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INTRODUCTION

Endometriosis is defined as the presence of functional endometrial glands and stroma outside the uterine cavity and myometrium (Olive and Schwartz, 1993). This ectopic tissue is hormonally responsive and may undergo bleeding, inflammation, fibrosis, and adhesion formation, leading to pelvic pain and infertility (Bennett et al., 2010).

The prevalence of endometriosis is significantly higher in women who are infertile than in women who are fertile (Eskenazi and Warner, 1997; Ozkan et al., 2008). Endometriosis is associated with a spectrum of imaging findings ranging from microscopic implants to a focal cystic collection that is referred to as an “endometrioma” or “endometriotic cyst.”

Although the diagnostic gold standard remains laparoscopy, diagnostic imagers are often called on to evaluate for endometriosis in a patient with pelvic pain or infertility and to consider the possibility of an endometrioma in the evaluation of an adnexal mass.

Although the ovary is the most common site of involvement, endometriosis may occur in other sites and can mimic other disease processes, both clinically and at imaging.

Finally, although histological assessment is needed to confirm the diagnosis of endometriosis, there is not a common agreement about the best

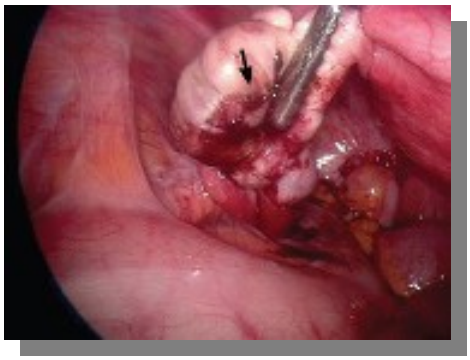
medical/conservative/surgical therapy to treat this syndrome and to assure successful follicologenesis and pregnancy expectation.

ENDOMETRIOSIS

Definitions

Endometriosis is a chronic and recurrent disease characterized by the presence and proliferation of functional endometrial glands and stroma outside the uterine cavity (Child and Tan, 2001; Schweppe, 2001; Valle and Sciarra, 2003).

The most common locations of the ectopic endometrial tissue are represented by the ovaries and the pelvic peritoneum, followed by deep infiltrating sites (Figure 1) (in descending order of frequency, the utero-sacral ligaments, the recto-sigmoid colon, the vagina and the bladder) (Jenkins et al., 1986; Cornillie et al., 1990).



Laparoscopic view of deposits of endometrial tissue (arrow) on the ovary. (Mounsey et al., 2006)

This is a common clinical condition affecting women of reproductive age. The recurrent cyclic bleeding, progressive fibrosis, and adhesions occurring

in these ectopically located endometrial glands cause varying symptoms depending on the organ of involvement.

Epidemiology and Pathogenesis

Although endometriosis is seen primarily among women of reproductive age (Crosignani et al., 2006), this disease also can affect post-menopausal women and adolescents—especially adolescents with uterine abnormalities (Valle et al., 2003). Endometriosis is estimated to affect approximately 5–10% of the female population (Olive and Schwartz, 1993). Peak incidence is in the third decade; however, endometriosis may also affect women younger than 20 years old, who generally present with chronic pelvic pain or dyspareunia.

There are several theories of the pathogenesis of endometriosis; however, the most widely accepted is the metastatic theory, which holds that endometrial cells and stroma implant in ectopic locations within the pelvis, most likely secondary to retrograde menstruation with reflux of endometrial tissue through fallopian tubes into the peritoneal cavity (Olive and Schwartz, 1993). Once transported, the endometrial cells implant on

the serosal surfaces and remain viable. However, retrograde menstruation can be observed in up to 90% of women, suggesting the involvement of additional factors in the implantation and growth of endometriotic lesions in women who go on to develop the disease (Gazvani et al., 2002). Two other possibilities are the celomic metaplasia and embryonic rests theories. The former hypothesizes that endometriosis develops from metaplastic transformation of cells lining the pelvic peritoneum since both endometrial and peritoneal cells derive from the coelomic wall epithelium. The latter theory hypothesizes that Müllerian remnants in the recto-vaginal region differentiate into endometrial tissue. In particular, endometriosis is more common in women with Müllerian anomalies resulting in outflow obstruction (increasing retrograde menstrual flow) (Olive and Henderson, 1987), as well as in women with prolonged menstruation and shorter cycles (27 days or less) (Bérubé et al., 1998). A woman's risk for endometriosis increases with increased exposure to endometrial material; thus, shorter menstrual cycles, longer bleeding, and early menarche are risk factors (Table 1) (Eskenazi and Warner, 1997; Cramer et al., 1986). Being overweight and smoking have been associated with a lower risk of endometriosis (Cramer and Missmer, 2002).

Risk Factors for Endometriosis

Risk factor/comparison	*Odds ratio*	*95% confidence interval*
Mother or sister has endometriosis/mother and sister do not have endometriosis	7.2	2.1 to 24.3[6]
Menstrual flow six days or more/flow less than six days	2.5	1.1 to 5.9[7]
Menstrual cycle less than 28 days/cycle of 28 to 34 days	2.1	1.5 to 2.9[8]
Consuming one or more alcoholic drinks per week/no alcohol consumption	1.8	1.0 to 3.2[9]
Never used OCPs/ever used OCPs	1.6	1.2 to 2.2[10]
Use of pads and tampons/use of either pads or tampons	1.4	0.9 to 2.0[2]

OCPs = oral contraceptive pills.

Information from references 2 and 6 through 10.

(Mounsey et al., 2006)

Susceptibility to endometriosis is thought to depend on the complex interaction of genetic, immunologic, hormonal and environmental factors (Bellelis et al., 2011). Endometriosis appears to be a multifactorial genetic disorder, in which allelic variants of many genes (including cancer susceptibility genes and genes coding for cytochrome P450 enzymes, nuclear receptors and immunologic mediators) can predispose women to develop endometriosis, depending on environmental conditions (Wenzl et al., 2003). Increasing evidence points to the role of immunologic factors and angiogenesis in the disease pathogenesis.

Women with endometriosis appear to have altered function of peritoneal macrophages, natural killer cells and lymphocytes, as well as changes in

growth factors and inflammatory mediators in the peritoneal fluid (Gazvani et al., 2002). The growth of endometriotic lesions is also estrogen dependent, with lesions becoming inactive and gradually undergoing regression during states of ovarian down-regulation, such as amenorrhoea or menopause (Bulun et al., 1999; Gurates and Bulun, 2003; Valle et al., 2003).

Symptoms

A patient survey of women in the United Kingdom and United States who were referred to university-based endometriosis centers found that 70 to 71 percent presented with pelvic pain, 71 to 76 percent with dysmenorrhea, 44 percent with dyspareunia, and 15 to 20 percent with infertility (Kuohung et al., 2002).

Because ectopic endometrial tissue usually retains responses to cycling reproductive hormones (governing proliferation, differentiation and bleeding), pelvic pain associated with endometriosis generally is cyclical, although the pain may become continuous as the disease worsens (Child et al., 2001; Chwalisz et al., 2002). Excessive menstrual bleeding occurs in

75% of cases and increases with the duration of the condition (Sushilkumar et al., 2011; Hensen et al., 2006). Dyspareunia can occur with deposits in the cul-de-sac or upper vagina. Backache occurs with the endometrial deposits on the utero-sacral ligaments or the rectal wall (Table 2).

Primary symptoms	Dysmenorrhoea Deep dyspareunia
Symptoms commonly associated with endometriosis	Pelvic pain Low abdominal pain (with no bowel symptoms and no vomiting)
Related symptoms	Low back pain not due to mechanical problems Irregular bleeding Abdominal pain on urination Urinary symptoms not specified as with cycle (frequency, dysuria, haematuria, presumed urinary tract infection) Menstrual haematuria
Symptoms associated with endometriosis, non-specific pelvic, and abdominal symptoms	Pain on defecation not due to haemorrhoids or anal fissure Abdominal bloating Bowel symptoms specified in notes as due to IBS Rectal bleeding not due to haemorrhoids or anal fissure Cyclical extrapelvic pain
Other gynaecological symptoms	Post-coital bleeding Menopausal symptoms Premenstrual symptoms Superficial dyspareunia

IBS = irritable bowel syndrome.

(Pugsley and Ballard, 2007)

In addition to pain symptoms, effects on fertility are associated with endometriosis. Infertility is a problem for many women with this disorder,

although the mechanisms of endometriosis-associated infertility still are not completely understood. (D'Hooghe et al., 2003; Gianetto-Berrutti and Feyles, 2003). Generally, it is agreed that the most advanced stages of endometriosis are strongly correlated with infertility, particularly if pelvic adhesions distort normal pelvic anatomy and impair tubo-ovarian function (D'Hooghe et al., 2003; Gianetto-Berrutti et al., 2003). In addition, evidence suggests that even mild disease could negatively impact oocyte development, embryogenesis or implantation.

