

## Endometriosis Locations and Coexistence with other Uterine Conditions in a Bulgarian Sample of Patients

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### Abstract

Endometriosis is a non-tumor, estrogen-dependent, chronic gynecological disease, which is characterized by the presence of endometrial glands and stroma outside the endometrium of the uterus. Endometriosis affects between 10% and 15% of women in reproductive age. It is often associated with chronic pelvic pain and reproductive difficulties. Endometriosis can be classified as ovarian, extra-ovarian or mixed. Adenomyosis is considered, by some authors, as a separate variant of endometriosis. It is diagnosed as the presence of ectopic benign endometrial glands and stroma in the myometrium, where the minimal distance from the endometrio-myometrial junction is 2-4 mm. Our study includes 224 cases of women with endometriosis with different locations - in the myometrium (adenomyosis), in the ovaries, fallopian tubes, soft tissues and appendix as well as in combination with other conditions of the uterine body, such as endometrial carcinoma, leiomyomas, endometrial hyperplasia, polyps and atrophy and cervical cancer. There are cases of coexistence of several conditions in the same patient, and we are trying to find the reason behind this.

**Keywords:** Endometriosis, Localization, Adenomyosis, Combination with other Uterine Pathology

### 1. Introduction

Endometriosis (EM) is the second most common reason for surgical procedures in women before menopause after the uterine leiomyomas (Overton C., 2007). It usually affects women in reproductive age and is not observed in girls before puberty. The incidence of endometriosis in premenopausal women is 10-15% (Giudice LC, 2004). Clinically it is manifested as pelvic pain during menstruation, dysmenorrhoea, dyspareunia, infertility, menorrhagia, etc. (Eskenazi B, 2001). There are four main theories trying to explain the etiology of endometriosis: embryonal (ectopic foci of Mullerian epithelium); transplantational (in retrograde menstruation or surgery there are vital endometrial cells which can colonize the peritoneum, cervix or a cicatrix from an operation); metastatic (during menstruation necessary endometrial elements can enter the lymphovascular spaces of the uterus and ‘metastasize’ to distant sites such as brain, lungs) and metaplastic (under the influence of estrogen, the Mullerian epithelium can transform into endometrial. This is how endometriosis in men, who are treated with estrogen therapy, is explained) (Karagiozov, 2005)

Depending on the location of the endometriotic lesions, endometriosis is predominantly found in the ovaries, followed by soft tissue, gastrointestinal and urinary tract (Lee HJ, 2015). In Bulgarian medicine, adenomyosis is also a type of endometriosis, but in the western countries, it is separated as an individual entity, which is represented by



benign ectopic endometrial glands and stroma in the myometrium ( Robboy St, 2008). The endometrio-myometrial junction is uneven, and many times this makes it challenging to determine adenomyosis. That is why, from a practical point of view the minimal distance from the endometrio-myometrial junction to the focus of adenomyosis needs to be 2-4mm or one medium power field ( Robboy St, 2008; Overton C, 2007).

There are studies which try to find an association between the coexistence of several conditions of the uterus and for most of them hyperestrogenism is to be blamed. The presence of adenomyosis in determining the prognosis of endometrial carcinoma remains controversial (Seza Tetikkurt, 2018).

## 2. Materials and methods

Our study involves a retrospective analysis of 224 patients diagnosed with EM over three years (2016-2018), at University hospitals 'St. George' and 'Pulmed,' Plovdiv, Bulgaria. All histological specimens were processed and prepared at the morphological center of Medical University-Plovdiv and the laboratory of the Department of clinical pathology at University Hospital 'St. George'. The cases were analyzed according to localization of the endometriotic lesions, age and combinations of endometriosis with other conditions of the uterus.

We have used routine staining with Hematoxylin/Eosin for this phase of our study.

## 3. Results

In our study, we have analyzed 224 cases of endometriosis, and we must clarify that this is the total number of patients with endometriosis, including cases with other leading uterine pathology in combination with endometriosis. The patients only with endometriosis were 208 (79.7%).

