

## Accepted Manuscript

Title: Extra pelvic endometriosis: Epidemiologic analysis on 200 cases from two different centers

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PII: S0301-2115(17)30389-5  
DOI: <http://dx.doi.org/10.1016/j.ejogrb.2017.08.019>  
Reference: EURO 10025

To appear in: *EURO*

Received date: 30-1-2017  
Revised date: 15-7-2017  
Accepted date: 12-8-2017

Please cite this article as: Matalliotakis Michail, Goulielmos George N, Kalogiannidis Ioannis, Koumantakis Georgios, Matalliotakis Ioannis, Arici Aydin. Extra pelvic endometriosis: Epidemiologic analysis on 200 cases from two different centers. *European Journal of Obstetrics and Gynecology and Reproductive Biology* <http://dx.doi.org/10.1016/j.ejogrb.2017.08.019>

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**Extra pelvic endometriosis: Retrospective analysis on 200 cases in two different countries.****Extra pelvic endometriosis: Epidemiologic analysis on 200 cases from two different centers**

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**Objective(s):** The purpose of the study was to review patients' characteristics and the location of extrapelvic endometriosis.

**Study Design:** Out of 1000 women with endometriosis during a 20 year period, we found 200 cases with extra pelvic endometriosis. Medical reports were evaluated and the diagnosis was confirmed on the pathological specimen.

This study involved cases from two different geographical areas, New Haven and Crete. The age, parity, symptoms, previous surgeries, diagnostic modalities, histopathological evaluation and location of endometriotic implants found in other areas were recorded and analyzed from the patient's charts.

Main outcome measure(s): Statistical methods included  $\chi^2$  and Mann-Whitney U test s measuring incidence of right-VS left sided endometriosis.

**Results:** 200 patients with extrapelvic endometriosis and 800 patients with pelvic endometriosis were included in the study. The gastrointestinal tract represents the most common location of extrapelvic endometriosis with 104/200(52%) cases ( $p<0, 01$ ), followed by the urinary system with 70/200(35%) cases.

We observed the Left-sided ureter being involved in 49/200(24, 5%) cases, significantly higher compare with the right-sided ureter 21/100(10, 5%) ( $p<0, 01$ ).

All women had similar characteristics involving age, weight, main complaints, age of menarche, endometriosis stages, gravid and family history of endometriosis.

**Conclusion(s):**

The gastrointestinal tract and the urinary system are the most common sites of the extrapelvic endometriosis, which was obvious in both countries.

Moreover, we observed that there are no significant differences in demographic variants, menstrual and reproductive characteristics in women with extrapelvic and pelvic endometriosis.

**Key words:** Extra pelvic endometriosis, gastrointestinal tract, left-sided ureter

## Introduction

Endometriosis is a benign, estrogen-determinant disorder that occurs in 10% of women of the reproductive age and appears in 50% of women with infertility, which leads to the estimate

that some 15 million women in Europe suffer from the condition. [1]. Endometriosis could have intra (or endo) and extra pelvic localization. Pelvic endometriosis refers to lesions proximal to the uterus such as the ovaries, the fallopian tubes, the uterine ligaments and the surrounding pelvic peritoneum. However, extra pelvic endometriosis is a rare and complex entity, which can pose a differential diagnostic problem. In this case, the endometriotic tissue is attached in any other location of the body. [2-5].

Areas that are close to the uterus are more likely affected by this phenomenon (e.g bladder, colon) than those in distant locations (e.g lungs, brain). In current literature, the exact prevalence of extrapelvic endometriosis is unknown due to the small number of well-designed epidemiological studies. Data derived mainly from case series and case reports that describe endometriotic implants in every part of the female body [6-8].

In the framework of this study we sought to review patient's characteristics with extrapelvic endometriosis and further to evaluate menstrual and other epidemiological characteristics in women with pelvic endometriosis in comparison with extrapelvic endometriosis.

#### **Material and methods:**

This study was conducted in the Obstetrics and Gynecology Department of Venizeleio General Hospital of Heraklion of Crete and involved 1000 women with endometriosis from two different geographical areas, over a 20- year period. All women were diagnosed by laparoscopy or laparotomy. We retrospectively review, 600 medical records of women with endometriosis between 1996-2005, from the Division of Reproductive Endocrinology at Yale University School of Medicine and 400 cases, between 2000 and 2016, from the department of obstetrics and Gynecology of the University of Crete and the department of Venizeleio General Hospital of Heraklion. The Human Committee of Yale University School of Medicine approved the study for this evaluation (HIC #12590).The Venizeleio General Hospital Ethics Committee for Human Research of Crete also approved the protocol after obtaining the written approval of the patients.The stage of endometriosis was scored according to the revised classification of the American Fertility society [9] and the biopsy specimen was taken to confirm the diagnosis histological.