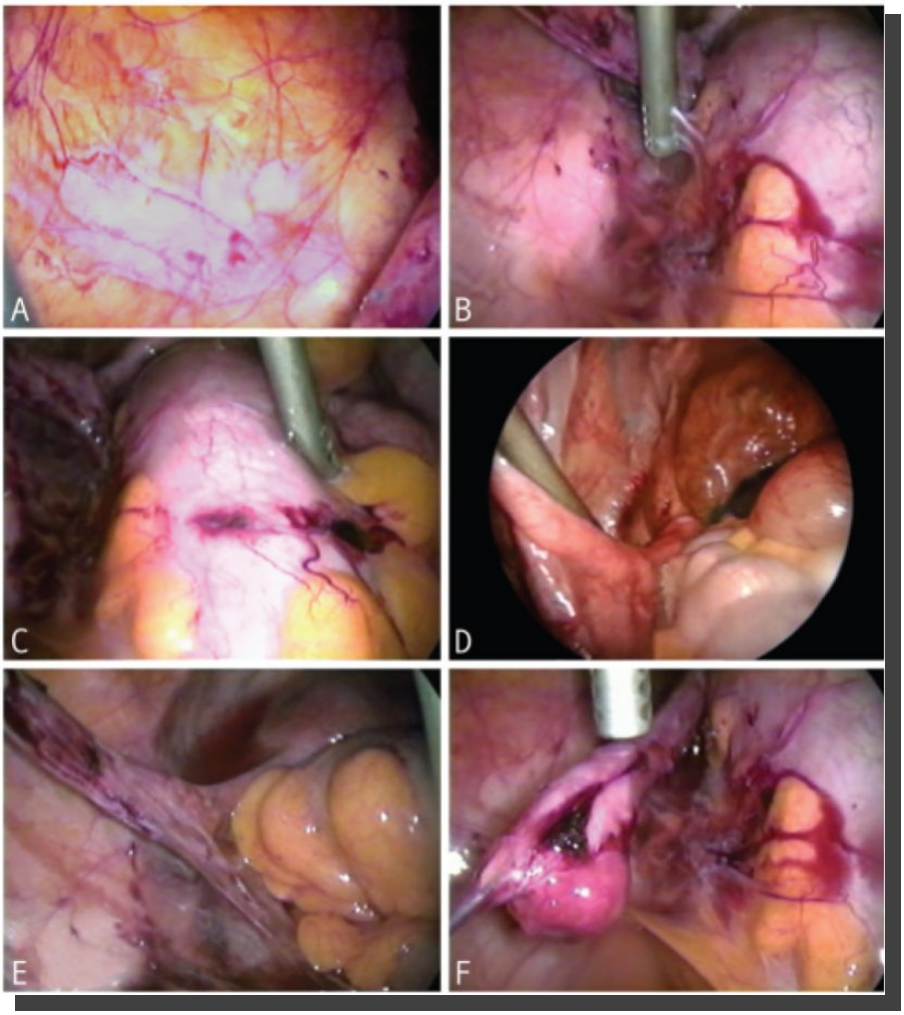
A meta-analysis of 22 studies evaluating in vitro fertilization outcomes found that patients with endometriosis had a pregnancy rate of nearly one half that of patients without endometriosis, with decreases in fertilization, implantation, and oocyte production rates (Barnhart et al., 2002).

Endometriosis also negatively impacts women's quality of life (Jones et al., 2002; Marques et al., 2004). Because of the chronic nature of endometriosis, recurrences of symptoms are common over the long term (Valle et al., 2003). For this reason, medical therapies that can be administered for only a few months due to safety concerns or poor tolerability are not ideal for women with symptomatic endometriosis (Vercellini et al., 2003a). In addition, repeated surgical procedures for recurring pain increases morbidity, as well as physician and patient frustration (Vercellini et al., 2000). Thus, chronic pain symptoms and the effects of poorly tolerated, ongoing, or repeated treatment courses can

contribute to poor quality of life for women with endometriosis, disrupting job performance, social relationships, or sexual functioning (ESHRE Capri Workshop Group, 2001; Marques et al., 2004).

Clinical Presentation

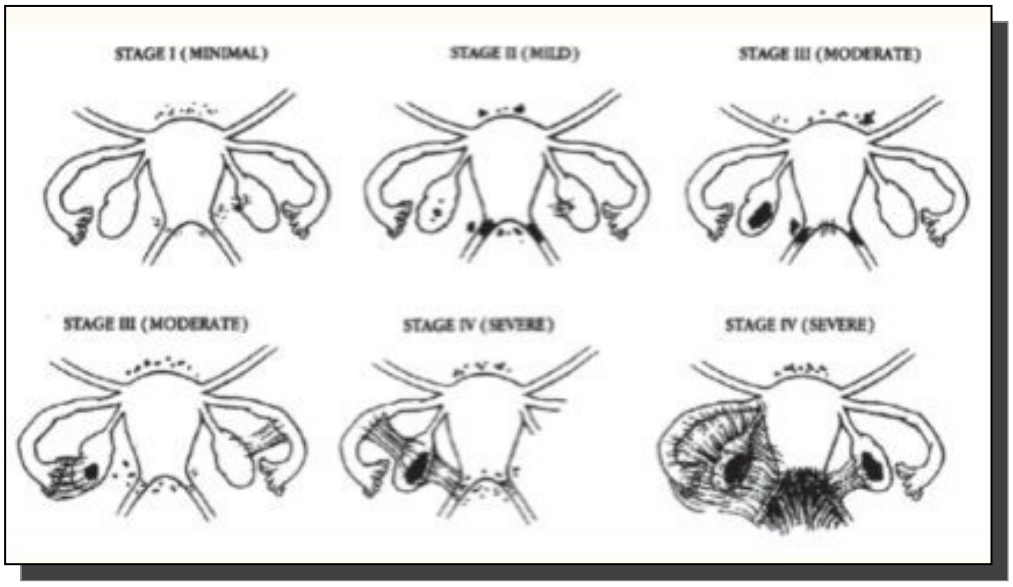
Endometriotic lesions are highly variable in size, shape and color when viewed at laparoscopy (Figure 2). They can range in size from microscopic measurements to 10 cm endometriomas.



Laparoscopic visualization of endometrial lesions (A – F) (A) Isolated red lesions located on broad ligament. (B)Multiple red lesions adjacent to sigmoid colon. Laparoscopic instrument visualized in the top center portion of image. Lesions visualized directly to left of instrument. (C) Hemorrhagic lesion located on sigmoid colon in the center of the image. (D) Hemorrhagic lesion on broad ligament posterior to round ligament. Lesion is located immediately to right of laparoscopic instrument. (E) Adhesions formed at base of oviduct adjacent to the uterus. Hemorrhagic endometrial lesions located at left of image with filmy adhesions. (F) Filmy adhesions and hemorrhagic lesion located at distal portion of oviduct. (Bloski and Pierson, 2008)

The ASRM has developed classification and staging guidelines to assist with diagnosis, prognosis, treatment, subsequent progress and communication among medical professionals (ASRM, 2006; Wellbery, 1999). In this standardized scheme, endometriosis is classified into four stages as illustrated in Figure 3: Stage I (minimal), Stage II (mild), Stage III (moderate) and Stage IV (severe). Staging is based on the extent of the

spread of lesions, density of pelvic adhesions, involvement of pelvic organs and degree of fallopian tube occlusion (ASRM, 2006). It's important to remember that the stage of endometriosis is not reflective of degree of pain, risk of infertility or predictive of the patient's ability to conceive after therapy (ASRM; Audebert et al., 1992). The variability in clinical presentation and stage of disease likely reflects of our lack of understanding of the pathophysiology of endometriosis.



Schematic classification examples of extent and location of endometriosis Adapted from the Revised American Society for Reproductive Medicine Classification of Endometriosis (1996).

Three different types of endometriosis were subsequently distinguished.

Peritoneal Endometriosis

Peritoneal endometriosis, also known as "superficial endometriosis", has many appearances ranging from red, vesicular and hemorrhagic; puckered,

blue-black powder-like burn patterns; or fibrotic lesions white to black in color. The red lesions are highly vascular, bleed into the peritoneal cavity during menstruation, and are associated with early neoangiogenesis, adhesion formation and inflammation. Dark or white lesions are correlated with higher amounts of fibrosis, decreased vascularity and decreased bleeding (Brosens et al., 2004; Brosens, 1997a, 1997b).

The anatomic distribution of ectopic endometrium supported the hypothesis of retrograde menstruation as the primary model of development of endometriosis (Brosen and Benangiano, 2011; Jenkins et al., 1986). From all published evidence Evers et al (Evers et al., 1998) concluded that peritoneal endometriosis appears to be a dynamic disease, especially in the early phase, when subtle, atypical lesions may emerge and vanish again. The dynamic phase of the disease may involve a varying interval of each patient's life (e.g. a period of amenorrhoea or pregnancy).