The most common site of endometriosis was in the myometrium (adenomyosis), presented by 157 (75.5%) cases. The second most common localization in our patients was ovarian endometriosis, observed in 50 (24%) cases. There were 10 (5%) cases of endometrial glands and stroma found in soft tissues, mainly in the abdominal wall, after different surgical interventions. We also registered 2 (1%) cases of endometriosis of the fallopian tubes and one (0.5%) case of endometriosis in the appendix. These results are presented in table 1.

Table 1. Number and percentage of patients with endometriosis according to its location

|            | Location   |         |                 |              |          |
|------------|------------|---------|-----------------|--------------|----------|
|            | Myometrium | Ovaries | Fallopian tubes | Soft tissues | Appendix |
| Number (%) | 157 (75.5) | 50 (24) | 2 (1)           | 10 (5)       | 1 (0.5)  |

We also studied the combination of endometriosis with other uterine pathology as endometrial carcinoma (EC), leiomyomas, endometrial polyps, endometrial hyperplasia and atrophy, and cervical cancer. Most of our cases had a combination of endometriosis and leiomyomas - 134 (59.8%). The next most common combination we established is the one between endometriosis and endometrial hyperplasia - 34 (5.2%) cases. The combination of endometriosis with endometrial atrophy was observed in 28 (12.5%) cases, with endometrial polyps - in 23 (10.3%) cases, with endometrial carcinomas - in 11 (5.8%) cases. We had only one (0.4%) case with EM and cervical carcinoma (table 2).

Table 2. Number and percentage of patients with different combinations of endometriosis and other conditions of the uterus.

| Endometriosis and: | EC            | Leiomyoma    | Endometrial polyps | Endometrial hyperplasia | Cervical carcinoma | Endometrial atrophy |
|--------------------|---------------|--------------|--------------------|-------------------------|--------------------|---------------------|
| Number of patients | 11            | 134          | 23                 | 34                      | 1                  | 28                  |
| % of patients      | 5,8           | 59,8         | 10,3               | 15,2                    | 0,4                | 12,5                |
| Average age ± SD   | 61.14 ± 11.56 | 51,40 ± 9.32 | 56,30 ± 10.95      | 49.27 ± 5,12            | 64                 | 64,04 ± 10,43       |

We analyzed our results also according to the average age of our patients in the different groups of combinations. The oldest patients were observed in the cases with combination between EM and endometrial atrophy with average age 64.04 years. In second place is the case with EM and cervical cancer - 64 years. After that follow the cases with EM and endometrial carcinoma (EC) - 61.14 years, EM and endometrial polyps - 56.30 years, EM and leiomyomas - 51.40 years. The youngest group of patients had a combination of EM and endometrial hyperplasia - 49.27 years. The ANOVA analysis of the average age of patients with different combinations of EM and other uterine pathology



established a significant difference ( $p=0.004$ ). There are significant differences also in the average age of the patients with the following combinations: EC and leiomyomas ( $p<0.001$ ), EC and endometrial hyperplasia ( $p=0.001$ ), leiomyomas and endometrial polyps ( $p=0.005$ ), leiomyomas and endometrial atrophy ( $p=0.011$ ), endometrial polyps and endometrial hyperplasia ( $p=0.049$ ) and endometrial hyperplasia and endometrial atrophy ( $p=0.008$ ).

This data is graphically presented in fig. 1.

