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Ultrasound findings in infertile women with endometriosis: evidence of concomitant uterine disorders

Tommaso Capezzuoli, Silvia Vannucci, Giulia Fantappiè, Giulia Orlandi, Francesca Rizzello, Maria Elisabetta Coccia and Felice Petraglia

*Department of Clinical and Experimental Biomedical Sciences, University of Florence, Florence, Italy; \(^b\)Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy

**ABSTRACT**

Endometriosis is a gynecological disease characterized by pain and infertility. The diagnosis is very often made during the infertility work-up, together with other reproductive diseases and uterine disorders. A retrospective cohort study was conducted on infertile women with clinical or ultrasound suspect of endometriosis, undergoing an ultrasound (US) evaluation by a team of expert sonographers (n = 419), with the aim to evaluate the prevalence of concomitant uterine disorders. The US coexistence of endometriosis with uterine fibroids and/or adenomyosis was investigated according to three age intervals (<35 years; 35 ≥ years <45; ≥45 years) and to endometriosis phenotypes: ovarian endometriosis (OMA), deep infiltrating endometriosis (DIE), or both. The US diagnosis of fibroids was made in 3.1% of cases, adenomyosis was found in 21.2%, and the co-existence of both uterine disorders with endometriosis was reported in 14.6% of patients. When analyzed according to age, patients aged >35 years were more likely to be affected by uterine fibroids (\(p = .003\)), adenomyosis (\(p = .030\)) and both adenomyosis and fibroids (\(p < .0001\)). No statistically significant association was found between endometriosis phenotypes and myometrial pathologies. Uterine disorders coexistence should be considered in the assessment of women with endometriosis, in order to better define a treatment strategy for infertility, especially in women older than 35 years.

**KEYWORDS**

Adenomyosis; endometriosis; infertility; transvaginal ultrasound; uterine fibroids

**INTRODUCTION**

Endometriosis is defined as the presence of ectopic endometrial tissue outside of the uterine cavity [1]. It is a common disease, affecting approximately 5–10% of fertile age women, presenting with either pain or infertility. According to the localization of ectopic tissues in the pelvis, endometriosis is classified into three main phenotypes: ovarian endometriosis (OMA), superficial peritoneal endometriosis (SUP), and deep infiltrating endometriosis (DIE) [2,3]. Epidemiological data show that endometriosis is observed in 5% of fertile age women [4], but no data exist on the coexistence of adenomyosis and uterine disorders in those patients.

Adenomyosis is the presence of endometrial glands and stroma into the myometrium, causing pain and abnormal uterine bleeding [5]. Data obtained from surgical dataset showed a prevalence of adenomyosis in women with endometriosis ranging between 20 and 80% [3–8]. These data were collected pre-operatively by transvaginal ultrasound (TVUS) or magnetic resonance (MRI). No study investigated the prevalence of adenomyosis in women with endometriosis, referred to infertility clinics, independently from the surgical treatment.

Similarly, imaging studies are available on the prevalence of uterine fibroids in endometriosis, originating from surgical and histological reports in perimenopausal women. Uimari et al. [9] detected uterine fibroids in 25.8% of patients undergoing surgery for endometriosis and, conversely, in 19.6% of patients operated for uterine fibroids. According to another surgical report, premenopausal women requiring an hysterectomy for benign uterine disorders had endometriosis and adenomyosis in 40.4%, endometriosis and uterine fibroids in 22.7%, both conditions in 34.1% [10]. In a similar report on women undergoing surgery for benign gynecologic disease, the coexistence of endometriosis with uterine fibroids, adenomyosis, and benign ovarian cysts were 28, 43.5, and 50%, respectively [11]. Coexisting uterine fibroids and endometriosis were identified in 21.2% of patients undergoing laparoscopy myomectomy [12], but no data are available on the sonographic association between endometriosis and uterine fibroids in infertility clinics.

The aim of this study was to evaluate the sonographic prevalence of adenomyosis and uterine fibroids in patients with endometriosis at different age intervals in an infertility center.

**MATERIALS AND METHODS**

A retrospective cohort study was performed on women with clinical or ultrasound suspect of endometriosis, referred from 2015 to 2018 to our Endometriosis outpatient clinic during the infertility work-up (Careggi, University Hospital, Florence, Italy). They underwent a further TVUS evaluation performed by expert sonographers (\(n = 586\)). The included cases were infertile women in reproductive age (25–52 years old) with ultrasound evidence of endometriosis lesions. Clinical and US reports and images were reviewed and an electronic database was built.