Recto-Vaginal Endometriosis

A strong correlation between pelvic pain and the depth of invasion was described in the presence of implants more than 10 mm deep (Cornillie et al., 1990; Koninckx and Martin, 1992). In contrast with superficial peritoneal endometriosis, these lesions have a structure closely resembling the adenomyomas described by Cullen (Cullen, 1908). In the late 1990s

rectal endoscopic ultrasonography was proposed to diagnose the presence of deep bowel infiltration and select patients for surgery (Fedele et al., 1998). These endometrial lesions can be found in the rectovaginal septum, uterosacral ligaments, utero-ovarian ligaments and muscular wall of pelvic organs. Endometrial glands and stroma invade into adjacent fibromuscular tissue along loose connective tissue, but are arrested at the underlying fat tissue level (Brosens, 1997b).

Ovarian Endometrioma

Ovarian endometriosis can present itself as very early lesions, plaques with free-floating adhesions, deep non-cystic lesions and typical chocolate cysts with adhesions. In a detailed study of 29 ovary specimens with chocolate cysts, Hughesdon (Hughesdon, 1957) found that in 90 percent of them the ovarian endometrioma was formed by a pseudocyst. The surface of the ovary is adherent, usually to the posterior side of the parametrium and part of the ovarian cortex is invaginated. Endometriotic tissue is found at the site of adhesion and a thin layer of superficial endometrium-like tissue extends to cover partially or fully the invaginatedcortex. Hughesdon concluded that ectopic endometrium does not simply erode its way into the ovary: the ovary is actively invaginated, thus, providing a pseudocyst mimicking a uterus.

Bleeding or rupture of an ovarian endometrioma can cause an acute abdominal emergency requiring surgery in approximately 5 percent of women with endometriosis (Schenken, 1996).

Using an endoscopic technique Brosens et al (Brosen et al., 1994) investigated a series of endometriotic cysts in situ in young women with infertility and confirmed that the wall of the cyst is constituted by cortex lined by endometrial cells. They suggested that surgery should be adapted to the structure of endometrioma by adhesiolysis with opening and eversion of the cyst and followed by ablation of the superficial endometriotic tissue lining the cortex and excision of the implants at site of the adherent parametrium or ligaments. It must be stressed that surgical treatment of ovarian endometriomas is more complex than simple drainage and coagulation.

Endometriosis and Ovarian Cancer

Although endometriosis is recognised as a benign disease, its association with ovarian cancer has been frequently described in the medical literature

since 1925. In that year, Sampson established the first histopathological criteria, which are still in use, to identify malignant tumours rising from endometriosis: (1) clear evidence of endometriosis close to the tumour, (2) the carcinoma must be seen to arise in endometriosis, and not to be invading it from other sources, and (3) presence of tissue resembling endometrial stroma surrounding characteristic glands (Sampson, 1925). Later in 1953, Scott has added a fourth criterion which is the demonstration of a histology-proven transition from benign endometriosis to cancer (Scott, 1953). The application of all these four criteria has rarely been fulfilled in the literature, which supports the idea that the malignant transformation of endometriosis is a rare event (Somigliana et al., 2006). The estimated effect size is modest varying between 1.32 and 1.9. A causative relationship between the two incidences cannot be confirmed (Sayasneh et al., 2011) (Table 3).

Review	Language of literature searched	Type of studies included	Quality assessment tool used in the review	Overall results	Application of results
Ness 2003 [7]	English	In vitro, animal, clinical, and epidemiologic studies	Not specified	Consistent with the association between endometriosis and ovarian cancer.	Possible chemoprevention for women with endometriosis.
Somigliana et al. 2006 [4]	English	Observational, cohort, and case-control	Studies have been critically analysed.	Increased risk of ovarian cancers: effect size: 1.3–1.9.	Modifications of the standard treatment options for the disease are not justifiable.
Vigano et al. 2007 [8]	English	Observational, cohort, and case-control epidemiologic, biological, and genetic studies	Nineriteria, by Austin Bradford Hill [13]	The criterion of strength has not been fulfilled. There were insufficient data for four criteria, and four criteria were fulfilled.	The low magnitude of the risk observed is consistent with the view that ectopic endometrium undergoes malignant transformation with a frequency similar to its eutopic counterpart.
Nezhat et al. 2008 [9]	English	Observational, cohort, and case-control epidemiologic, histopathological, and molecular studies	Not specified	Histological transition from benign endometriosis to ovarian malignancy.	The malignant potential of endometriosis holds serious implications for management.
Baldi et al. 2008 [10]	English	Not specified	Not specified	Further epidemiological and genetic studies are required.	Appropriate physical screening and imaging testing are recommended.
Vlahos et al. 2010 [11]	No search criteria specified	No search criteria specified	Not specified	Endometriosis is associated with specific types of ovarian cancer (endometrioid and clear cell).	More studies are needed to establish the risk factors that may lead to malignant transformation.
Kobayashi 2010 [12]	English	Studies on screening, epidemiology, clinical diagnosis, natural history, preclinical and clinical trials, and promising molecular targets on epithelial ovarian cancer (EOC).	Not specified	Ovarian endometrioma could be viewed as a neoplastic process.	Understanding the mechanisms of endometriosis development and elucidating its pathogenesis and pathophysiology are intrinsic to prevention.

However, there is increasing evidence on the role of genetic mutations in ovarian clear-cell and endometrioid carcinoma developing from endometriosis.

DIAGNOSTIC STRATEGY

The diagnostic hypothesis of endometriosis is based on the clinical history, along with the results from gynecological examinations, laboratory tests and transvaginal ultrasound (Houston, 1984; Redwine, 1987). Some clinical characteristics, the physical examination itself, laboratory test results and evidence from imaging examinations may suggest the diagnosis (Abrao et al., 2003).

However, the preferred method for the diagnosis of endometriosis is direct visualization of ectopic endometrial lesions (usually via laparoscopy) accompanied by histologic confirmation of the presence of at least two of the following features: hemosiderin-laden macrophages or endometrial epithelium, glands, or stroma (ACOG, 2000). Diagnosis based solely on visual inspection requires a surgeon with experience in identifying the many possible appearances of endometrial lesions; nonetheless, there is relatively poor correlation between visual diagnosis and confirmed histology.

Moreover, the possibility of malignancy must be considered.

The American College of Obstetricians and Gynecologists recommends a pre-treatment diagnostic strategy to exclude other causes of pelvic pain such as chronic pelvic inflammatory disease, fibroid tumors, and ovarian

cysts (ACOG, 2000). Non gynecologic causes of pain also should be excluded (Table 4).

Differential Diagnosis of Endometriosis by Symptom

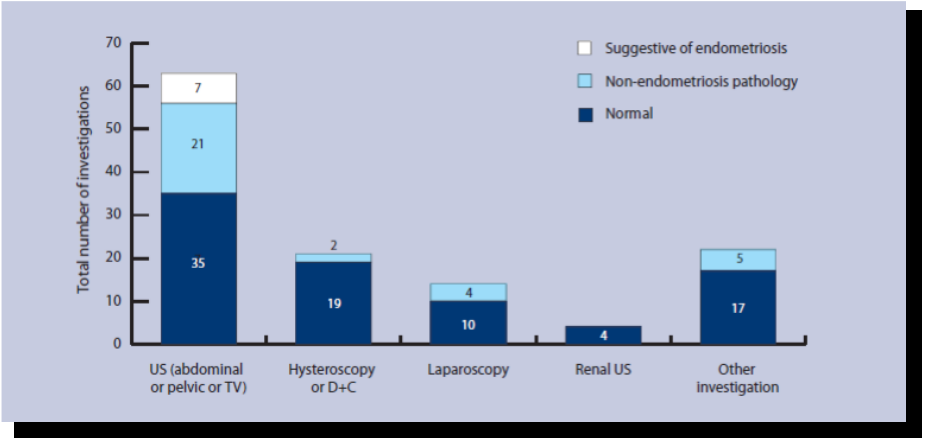
Dysmenorrhea	**Generalized pelvic pain**
Primary	Endometritis
Secondary (e.g., adenomyosis, myomas, infection, cervical stenosis)	Neoplasms, benign or malignant
Dyspareunia	Nongynecologic causes
Diminished lubrication or vaginal expansion because of insufficient arousal	Ovarian torsion
Gastrointestinal causes (e.g., constipation, irritable bowel syndrome)	Pelvic adhesions
Infection	Pelvic inflammatory disease
Musculoskeletal causes (e.g., pelvic relaxation, levator spasm)	Sexual or physical abuse
Pelvic vascular congestion	**Infertility**
Urinary causes (e.g., urethral syndrome, interstitial cystitis)	Anovulation
	Cervical factors (e.g., mucus, sperm, antibodies, stenosis)
	Luteal phase deficiency
	Male factor infertility
	Tubal disease or infection

Information from reference 16.

(Mounsey et al., 2006)

Pelvic and rectal examinations should be performed, although the yield of the physical examination is low. Findings of a retroverted uterus, decreased uterine mobility, cervical motion tenderness, and tender utero-sacral nodularity are suggestive of endometriosis when present, but these findings often are absent. Laboratory tests and radiologic examinations usually are not warranted. Measurement of CA 125 levels may be useful for monitoring disease progress, and MRI has high sensitivity in detecting endometrial cysts but poor diagnostic accuracy for endometriosis in general.

