.0%)	32 (40.0%)	2.631 <sup>∞</sup>	0.105
Present	20 (19.0%)	8 (40.0%)	12 (60.0%)		
<b>History of uterine surgery:</b>					
Absent	190 (95%)	115 (60.5%)	75 (39.5%)	0.439 <sup>∞</sup>	0.508
Present	10 (5%)	5 (50.0%)	5 (50.0%)		
<b>History of IVF:</b>					
Absent	191 (95.5%)	117 (61.3%)	74 (38.7%)	Fisher <sup>∞</sup>	0.19
Present	9 (4.5%)	3 (33.3%)	6 (66.7%)		
<b>History of PID:</b>					
Absent	185 (92.5%)	115 (62.2%)	70 (37.8%)	4.805 <sup>∞</sup>	0.028*
Present	15 (7.5%)	5 (33.3%)	10 (66.7%)		
<b>Spontaneous rupture:</b>					
Absent	187 (93.5%)	116 (62.0%)	71 (38.0%)	4.95 <sup>∞</sup>	0.026*
Present	13 (6.5%)	4 (30.8%)	9 (69.2%)		
<b>Menstrual irregularities:</b>					
Absent	185 (92.5%)	113 (61.1%)	72 (38.9%)	1.201 <sup>∞</sup>	0.273
Present	15 (7.5%)	7 (46.7%)	8 (53.3%)		
<b>Lower UTI:</b>					

Absent	188 (94%)	116 (61.7%)	72 (38.3%)	3.783 <sup>∞</sup>	0.042
Present	12 (6%)	4 (33.3%)	8 (66.7%)		
<b>DM:</b>					
Absent	188 (94%)	116 (61.7%)	72 (38.3%)	3.783 <sup>∞</sup>	0.032
Present	12 (6%)	4 (33.3%)	8 (66.7%)		
<b>Hypertension:</b>					
Absent	190 (95%)	115 (70.5%)	75 (39.5%)	0.439 <sup>∞</sup>	0.508
Present	10 (5%)	5 (50%)	5 (50%)		

¥ Mann Whitney test t independent ample t test ∞Chi square test \*p<0.05 is statistically significant

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**Table 3. Binary logistic regression analysis of factors associated with combined OE+TAH among the studied patients.**

	$\beta$	Wald	p	AOR	95% C.I.	
					Lower	Upper
Spontaneous rupture of cyst	1.037	2.567	0.109	2.819	0.793	10.018
Previous history of PID	0.935	2.47	0.116	2.547	0.794	8.175

AOR adjusted odds ratio CI confidence interval

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