Ultrasoundography was performed by using two ultrasound machines (Voluson E8, GE) and a transvaginal probe (5–7.5 MHz) (RIC 6-12-D, GE) by three gynecologists with high level expertise on gynecological US. During the examination, uterus,
We described the uterine disorder characteristics and the International Ovarian Tumor Analysis (IOTA) consensus [14]. Those are statements on terms, definitions and measurements that may be used to describe and report the sonographic features of endometriosis, myometrium, and ovarian masses, respectively.

OMA lesions were described according to IOTA criteria, identifying the ultrasound-homogeneous ‘tissue’ with homogeneously dispersed echogenic cystic contents (‘ground glass’ appearance) [14]. DIE lesions were described according to IDEA criteria [2]. Anterior compartment DIE ultrasound appearance included hypoechoic linear or spherical lesions, with or without regular contours involving the muscularis or submucosa of the bladder. In the posterior compartment, DIE lesions can appear as hypoechoic thickening of the wall of the bowel or vagina or ad hypoechoic solid nodules with smooth or irregular contours.

Uterine fibroids and adenomyosis were described according to MUSA criteria [13]. Ultrasound appearance of fibroids is typically described as a well-defined round lesion within the myometrium or attached to it, often showing shadows at the edge of the lesion and/or internal fan-shaped. On color- or power-Doppler imaging, circumferential flow around the lesion is often visible. Size, localization, and types of uterine fibroids were described.

Adenomyosis was described as diffuse, if present in the myometrium as dispersed, or focal, if forming a confined lesion. In case it was present as a large cyst, a cystic adenomyosis was identified. Both 2-dimensional (2D) and 3-dimensional (3D) features of adenomyosis were used: enlarged uterus with myometrial anteroposterior asymmetry; junctional zone (JZ) thickened (regular or irregular); and/or interrupted; myometrial lesions with ill-defined outline, shape, and/or contour; no rim; no edge shadows or fan-shaped shadowing; non uniform/mixed echogenicity with cyst and translesional vascular flow [13].

A total number of 419 patients with US confirmed endometriosis were included in the study. Histological confirmation of endometriosis was not considered an inclusion criterion to the study, only a small percentage of women had a history of previous surgery for endometriosis (12%), as most of women were a first referral for a clinical or sonographic suspect of endometriosis. The flowchart of study population and the subgroups according to endometriosis phenotypes are shown in Figure 1. We described the uterine disorder characteristics and the presence of gynecological comorbidities in Table 1. The ultrasound coexistence with uterine fibroids and/or adenomyosis was investigated and the study group was subdivided into three groups of patients according to age (<35 years; 35 ≥ years >45; ≥45 years). In particular, we evaluated whether the prevalence of uterine fibroids and adenomyosis was different in the three subgroups and whether age influenced the coexistence of endometriosis and uterine disorders. Moreover, we compared the endometriosis phenotype prevalence (OMA, DIE, or both) in the three subgroups. Finally, we analyzed if a particular endometriosis phenotype (OMA, DIE, or both) was associated with uterine fibroids and adenomyosis, independently of age. We have not evaluated the influence of lesions size on the variables analyzed because, with the exception of OMA, the measurements are not standardized and poorly reproducible. Similarly, the reported history of multiple and temporally heterogeneous medical treatments did not allow to obtain reliable results on the influence of previous interventions on uterine comorbidities prevalence. The study follows the principles of the Declaration of Helsinki. Participants gave written informed consent for participating in the study. Continuous and binomial variables were collected and an electronic database was analyzed by using SPSS (SPSS 22.0 version). ANOVA test and χ² test were used as appropriate. Significance level was stated at <.05.

Results

US prevalence of uterine disorders in patients with endometriosis is shown in Table 1. In these patients, uterine fibroids were identified in 419/586 cases (74.2%). Ovarian endometriosis was identified in 244/419 (58.2%) cases, and deep infiltrating endometriosis in 89 (21.2%) cases. Ovarian and deep infiltrating endometriosis was identified in 86 (20.5%) cases.

Table 1. Gynecological comorbidities in patients with ultrasound diagnosis of endometriosis.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>419/586</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>35.6 ± 8.0</td>
</tr>
<tr>
<td>Uterine disorders comorbidities</td>
<td></td>
</tr>
<tr>
<td>a. Uterine fibroids</td>
<td>13/419 (3.1%)</td>
</tr>
<tr>
<td>b. Adenomyosis</td>
<td>89/419 (21.2%)</td>
</tr>
<tr>
<td>c. Both fibroids and adenomyosis</td>
<td>61/419 (14.6%)</td>
</tr>
<tr>
<td>Type of uterine fibroids</td>
<td></td>
</tr>
<tr>
<td>a. Submucous</td>
<td>5 (1.2%)</td>
</tr>
<tr>
<td>b. Intramural</td>
<td>49 (11.7%)</td>
</tr>
<tr>
<td>c. Subserous</td>
<td>36 (8.6%)</td>
</tr>
<tr>
<td>Uterine congenital malformations</td>
<td></td>
</tr>
<tr>
<td>a. Yes</td>
<td>5/419 (1.2%)</td>
</tr>
<tr>
<td>b. No</td>
<td>414/419 (98.8%)</td>
</tr>
<tr>
<td>Polycystic ovary ultrasound appearance</td>
<td></td>
</tr>
<tr>
<td>a. Yes</td>
<td>39/419 (9.3%)</td>
</tr>
<tr>
<td>b. No</td>
<td>380/419 (90.7%)</td>
</tr>
</tbody>
</table>