A consistent body of literature supports the accuracy of transvaginal ultrasound for the detection of ovarian endometriomas (Somigliana et al., 2010). Sensitivity and specificity of this method have been reported to be 84–100% and 90–100%, respectively (Garcia-Velasco and Somigliana, 2009; Savelli, 2009). Detection of deep infiltrating lesions is however more challenging. Several imaging methods, such as transvaginal ultrasonography, transrectal ultrasonography, computerized tomography and magnetic resonance imaging (MRI) have been used in an attempt to improve the non-invasive diagnosis of this form of endometriosis (Abrao et al., 2007) (Table 5).



Types and number of investigations carried out on women prior to a surgical diagnosis of endometriosis. US = ultrasound. TV = transvaginal. D+C = diltation and curettage. (Pugsley and Ballard 2007)

Physical Examination

There are few well-studied clinical maneuvers for use in the diagnosis of endometriosis. Signs may be absent or may include tender nodules in the posterior vaginal fornix, uterine motion tenderness, a fixed and retroverted uterus, or tender adnexal masses resulting from endometriomas. One study determined the usefulness of clinical signs and symptoms in the diagnosis of endometriosis in women who present with infertility (Matorras et al., 1996). Although no test provides strong evidence for the presence of endometriosis, the symptom of utero-sacral pain has the highest positive likelihood ratio.

Laboratory Tests related to ovarian endometrioma

Although there is a wealth of interest in the use of serum markers to diagnose endometriosis, none are accurate enough to be used in routine clinical practice.

CA 125 and other experimental markers

Elevation in levels of CA 125 (i.e., greater than 35 IU per mL), more commonly known for its use in the diagnosis or monitoring of ovarian cancer, is of limited diagnostic value; however, given its high specificity, CA 125 may be useful as a marker for disease monitoring and treatment follow-up. In addition, a well-designed meta-analysis found that measurement of serum CA 125 levels may be useful in identifying patients with infertility who may have severe endometriosis and could benefit from early surgical treatment (Mol et al., 1998).

One report on the use of serum cancer antigen 19-9 (CA 19-9) in the diagnosis of endometriosis found that CA 19-9 has inferior sensitivity to CA 125 but may be of some use in determining disease severity (Harada et al., 2002). There is emerging interest in a variety of other markers. One relatively small study found that the cytokine interleukin-6 (at a cut-off value of 2 pg per mL) may be more sensitive and specific than CA 125 (Bedaiwy and Falcone, 2004). Measurement of tumor necrosis factor a in the peritoneal fluid also has shown diagnostic promise, with sensitivity and specificity of 1 and 0.89, respectively. However, this test requires an invasive procedure to obtain the fluid. It may prove useful as an adjunct to less obvious surgical diagnosis.

HE 4

HE-4 s a new marker to diagnose ovarian carcinoma (Li et al., 2009). The crucial role in the early diagnosis of ovarian masses is in the affecting medical and surgical therapy. Up to now the unique biomarker validated for the diagnosis of ovarian carcinoma has been the Ca-125, that results increased in all the ovarian carcinoma, but with several limitations.

Only the half of carcinoma in an initial stage express increased levels of this antigen, moreover is not specific for neoplastic pathologies.

L'HE-4 (WFDC2 gene) is a protease inhibitor, hyper-expressed in ovarian carcinoma, with a sensibility of 73% and a specificity of 94%. Moreover, HE-4 is not altered in benign masses.

ROMA Index

A novel algorithm has been shown to be more sensitive than a widely used risk of malignancy index for predicting epithelial ovarian cancers in women who present with a pelvic mass or ovarian cyst.

The Risk of Ovarian Malignancy Algorithm (ROMA) stratifies women as being at high or low risk for epithelial ovarian cancer based on menopausal status and preoperative serum levels of two biomarkers: human epididymis protein 4 (HE4) and cancer antigen 125 (CA 125). Investigators found that the algorithm correctly classified 94% of women with epithelial ovarian

cancer in a prospective, double-blind, multicenter trial with 457 evaluable patients (Moore et al., 2009).

A new secondary analysis of trial data comparing patients with benign disease and all stages of epithelial ovarian cancer determined ROMA's sensitivity to be 94.3%, vs. 83.7% (P = .0080) for the risk of malignancy index (RMI), when selectivity for both was set at 75%. ROMA also was more sensitive than RMI in a comparison of patients with benign disease, tumors with a low potential for malignancy, and epithelial ovarian cancer (89% vs. 80.7%; P = .0495).

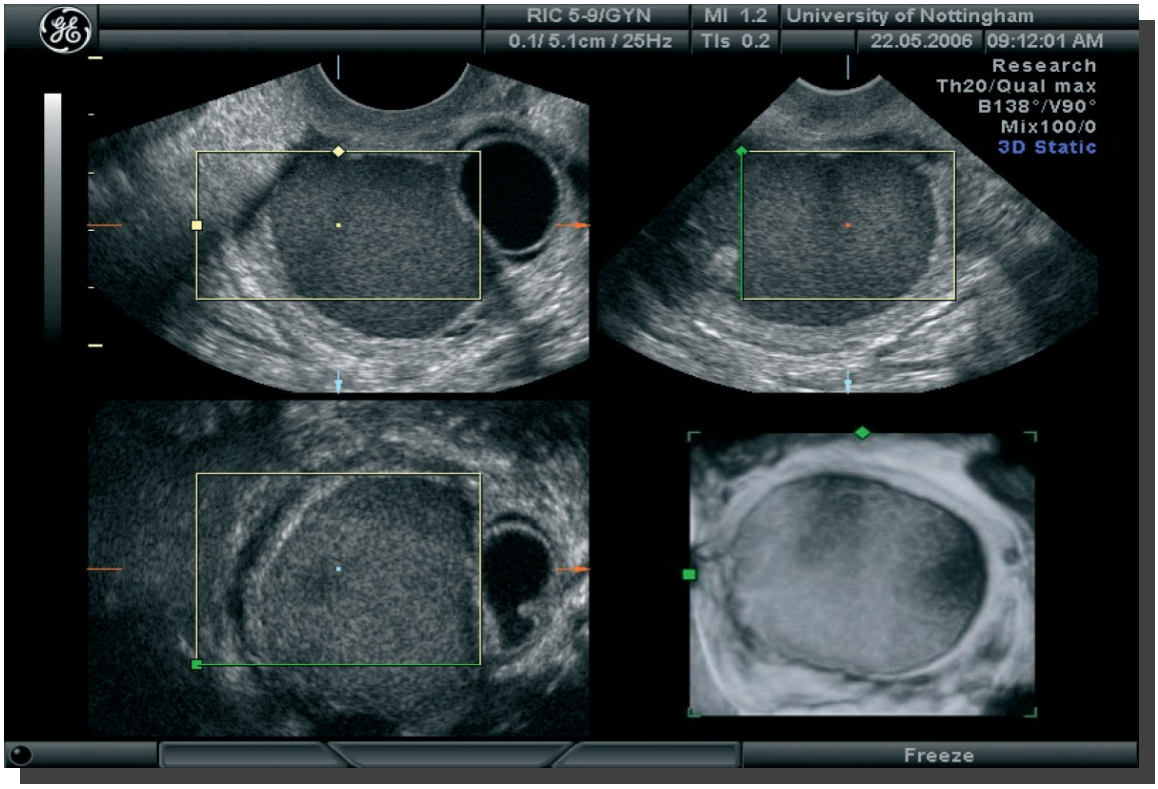
Diagnostic Imaging in ovarian endometrioma

Diagnosis of endometriosis can be difficult, given the non-specific nature of many of its symptoms, the common occurrence of pelvic pain in women without endometriosis and the considerable overlap with other conditions (e.g. pelvic inflammatory disease or irritable bowel syndrome) (Child et al., 2001; Kennedy et al., 2005).

For this reason, a diagnosis can be confirmed only by a surgical procedure (generally laparoscopy) to excise and histologically evaluate disease implants (Rice, 2002). However, preliminar investigations by transvaginal (TVS), transrectal (TRS) or rectal endoscopic (RES) sonography as well as magnetic resonance imaging (MRI) have all been recommended for its diagnosis and for determining its location (Bazot et al., 2003; 2004; Bazot and Darai, 2005).