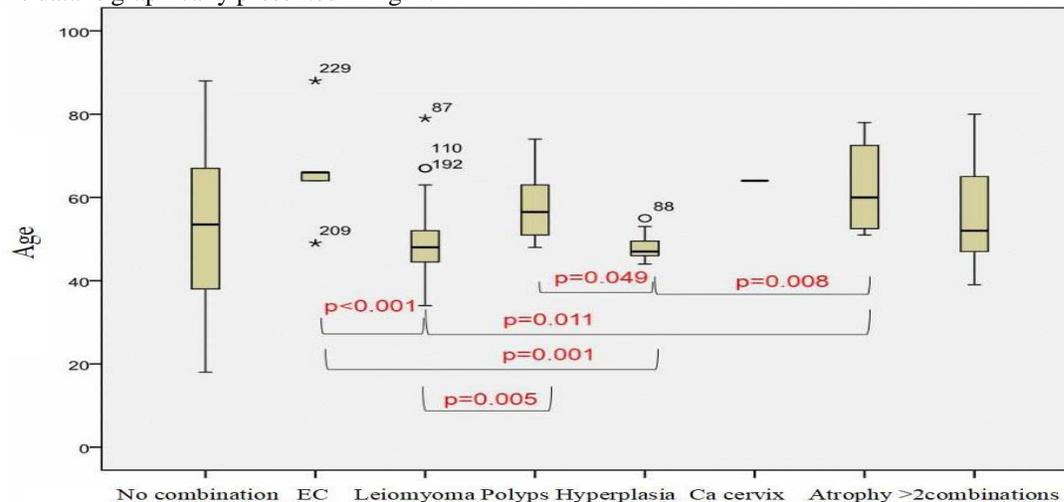


Figure 1. Differences in the average age of patients according to the combination of diagnoses

We observed two or more combinations of the mentioned diseases in 57 (28.1%) patients.

#### 4. Discussion

Depending on the location of the endometriotic lesions, endometriosis is predominantly found in the ovaries, followed by soft tissue, gastrointestinal and urinary tract, according to some authors (Lee HJ, 2015). In Bulgarian medicine, adenomyosis is also a type of endometriosis, but in the western countries, it is separated as an individual entity, which is characterized by the presence of benign ectopic endometrial glands and stroma in the myometrium (Robboy St, 2008). The endometrio-myometrial junction is even, and many times this makes it challenging to determine adenomyosis. That is why, from a practical point of view the minimal distance from the endometrio-myometrial junction to the focus of adenomyosis needs to be 2-4mm or one medium power field or 25% of the thickness of the myometrium (Robboy St, 2008; Overton C, 2007). Some studies have reported an incidence of adenomyosis as high as 21-25% of hysterectomies (Parazzini F, 1997). An interesting fact to mention is that the depth of adenomyosis does not correlate with the severity of the clinical symptoms. Sometimes even very superficial adenomyosis can cause significant menorrhagia (McCausland AM, 1996).

In our study we also established that most cases are with adenomyosis (157, 75.5%), followed by endometriosis in the ovaries (50, 24%), soft tissues (10, 5%), fallopian tubes (2, 1%) and appendix (1, 0.5%), which is in correspondence with the data from other studies.

Ovarian cysts, adenomyosis, endometriosis, and leiomyomas are benign diseases, which often affect women in reproductive age. Sometimes different combinations between these diseases are found in the same patient. Many authors suggest comorbidity of endometriosis and other gynecological conditions, including the ones mentioned above (Matalliotaki C, 2017).

In our study, we analyzed patients with endometriosis according to the localization of the lesions and also in combination with other conditions such as EC, leiomyomas, endometrial hyperplasia, endometrial polyps, endometrial atrophy, and cervical carcinoma.

Most of our cases were diagnosed with a combination between EM and leiomyomas (134, 59.8%). The connection between these two diseases is not well established, but both of them are often a cause of chronic pain and infertility in women (Nezhat C, 2016).

Leiomyomas of the uterus are benign tumors of the smooth muscle tissue and are observed in 20-25% of women in reproductive age (Wecher M, 2011, Cardozo E, 2012, Stewart E, 2001). Their development is associated with multiple factors, some of the most common being high estrogen levels, hereditary predisposition and negroid race

(Buttram V, 1981). Other factors related to the growth of uterine leiomyomas are somatotropin and human placental lactogen ( Vollenhoven, 1990, Hua Yang L, 2013).

In a study of Nezhad C, 2016, which aims to determine the incidence of combination between symptomatic uterine leiomyomas and EM, the results showed that 87.1% of the patients with leiomyomas also had histologically diagnosed endometriosis.

Leiomyomas can be easily identified with ultrasound and are often treated by surgery. In reproductive age, the methods of choice are hysteroscopic and laparoscopic techniques which can easily miss concomitant endometriosis. This is one of the significant reasons for the ineffective treatment of the symptoms in such patients (Huang J, 2010). This data from the available literature confirms our results, where we also report a very high number of patients diagnosed with EM and leiomyomas (134, 59.8%).