Figure 1. Flow chart with of study population.
examination after hysterectomy [5]. In addition, TVUS is a rela-

tively accessible imaging modality and it has an increasing role 
in the differential diagnosis between the two conditions [13].

Adenomyosis is often associated with pelvic endometriosis and seems to be more frequent in severe forms of disease. In fact, a recent study on pre-surgical US evaluation of reproductive age women before undergoing laparoscopic surgery for pelvic pain described a strong association between uterine adenomyosis and stage IV endometriosis [16]. Similar to previous studies [3, 6], we found that a prevalence of isolated adenomyosis in patients with pelvic endometriosis was 21.2%. The association between uterine fibroids and endometriosis is less clear, even if the histological prevalence of uterine fibroids in women with endometriosis ranges between 20 and 30% [10–12].

The majority of studies evaluating the association between uterine disorders and endometriosis are based on pre-surgical assessment of patients with pelvic endometriosis or uterine fibroids. Concerning adenomyosis, Di Donato et al. showed a prevalence of 21.8% in patients undergoing surgery for endometriosis, detecting a statistically significant association with parity, age, dysmenorrhea intensity and the presence of DIE [6]. A higher prevalence of adenomyosis was found by Eisenberg et al., who observed a 89.4% prevalence of US signs of adenomyosis in women with history of surgery of endometriosis [8]. On the contrary, Lazzeri et al. found a 47.8% prevalence of adenomyosis in women with DIE, influencing significantly the pre- and post-surgical dysmenorrhea severity [7]. A similar prevalence of adenomyosis (59.9%) was detected by using MRI in symptomatic women younger than 42 years, undergoing surgery for benign gynecological pathologies [3]. Finally, Naftalin et al. observed a 20.9% prevalence of adenomyosis by using TVUS in a general population of patients attending a gynecological clinic. Adenomyosis was associated to an older age, higher gravidity and parity, and presence of pelvic endometriosis [17].

Considering uterine fibroids, Ujmari et al. showed a 25.8% prevalence in patients operated for endometriosis, while in patients undergoing surgery for fibroids the prevalence of endometriosis was 19.6% [9]. A modest further increased prevalence of endometriosis in surgery for fibroids was detected by Tanamhasut (28%) [11]. Endometriosis was more common in those with subfertility and less common in those with bleeding disorders [12].

Endometriosis, uterine fibroids, and adenomyosis can affect fertility in different ways. Endometriosis-related infertility is associated with ovarian damage and alteration of pelvic cavity due to inflammation and adhesions with distortion of pelvic architecture, inflammatory changes in peritoneal fluid and altered endometrium [18].

The prevalence of infertility in women with endometriosis is very high and the disease is one of the main causes of female

<table>
<thead>
<tr>
<th>Uterine disorders comorbidities</th>
<th>Ovarian endometriosis (OMA)</th>
<th>Deep infiltrating endometriosis</th>
<th>Both OMA and DIE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine fibroids</td>
<td>7 (2.9%)</td>
<td>2 (2.2%)</td>
<td>4 (4.7%)</td>
</tr>
<tr>
<td>Adenomyosis</td>
<td>58 (23.8%)</td>
<td>14 (15.7%)</td>
<td>17 (19.8%)</td>
</tr>
<tr>
<td>Both uterine fibroids and</td>
<td>38 (15.6%)</td>
<td>14 (15.7%)</td>
<td>9 (10.5%)</td>
</tr>
<tr>
<td>adenomyosis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Uterine disorders in women with endometriosis according to age intervals.