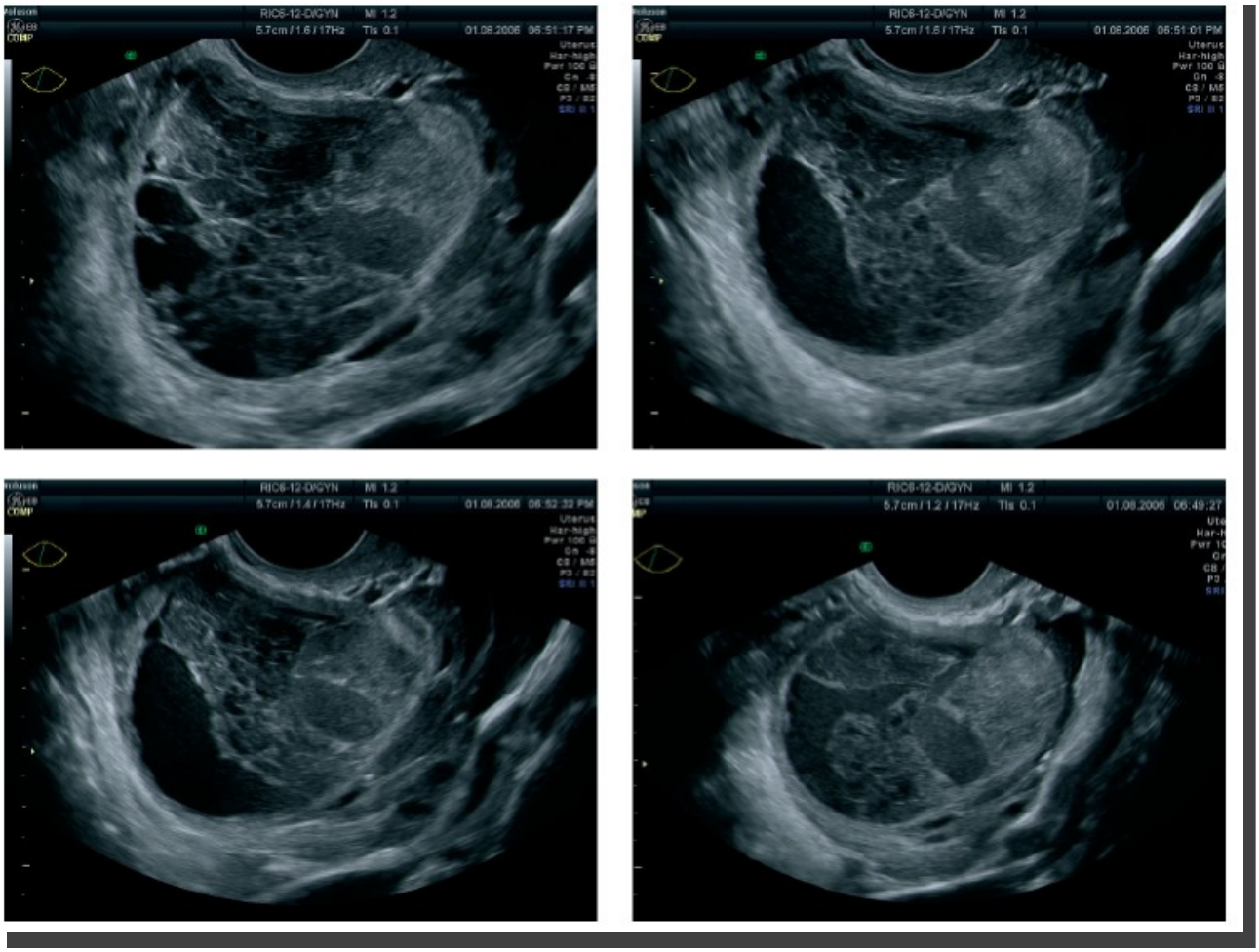
Ultrasonography

Ultrasound is the imaging modality of choice in the assessment of an adnexal mass, given its high accuracy in evaluating the likelihood of malignancy (Raine-Fenning et al., 2008) (Fig. 4).



A three-dimensional multiplanar image of an endometrioma. The simultaneous display of three orthogonal images, which provides the reader with spatial information, together with a rendered view of the cyst (lower right image) are shown (Raine-Fenning et al., 2008).

Moreover, for some histological types of ovarian cyst, such as endometriomas, it is possible not only to predict if the cyst is benign or malignant by means of TVS, but even to predict the likely histological nature of the mass (socalled 'sonohistology') (Fig.5).



A series of two-dimensional images of a hemorrhagic cyst showing the characteristic heterogeneous patterns seen with different degrees of fibrin clot formation as the cyst becomes organized (Raine-Fenning et al., 2008).

Two different approaches, TVS and RES, can be chosen for US investigation (Bazot et al., 2007).

TVS permits accurate diagnosis of intestinal and bladder endometriosis but that it is less reliable for utero-sacral, vaginal and recto-vaginal septum involvement (Bazot et al., 2003) (Tab. 6). RES with a high-frequency probe is more widely used compared with TRS because it provides an overview of the rectosigmoid colon (Tab.7).

Table 3 Assessment of pelvic endometriosis by transvaginal sonography in comparison to surgical and histological findings in 81 patients

Site	Sensitivity (% (n))	Specificity (% (n))	PPV (% (n))	NPV (% (n))	Accuracy (% (n))	+LR	−LR
USL	80.8 (59/73)	75.0 (6/8)	96.7 (59/61)	30.0 (6/20)	80.3 (65/81)	3.2	0.25
Vagina	50.0 (13/26)	96.4 (53/55)	86.7 (13/15)	80.3 (53/66)	81.5 (66/81)	1.1	0.52
RVS	11.1 (1/9)	100 (72/72)	100 (1/1)	90.0 (72/80)	90.1 (73/81)	0.2	0.89
Intestine	92.6 (50/54)	100 (27/27)	100 (50/50)	87.1 (27/31)	95.1 (77/81)	—	0.17
Ovary	94.3 (33/35)	84.8 (39/46)	82.5 (33/40)	95.1 (39/41)	88.9 (72/81)	5.9	1.4

+LR, positive likelihood ratio; −LR, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; RVS, rectovaginal septum; USL, uterosacral ligament.

(Wykes et al., 2004)

Table 4 Assessment of pelvic endometriosis by rectal endoscopic sonography in comparison to surgical and histological findings in 81 patients

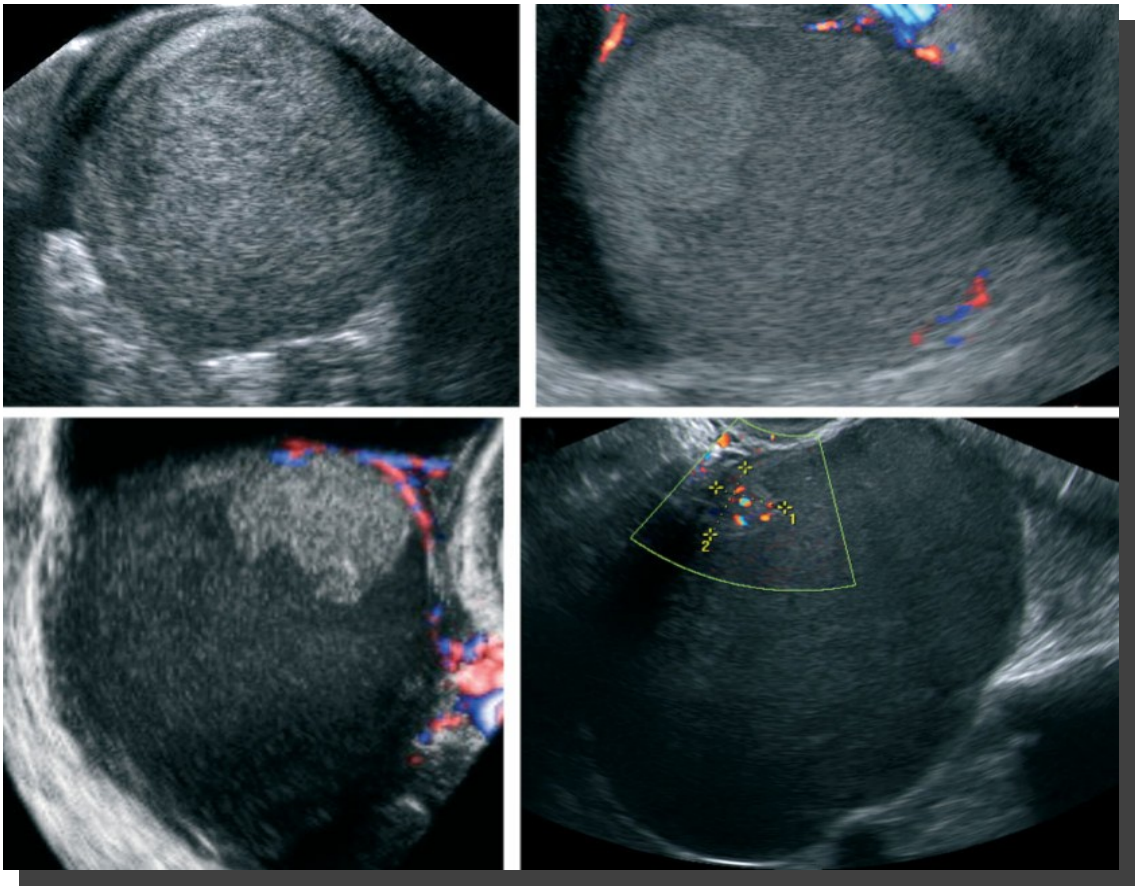
Site	Sensitivity (% (n))	Specificity (% (n))	PPV (% (n))	NPV (% (n))	Accuracy (% (n))	+LR	−LR
USL	46.6 (34/73)	50.0 (4/8)	89.5 (34/38)	9.3 (4/43)	46.9 (38/81)	0.9	1.1
Vagina	7.7 (2/26)	98.2 (54/55)	66.7 (2/3)	69.2 (54/78)	69.1 (56/81)	—	0.9
RVS	22.2 (2/9)	93.1 (67/72)	28.6 (2/7)	90.5 (67/74)	85.2 (69/81)	3.2	0.8
Intestine	88.9 (48/54)	92.6 (25/27)	96.0 (48/50)	80.6 (25/31)	90.1 (73/81)	12.0	0.12
Ovary	68.6 (24/35)	91.3 (42/46)	85.7 (24/28)	79.2 (42/53)	81.5 (66/81)	9.0	0.4

+LR, positive likelihood ratio; −LR, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; RVS, rectovaginal septum; USL, uterosacral ligament.