Concerning the average age of our patients with EM and leiomyomas, a study of Day Baird D, 2003, reports an incidence of nearly 70% in Caucasian women by age 50, which is a very close result to ours (51.40 years).

The next most common combinations in our study are between EM and endometrial hyperplasia (34, 15.2%) and EM and endometrial polyps (23, 10.3%). In a survey by Seza Tetikkurt, 2018, the percent of patients with a combination of adenomyosis, endometrial hyperplasia and polyps was 30.41%. In our study, we observed similar results of 25.5%.

Parazzini et al., 2009, establish a significant association between adenomyosis, endometrial hyperplasia, and polyps. The incidence of this combination of conditions is mainly explained by the common risk factors such as elevated estrogen levels, early menarche, no pregnancies, late menopause, estrogen therapy during menopause, polycystic ovarian disease, treatment with Tamoxifen, etc. (Chisholm A, 2019).

In the study of Seza Tetikkurt, 2018, the women with adenomyosis, combined with endometrial hyperplasia and polyps were mostly aged 41-55 years. Our results also fall in that category, as the patients in our study with this combination of conditions are between 48 years and 56 years.

Concerning the cases of endometriosis and atrophy of the endometrium - the average age of these patients is 64.04 years, i.e., postmenopausal. If endometriosis occurs in the postmenopausal period, it is less common, present in small foci and is less active. It has the same immunochemical profile as the disease occurring in premenopausal women and has the potential to reactivate (Cumiskey J, 2008). The postmenopausal disease could be enhanced in the presence of higher circulating levels of estrogen especially in the form of phytoestrogens and hormone therapy. Phytoestrogens have been known to exert estrogenic effects on the uterus, breast, and pituitary and promote the growth of endometriotic deposits (Shah D, 2014).

As for the case of endometriosis and cervical cancer in our results, we can conclude that it is a rare and uncommon combination and the two conditions are not related as we could not find any data from the available literature confirming such an association.

An impressive group of patients is the one with combination between EM and EC. We compared the FIGO stage of these patients with the FIGO stage of patients who had only EC, and we found that the patients who had EM and EC were diagnosed in a significantly higher FIGO stage. This association is established by other authors (Izmiil N, 2007) as well, who report deep myometrial invasion in 91.3% of patients with EC and adenomyosis, compared to 63.8% of patients only with EC. One of the suggested reasons for the deeper myometrial invasion of EC in combination with adenomyosis is that adenomyosis increases the contact area with the myometrium and facilitates the invasion of the EC (Izmiil N, 2007).

The average age of the patients with EM and EC is 61.14 years, which is similar to the results of other authors (Seza Tetikkurt, 2018, >55 years) observing this combination of conditions.

## 5. Conclusion

Endometriosis is a common gynecologic condition occurring most commonly in women in reproductive age. It is associated with infertility and chronic pelvic pain.

In conclusion, we can recommend evaluation and screening of patients in their premenopause who are diagnosed with leiomyomas, for endometriosis to provide effective treatment of the symptoms of these patients. Our results, as well as those of other authors, prove a high incidence of the coexistence of these two conditions.

Coexisting conditions, such as leiomyoma, endometriosis, endometrial polyp, endometrial hyperplasia, and endometrial carcinoma, are frequently associated with adenomyosis. The high incidence of these pathological lesions related to adenomyosis suggests the presence of a common underlying disorder, such as hyperestrogenism.

Although there are several cases of endometrial carcinomas and adenomyosis, the presence of adenomyosis in determining the prognosis of endometrial cancer remains controversial.

## Conflict of interests

The authors do not declare any conflict of interests.