Extra pelvic endometriosis was classified by Markham et al. system classification of extra pelvic endometriosis (10).

A detailed history was recorded, including the age, weight, medical and family history, age at menarche, menstrual characteristics, parity, symptoms, the stage, the size and site of endometriosis.

Among the 1000 cases, the patients were divided into two main Groups. Group 1 included 200 women with extraplevic endometriosis and Group 2 involved 800 patients with pelvic endometriosis. Furthermore, first Group was subdivided into 7 categories, according to the body area where extapelvic endometriotic tissue was abnormally implanted (Table 1).

Both student's t tests and  $\chi^2$  tests were used for comparison of the means of the various characteristics and outcome measures. The results were reported as mean $\pm$  SD.

A two tailed P value less than 0.05 was defined as statistically significant. Because the demographic data were not distributed normally, the Mann–Whitney U test was performed.

**Results:**

Women with extrapelvic endometriosis were slightly older in age (35, 4±6, 3) compared to cases with pelvic endometriosis (31, 2±4, 7) ( $p < 0,004$ ) (Table 2).

In our series, the gastrointestinal tract represents the major location of extrapelvic endometriosis. Out of 200 women, we found 104 (52%) cases with gastrointestinal tract implants. Predominantly, the sigmoid colon is mostly involved, followed by the rectum, ileum and the appendix (Table 1).

Moreover, we reported 70(35%) women with urinary tract endometriosis, leading to Bladder and ureteral defects.

The data suggests a slightly greater left-sided ureteral involvement compare to right-sided. Out of 200 cases, we observed 49(24, 5%) women with left side lesions and 21 (10, 5%) with right side ( $p < 0, 01$ ) (table 1).

Abdominal wall scar endometriosis, thoracic endometriosis, vaginal, vulval, umbilical cord and hepatic endometriosis were rarely reported (Table 1).

Additionally, we found that 155/200 (77, 5%) of our patients also had pelvic endometriosis (table 1).

Our data showed a relative risk of 20% for extrapelvic endometriosis between patients with endometriosis.

The clinical characteristics of 200 women with extrapelvic endometriosis and 800 with pelvic endometriosis are shown in Table 2.

The two groups share similar characteristics such as age, weight, main complaints, age of menarche, stage of endometriosis, grravida and family history of endometriosis.

Among the extrapelvic endometriosis patients, stages III and IV of endometriosis are obviously dominant (Table 2).

Finally, we conclude that women with extrapelvic endometriosis at Yale and in Greece had similar anatomic distributions of the lesions.

**Comment:**

According to several studies, the prevalence of endometriosis was estimated to be 5-10% in women of child-bearing age, but only a small proportion of this number is diagnosed as having the extrapelvic type of the disease [4,8,11].

The frequency of the disease decreases as distance to the uterus increases [10]. This is no uniformly accepted system for staging extrapelvic endometriosis. Markham et al system divides extrapelvic endometriosis into 4 categories. Class I, endometriosis that involves the gastrointestinal tract; Class U, involving the urinary tract; Class L, involving the lungs and thorax, and Class O, that involves any other site. A further staging involves the classification of the lesions based on the exact location and size of the defect [10].

In the current study, we divided extrapelvic endometriosis into seven anatomical locations. The gastrointestinal tract is the most common, followed by the urinary system. To the best of our knowledge, this is the first large report that analyses the distribution of the extrapelvic endometriosis. Previous small epidemiological studies from case series and case reports, describe endometriotic implants in several parts of the female body [1-8, 10, 12].

Various theories have been put forth to explain the mechanisms for the development of pelvic endometriosis. As in pelvic endometriosis, no clear consensus exists on which theory best explains the pathogenesis of the different types and locations of extrapelvic endometriosis [4,

5].

The mechanism through which endometriosis may be associated with extrapelvic implants is unclear. One possibility is that both share similar risk factors.

For instance, both forms have been linked to endometrial mesenchymal stem cells [13, 14]. Other possibilities include the existence of an unknown familial susceptibility that would predispose to this disease as well as immunological and/or genetic factors (Patel et al 2012), an issue that has to be investigated further. Data on the mutation status, rather than reporting family history, would alleviate this potential risk [15, 16].