(Wykes et al., 2004)

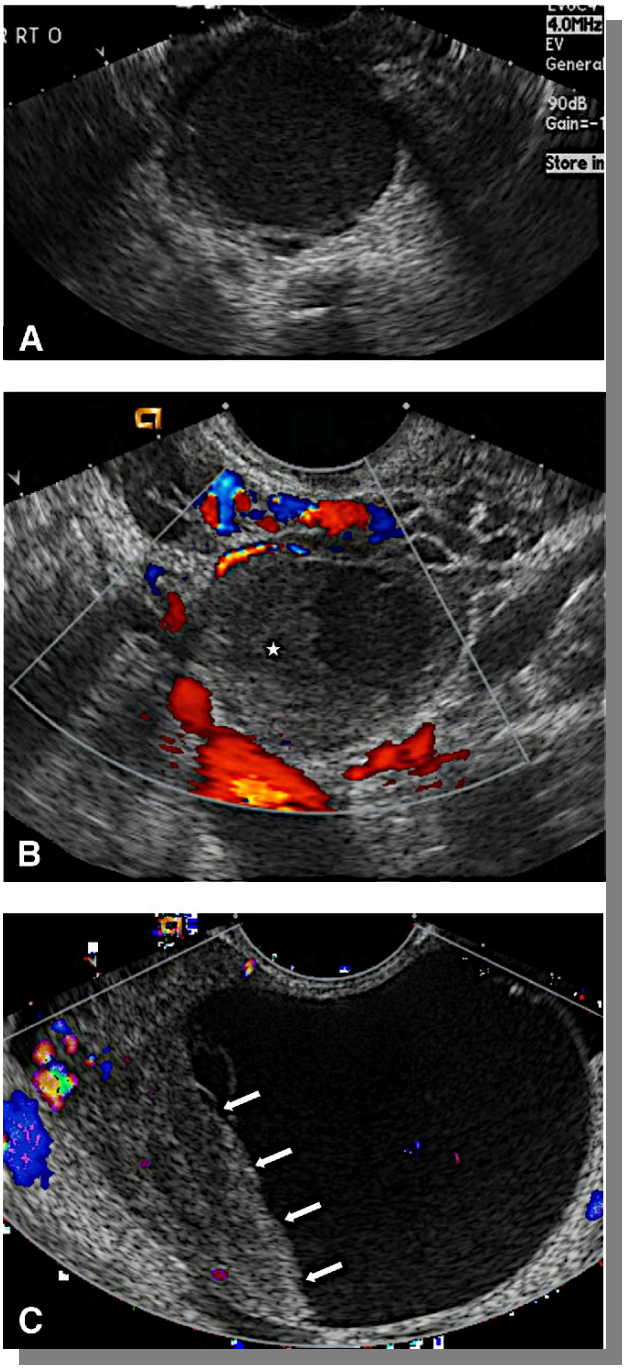
Moreover, TVS is well accepted and widely available. Although the higher probe frequency of RES offers better analysis of the different layers of the bowel wall, RES is no more effective than is TVS for the detection of rectal wall infiltration. Finally, RES sometimes necessitates general anesthesia, with its associated risks.

The ultrasound features of endometriosis are variable (Fig. 6) and overlap with a number of ovarian lesions.



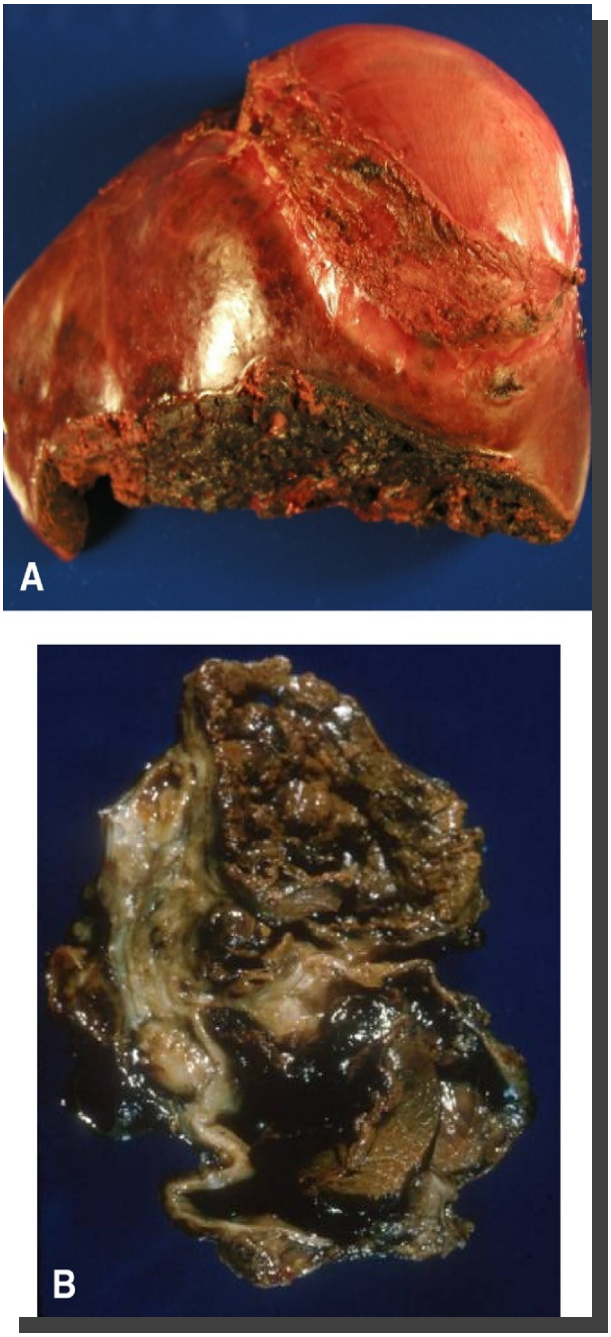
(a) A unilocular endometrioma with homogeneous ground glass echogenicity of the cyst fluid in a 28-year-old patient. The cyst wall is regular and thick (the largest diameter of the mass is 63 mm). This is the 'typical' ultrasound image of an endometrioma. (b) Endometrioma in a 27-year-old patient that presents as a unilocular cyst with heterogeneous ground glass echogenicity of the cyst content and minimal flow in the cyst wall (largest diameter 31 mm). (c) Unilocular-solid endometrioma (46 × 51 × 50 mm), in a 27-year-old-patient, with a thick cyst wall and one papillary projection (9 × 9 × 10 mm). The color score is 2 (minimal) but there is no flow inside the papillary projection. (d) Unilocular-solid endometrioma (88 × 62 × 71 mm) in a 54-year-old patient. The solid papillary projection (12 × 14 × 31 mm) contains internal flow (Van Holsbeke et al., 2010).

A commonly seen appearance is a single or multiple cysts with thickened walls, thick internal septations, and mural nodularity or solid areas devoid of vascularity on Doppler imaging because these are a result of recurrent bleeding and subsequent fibrosis. The presence of diffuse low-level internal echoes and fluid-fluid levels is due to internal hemorrhage at different stages (Fig 7).