## References

- Baird, D.D., Dunson, D.B., Hill, M.C., Cousins, D.S., & Schectman, J.M. (2003). High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *American journal of obstetrics and gynecology*, 188 1, 100-7 .
- Buttram VC, Jr, Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. *Fertil Steril*. 1981;36:433-445.
- Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual cost of uterine leiomyomata in the United States. *Am J Obstet Gynecol*. 2012;206:e211-e219.
- Cumiskey J, Whyte P, Kelehan P, Gibbons D. A detailed morphologic and immunohistochemical comparison of pre- and postmenopausal endometriosis. *J Clin Pathol*. 2008;61:455-9
- Eskenazi B, Warner M, Bonsignore L et al. Validation study of nonsurgical diagnosis of endometriosis. *Fertil Steril* 2001;76:929-35
- Giudice LC, Kao LC. Endometriosis. *Lancet*. 2004; 364:1789-99
- Hua Yang LZ, Shu Wang, Jinghe Lang, Tao Xu. Noninvasive diagnosis of moderate to severe endometriosis: the platelet-lymphocyte ratio cannot be a neoadjuvant biomarker for serum cancer antigen 125. *J Minim Invasive Gynecol*. 2013;22:373-377.
- Huang J.Q., Lathi R.B., Lemyre M., Rodriguez H.E., Nezhat C.H., Nezhat C., Coexistence of endometriosis in women with symptomatic leiomyomas (2010) *Fertility and Sterility*, 94 (2) , pp. 720-723.
- Ismiil N, Rasty G, Ghorab Z, Nofech-Mozes S, Bernardini M, Ackerman I, Thomas G, Covens A, Khalifa MA. Adenomyosis involved by endometrial adenocarcinoma is a significant risk factor for deep myometrial invasion. *Ann Diagn Pathol*. 2007;11:252-257.
- Lee HJ, Park YM, Jee BC, Kim YB, Suh CS. Various anatomic locations of surgically proven endometriosis: A single-center experience. *Obstet Gynecol Sci*. 2015;58(1):53-58. doi:10.5468/ogs.2015.58.1.53
- Matalliotaki C, Matalliotakis M, Ieromonachou P, et al. Co-existence of benign gynecological tumors with endometriosis in a group of 1,000 women. *Oncol Lett*. 2017;15(2):1529-1532. doi:10.3892/ol.2017.7449
- McKenney JK, Kong CS, Longacre TA. Endometrial adenocarcinoma associated with subtle lymph-vascular space invasion and lymph node metastasis: a histologic pattern mimicking intravascular and sinusoidal histiocytes. *Int J Gynecol Pathol* 2005;24:73-7
- Nezhat C, Li A, Abed S, et al. Strong Association Between Endometriosis and Symptomatic Leiomyomas. *JLSL*. 2016;20(3):e2016.00053.
- Overton C., C. Davis MD, L. McMillan, R. W. Shaw, Atlas of endometriosis, third edition, 2007, ISBN-10: 0 415 39573 9, ISBN-13: 978 0 415 39573 1
- Parazzini F, Vercellini P, Panazza S, Chatenoud L, Oldani S, Crosignani PG: Risk factors for adenomyosis. *Hum Reprod* 1997; 12:1275-1279.
- Karagiozov I, Iliev, Atanasov A., Doganov N., Pranchev N., Dimitrov A., Shterev A, Nalbanski B, Obstetrics and gynecology, 2005, ISBN 954-420-040-1
- Robboy St., Hubbard Chr., Madden J., Dash R., 'Robboy's pathology of the female genital tract', 2008 , ISBN 9780702033551
- Shah D. Postmenopausal endometriosis: An enigma revisited. *J Midlife Health*. 2014;5(4):163-164. doi:10.4103/0976-7800.145189
- Stewart EA. Uterine fibroids. *Lancet*. 2001;357:293-298.
- Tetik Kurt S, Çelik E, Taş H, Cay T, Işık S, Usta AT. Coexistence of adenomyosis, adenocarcinoma, endometrial and myometrial lesions in resected uterine specimens. *Mol Clin Oncol*. 2018;9(2):231-237.
- Vollenhoven BJ, Lawrence AS, Healy DL. Uterine fibroids: a clinical review. *Br J Obstet Gynaecol*. 1990;97:285-298.
- Wechter ME, Stewart EA, Myers ER, Kho RM, Wu JM. Leiomyoma-related hospitalization and surgery: prevalence and predicted growth based on population trends. *Am J Obstet Gynecol*. 2011;205:e491-e495.

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