<table>
<thead>
<tr>
<th>Uterine disorders comorbidities</th>
<th>Age &lt; 35 years</th>
<th>Age 35 ≥ and &lt; 45 years</th>
<th>Age ≥ 45 years</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine congenital malformations</td>
<td>4 (2.1%)</td>
<td>1 (0.5%)</td>
<td>0 (0%)</td>
<td>.291</td>
</tr>
<tr>
<td>Endometriosis phenotypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMA</td>
<td>108 (56.2%)</td>
<td>113 (61.7%)</td>
<td>23 (52.3%)</td>
<td>.390</td>
</tr>
<tr>
<td>DIE</td>
<td>39 (20.3%)</td>
<td>40 (21.5%)</td>
<td>10 (22.7%)</td>
<td>.905</td>
</tr>
<tr>
<td>Both OMA and DIE</td>
<td>45 (23.4%)</td>
<td>30 (16.4%)</td>
<td>11 (25%)</td>
<td>.178</td>
</tr>
</tbody>
</table>

The prevalence of infertility in women with endometriosis is very high and the disease is one of the main causes of female

Discussion

The present study evaluated the sonographic coexistence of uterine disorders (adenomyosis and uterine fibroids) in patients with endometriosis referred for infertility. We have observed that patients aged > 35 years were more likely to be affected by uterine fibroids (p < .003), adenomyosis (p < .030), or both uterine fibroids and adenomyosis (p < .0001). No statistically significant association was found between endometriosis phenotypes and uterine disorders.

Furthermore, no association was observed between patients’ age and endometriosis phenotype (Tables 2 and 3).
infertility. The monthly fecundity rate in endometriosis is reduced from 15–20% to 2–10%; an advanced stage of disease correlates with a greater decline of this rate. In patients undergoing laparoscopy for infertility, the prevalence of endometriosis is at least 30%, confirming the relevant impact on women’s life of the disease [4].

Adenomyosis can cause infertility by causing aberrant uterine contractility, abnormal myometrial activity, and deranged endometrial milieu with altered expression of implantation factors [5, 19]. Adenomyosis seems to affect fertility in a very strong way even in the absence of endometriosis, as described by a pioneer study in baboons [20] and then confirmed in subsequent reports in humans, even though the level of evidence and the epidemiological available data are still not strong enough to draw firm conclusions [21,22].

Uterine fibroids are present in 5–10% of infertile women, but they represent the unique cause of infertility only in 2–3% [23,24]. These data suggest that other mechanisms, such as endometriosis, can interfere with fertility in women with uterine fibroids. Uterine fibroids may determine distortion of the uterine cavity, alteration to the endometrial and myometrial blood supply, deviation or obstruction of the tubal ostia, alteration of the tubo-ovarian anatomic relation, chronic endometrial inflammation, and impairing implantation [23,24]. Considering the relevance of endometriosis in affecting fertility, the coexistence of other uterine disorders would interfere and possibly worsen the chance of conception, especially in those requiring ART. The understanding of concomitant gynecological conditions affecting fertility may allow a more comprehensive counseling and a better plan for fertility desire. The identification of coexistent uterine fibroids or adenomyosis allows to plan a pretreatment, either medical or surgical, before assisted reproductive technologies (ART).

Some limitations need to be acknowledged, as the study has a retrospective design and there are no controls. However, the research is one of the few US reports on the prevalence of coexistent uterine disorders in endometriosis, considering also fibroids. The results provide an epidemiological overview in infertile women with endometriosis. In addition, all the US have been performed by expert sonographer, using the same terminology and features to define a diagnosis.

In conclusion, we would like to reiterate the importance of US assessment in the evaluation of endometriosis, recommending to pay particular attention to eventually associated uterine disorders, such as uterine fibroids and adenomyosis, for a better management of the patient. This is crucial in the infertility clinic, where a global evaluation determines the choice of the correct treatment for conception and favorable pregnancy outcome. Moreover, the coexistence of endometriosis and uterine disorders may have significant implications for patient care and consequent medical and/or surgical treatment, independently from the desire to conceive.

TVUS is the first line imaging technique for the evaluation of suspected endometriosis and associated uterine disorders (uterine fibroids and adenomyosis). In fact, it permits the characterization of ovarian endometriomas and DIE lesions, as well as adenomyosis and uterine fibroids, driving the clinician to the correct approach. One of the main limit of TVUS is that SUP cannot be visualized. In case of diagnostic uncertainty, the prescription of continuous hormonal treatment can be used as clinical test, avoiding unnecessary diagnostic laparoscopies [25]. In infertility management, TVUS is necessary in the choice of the correct and patient-oriented treatment, considering endometriosis, uterine disorders, and other gynecological comorbidities. This diagnostic techniques help the clinician in the selection of surgical or ART approach, considering an huge amount of variables, for example the endometriosis phenotype and pelvic anatomy, the ovarian reserve, the presence of fibroids distorting the uterine cavity, and many others [25–27].

Personalized treatment is fundamental and the correct therapy is not the same for every patient, above all in a complex disease such as endometriosis.

Disclosure statement
No potential conflict of interest was reported by the author(s).

References