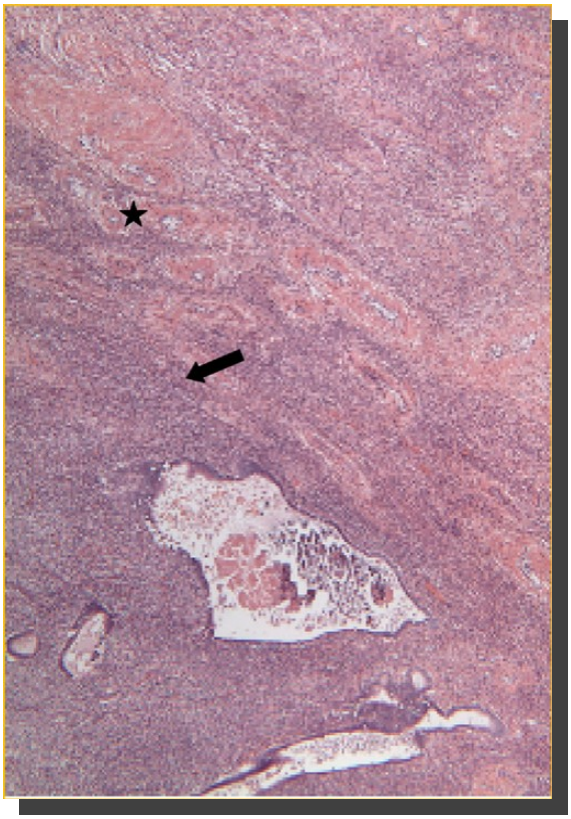
Endovaginal ultrasound appearances of surgically proven ovarian endometriosis in 3 different patients. (A) Patient 1—Thick- walled ovarian cyst with internal echoes. (B) Patient 2—Thick- walled cyst with internal echoes and peripheral retracted heme products (*). (C) Patient 3—A large cystic right ovarian lesion with internal echoes and fluid-hematocrit level (arrows). (Soniavane et al., 2011)

On gross pathology, internal hemorrhage with blood at different stages gives its characteristic appearance of "a chocolate cyst" (Fig 8).



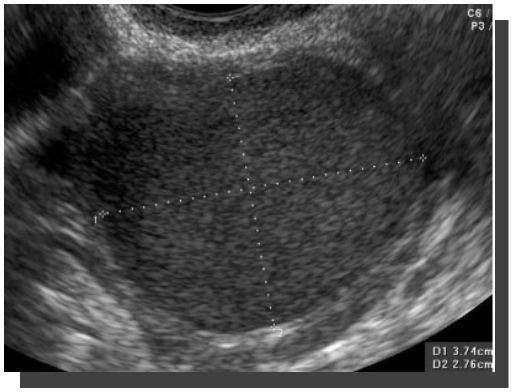
(A, B) Gross pathology specimens of ovarian chocolate cysts. (Soniavane et al., 2011)

Microscopic examination shows the presence of endometrial glands and stroma in the ectopic location (Fig 9).



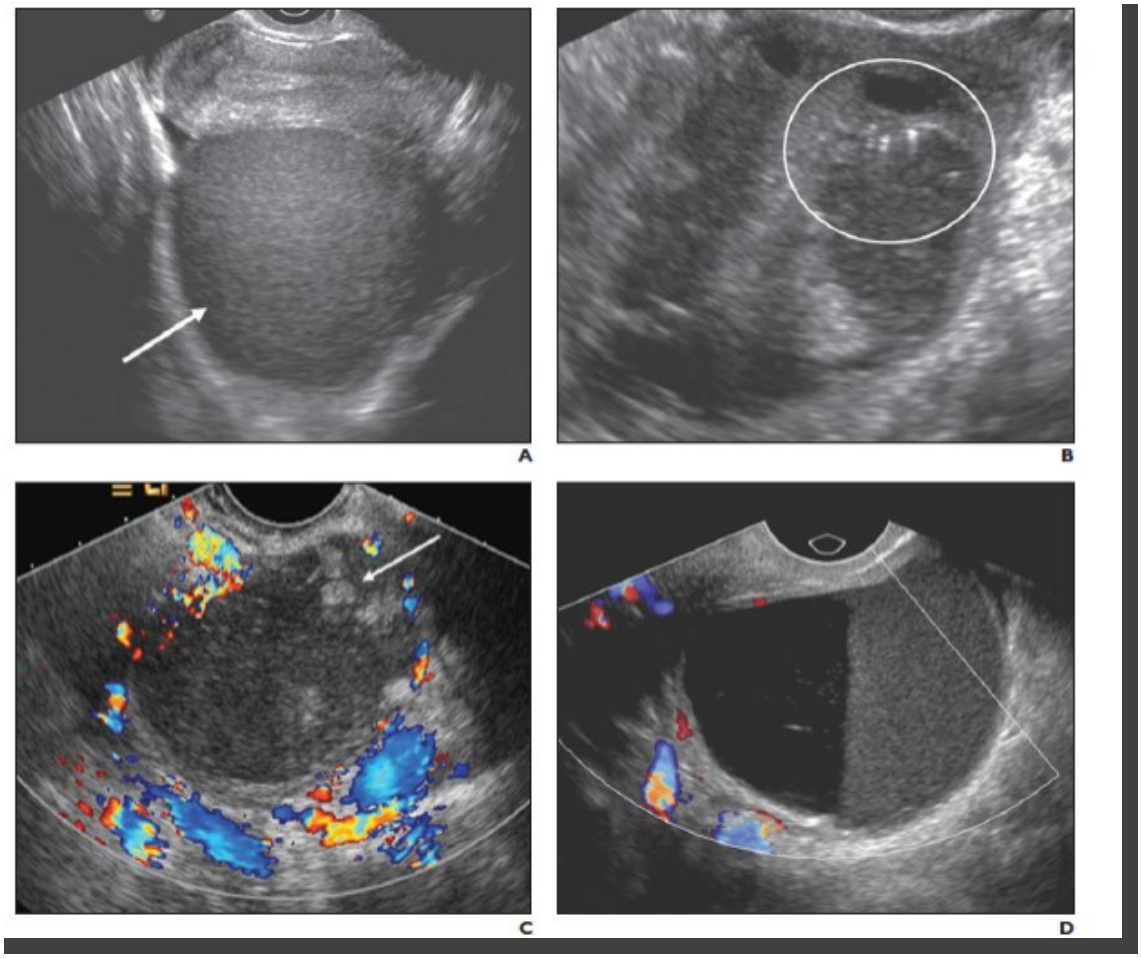
Histology of endometrioma demonstrating ectopic endometrial glands (*) and stroma (arrow) within a normal ovary on hematoxylin- eosin stain (x100). (Soniavane et al., 2011)

Several studies have described the ultrasound characteristics of endometriomas and attempted to define their typical ultrasound features (Fig. 10) (Valentin, 2004; Guerriero et al., 1994, 1996, 1998; Mais et al., 1993; Patel et al., 1993).



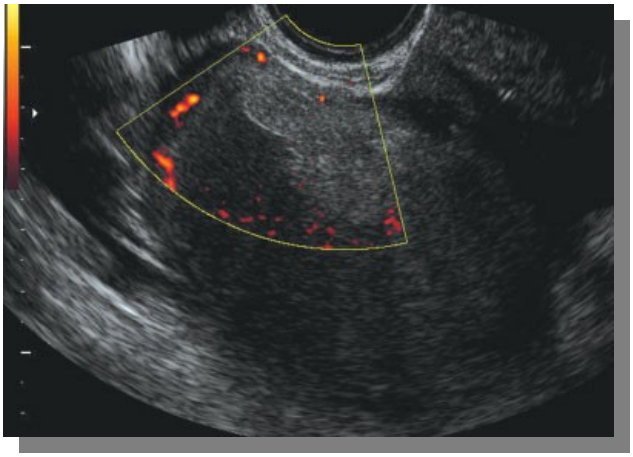
Transvaginal ultrasound image of a typical endometrioma. The content is homogeneous and composed of low-level echoes and the cyst wall is regular and smooth (Savelli, 2009).

The ‘typical’ endometrioma is a unilocular cyst with homogeneous low-level echogenicity (ground glass echogenicity) of the cyst fluid (Figure 11) but other morphological features have also been described (Valentin, 2004; Raine-Fenning et al., 2008; Asch and Levine, 2007; Kupfer et al., 1992).



Sonographic spectrum of endometriomas. Examples of endometriomas in four different patients are illustrated. A, Classic sonographic appearance of endometrioma. Complex cystic mass (arrow) with homogeneous low-level echoes, smooth wall, and no septations or solid component. B, Endometrioma containing echogenic wall foci with comet tail artifacts (circle). These foci are seen in 36% of endometriomas and only 6% of nonendometriomas, and when present, favor diagnosis of endometrioma. C, Complex appearance of endometrioma due to repeated episodes of bleeding. Clot may simulate solid component (arrow). No vascularity is visible with color Doppler imaging; this finding excludes solid mural nodule. Follow-up would be helpful to confirm stability. D, Complex endometrioma with fluid–fluid level due to recent hemorrhage. Hyperechoic level represents layering blood products. Hyperechoic component is dependent in an endometrioma, whereas hyperechoic component would be nondependent in a dermoid (Bennett et al., 2010).

Guerriero and Dogan were the first to perform studies to characterize atypical endometriomas (Guerriero et al., 1998) (Fig. 12).



Transvaginal ultrasound image of an atypical endometriotic cyst. Note the presence of focal wall nodularity with absence of blood flow. Power Doppler depicts sparse vascularization, the few blood vessels being confined to the cyst wall (Savelli, 2009)

Van Holsbeke (Van Holsbeke et al., 2010) found that almost 50% of the endometriomas had ultrasound characteristics other than the typical 'unilocular cyst with ground glass echogenicity of the cyst fluid', and that the ultrasound appearance of endometriomas differed between pre and postmenopausal patients (Tab. 8).