The existing information regarding the possible enrolment of genetic factors in the development of extrapelvic endometriosis is still poor. However, the expression of vascular endothelial growth factor (VEGF) and cyclooxygenase-2 (COX-2) has been examined previously in extrapelvic endometriotic lesions. VEGF as well as COX-2 immunoreactivity was distributed mainly in the cytoplasm of the adenocytes in inguinal tumors, but was not seen in ovarian tumors. It is well known that VEGF induces endothelial cell proliferation, migration, differentiation, and formation of capillaries, which contribute to the pathogenesis and progression of endometriosis, while accumulated data have shown high levels of VEGF in the peritoneal fluid, serum, mRNA expression, and proteins of patients with endometriosis [17,18]. Moreover, cyclooxygenase- 2 (COX-2), the key enzyme in the conversion of arachidonic acid to prostaglandins, has been mainly associated with the inflammatory response and is highly expressed in the endometriotic ovarian cyst. Together, these results suggested that angiogenesis may be involved in the pathogenesis of extrapelvic endometriosis [19].

Previously, we reported that the distribution of endometriosis was significantly higher in the left ovary in comparison with the right side [5]. Interestingly, in the current issue we observed a slightly greater left-sided ureteral involvement compare to right-sided.

In conclusion, our study demonstrates that the gastrointestinal tract and the urinary system are the most common locations of extrapelvic endometriosis and parallel confirms that the demographic variabilities in the menstrual and reproductive characteristics in women with extrapelvic and pelvic endometriosis are similar. *Overall, we consider that further research and more studies are required* to elucidate the pathogenesis of extrapelvic endometriosis, while genetic and transcriptomic studies will allow to understand the molecular mechanism(s) leading to the development of this condition.

#### Acknowledgments

**We would like to thank Professor Aydin Arici, all the clinicians of the Division of Reproductive Endocrinology and Infertility at Yale University and the colleagues of both University and Venizeleio Hospitals of Crete for providing the data used in this study.**

**“The authors declare that there are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.”**

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<b>Distribution of the location of extra pelvic endometriosis in 200 women</b>		
<b>Location</b>	<b>Number of cases</b>	<b>Percentage (%)</b>
Gastrointestinal tract:	Total :104	52%, P<0,01
a. Sigmoid colon	75	
b. Rectum	45	
c. Ileum	50	
d. Appendix	22	
Urinary system:	Total :70	35%
a. Bladder	52	
b. Left ureter	49	
c. Right ureter	21	
Abdominal wall scar endometriosis:	Total:20	Total (10%)
a. C section scar	16	(80%)
b. other surgeries	4	(20%)
Thoracic	Total:2	(1%)
Vaginal	Total:1	(0, 5%)
Umbilical scar endometriosis	Total:1	(0, 5%)
Vulvar	Total:1	(0, 5%)
Hepatic endometriosis	Total:1	(0, 5%)
Coexistence with Pelvic endometriosis	Total:155	(77, 5%)
Coexistence of Gastrointestinal and Urinary tract endometriosis	Total:65	(32, 5%)

**Table 1. Distribution of the location of extra pelvic endometriosis**



<b>Comparison of clinical characteristics between extra pelvic and pelvic endometriosis cases (Mean <math>\pm</math> SD).</b>		
<b>Characteristics</b>	<b>Extra pelvic endometriosis 200/1000(20%)</b>	<b>Pelvic endometriosis 800/1000(80%)</b>
Age(years)	35,4 $\pm$ 6,3	31,2 $\pm$ 4,7 p<0,04
Weight(kg)	66,1 $\pm$ 12	68,2 $\pm$ 17 N.S
Main complaint :		
a. Infertility	80/200(40%)	450/800(56, 25%) N.S
b. Pelvic pain	120/200(60%)	350/800(43, 75%) N.S
Menarche (age)	12,2 $\pm$ 1,2	12,3 $\pm$ 1,4 N.S
Endometriosis stage		
Stage I	32/200(16%)	198/800(24, 7%) N.S
Stage II	37/200(18,5%)	207/800(25, 8%) N.S
Stage III	65/200(32,5%)	180/200(22, 5%) N.S
Stage IV	66/200(33%)	215/800(26, 9%) N.S
Stage III+IV	131/200(70%) P<0,05	
Gravida:		
a. None	61/200(30, 5%)	360/800(45%) N.S
b. $\geq$ 1	139/200(69,5%)	440/800(55%) N.S
Family history of endometriosis	16/200(8%)	68/800(8, 5%) N.S

**Table 2. Comparison of extra pelvic and pelvic endometriosis cases.**