Demographic, clinical, or ultrasound variable	*Endometriomas (n = 713)*	*Benign tumors, other than endometrioma (n = 1847)*	*Malignant tumors (n = 951)*	*Endometriomas vs. other benign tumors: difference in % or θ values* as appropriate (95% CI)*	*Endometriomas vs. malignant tumors: difference in % or θ values* as appropriate (95% CI)*
Age (years, median (p_{25}–p_{75}))	34 (29–42)	45 (34–58)	56 (47–66)	0.71* (0.69; 0.73)	0.87* (0.86; 0.89)
Postmenopausal (*n* (%))	30 (4)	721 (39)	626 (66)	−34.8 (−37.4; −32.0)	−61.6 (−64.8; −58.1)
Personal history of ovarian cancer (*n* (%))	5 (0.7)	15 (0.8)	34 (3.6)	−0.1 (−0.8; 0.9)	−2.9 (−4.3; −1.5)
CA-125 (U/mL, median (p_{25}–p_{75}))†	44 (24–85)	15 (10–24)	168 (35–636)	0.79* (0.77; 0.82)	0.71* (0.68; 0.74)
Pain during ultrasound examination (*n* (%))	253 (35)	350 (19)	146 (15)	16.5 (12.6; 20.5)	20.1 (15.9; 24.3)
Type of tumor (*n* (%))					
Unilocular	463 (65)	673 (37)**	12 (1)	28.3 (24.1; 32.4)	63.7 (60.0; 67.1)
Unilocular-solid	60 (8)	215 (12)**	157 (17)	−3.3 (−5.7; −0.6)	−8.1 (−11.2; −4.9)
Multilocular	130 (18)	436 (24)**	57 (6)	−5.5 (−8.8; −1.9)	12.2 (9.1; 15.5)
Multilocular-solid	50 (7)	314 (17)**	384 (40)	−10.1 (−12.5; −7.4)	−33.4 (−36.9; −29.6)
Solid	10 (1)	200 (11)**	341 (36)	−9.5 (−11.1; −7.7)	−34.5 (−37.6; −31.3)
Echogenicity of cyst fluid (*n* (%))					
Anechoic	34 (5)	782 (42)	225 (24)	−37.6 (−40.2; −34.7)	−18.9 (−22.0; −15.7)
Ground glass	520 (73)	109 (6)	57 (6)	67.0 (63.5; 70.3)	66.9 (63.2; 70.3)
Low level	95 (13)	334 (18)	215 (23)	−4.8 (−7.7; −1.6)	−9.3 (−12.9; −5.6)
Hemorrhagic	13 (2)	32 (2)	7 (1)	0.1 (−0.9; 1.5)	1.1 (0.0; 2.4)
Mixed	41 (6)	390 (21)	106 (11)	−15.4 (−17.8; −12.7)	−5.4 (−8.0; −2.7)
No cyst fluid	10 (1)	200 (11)	341 (36)	−9.4 (−11.1; −7.7)	−34.5 (−37.6; −31.3)
Irregular cyst wall (*n* (%))	188 (26)	558 (30)	674 (71)	−3.8 (−7.6; 0.1)	−44.5 (−48.7; −40.0)
Presence of papillary projection (*n* (%))	73 (10)	304 (16)	379 (40)	−6.2 (−8.9; −3.3)	−29.6 (−33.4; −25.7)
Detectable blood flow within papillations (*n* (%))	18 (3)	76 (4)	287 (30)	−1.6 (−3.0; 0.1)	−27.7 (−30.8; −24.5)
Papillations with irregular surface (*n* (%))	31 (4)	166 (9)	314 (33)	−4.6 (−6.5; −2.5)	−28.7 (−32.0; −25.3)
Number of papillations (*n* (%))‡					
1	51 (70)	187 (62)	110 (29)		
2	8 (11)	41 (13)	37 (10)	0.54* (0.47; 0.61)	0.74* (0.68; 0.80)
3	6 (8)	34 (11)	42 (11)		
> 3	8 (11)	42 (14)	190 (50)		
Number of locules (*n* (%))§					
2	83 (46)	204 (27)	52 (12)		
3	40 (22)	137 (18)	50 (11)	0.66* (0.61; 0.70)	0.80* (0.75; 0.83)
4	26 (14)	84 (11)	58 (13)		
5–10	29 (16)	235 (31)	147 (33)		
> 10	2 (1)	90 (12)	134 (30)		
Color score (*n* (%))					
1	243 (34)	748 (41)	40 (4)		
2	317 (44)	615 (33)	212 (22)	0.51* (0.48; 0.53)	0.81* (0.79; 0.83)
3	134 (19)	416 (23)	407 (43)		
4	19 (3)	68 (4)	292 (31)		
Largest lesion diameter (mm, median (p_{25}–p_{75}))	53 (38–73)	65 (46–91)	93 (59–138)	0.62* (0.60; 0.64)	0.76* (0.74; 0.79)
Presence of solid parts (*n* (%))	120 (17)	730 (40)	882 (93)	−22.7 (−26.1; −19.0)	−75.8 (−78.8; −72.4)
Largest solid component diameter (mm, median (p_{25}–p_{75}))¶	19 (10–30)	25 (12–46)	54 (35–83)	0.60* (0.54; 0.65)	0.84* (0.79; 0.87)

*θ-value measuring the degree of overlap of a variable between groups (0.5 means maximal overlap, 1 means no overlap); 95% CIs for differences in percentage are based on a method using Wilson's score interval without continuity correction[29], for θ they are based on a previous report[30]. †Analysis of patients with available CA-125 level (456 endometriomas, 1340 other benign masses and 862 malignant masses). ‡Analysis of masses with a papillary projection (73 endometriomas, 304 other benign masses and 379 malignant masses). §Analysis of multilocular or multilocular-solid masses (180 endometriomas, 750 other benign masses and 441 malignant masses). ¶Analysis of masses with solid components (120 endometriomas, 730 other benign masses and 882 malignant masses). **In nine cases tumor type was noted to be not classifiable and therefore these numbers do not add up to 1847 but rather to 1838. p_{25}–p_{75}: 25th and 75th percentiles.

(Van Holsbeke et al., 2010)

The endometriomas in the postmenopausal patients were less often unilocular cysts and they were less likely to exhibit ground glass echogenicity. It was not possible to develop a rule to distinguish

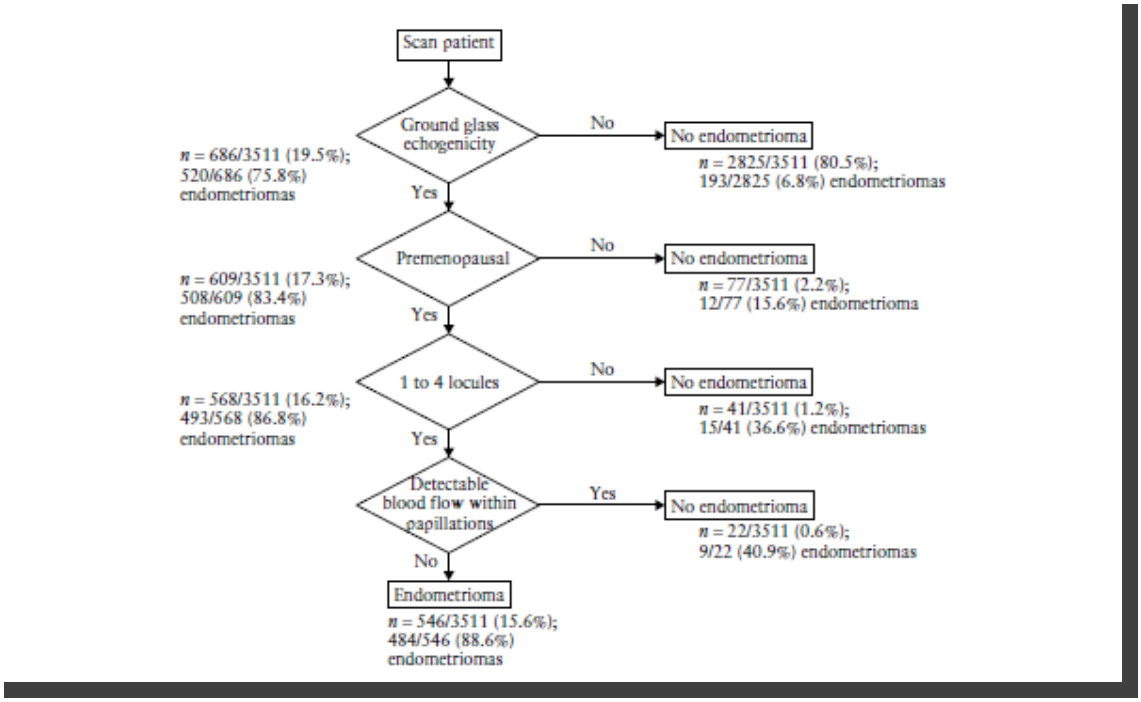
endometriomas from other types of adnexal masses specifically for postmenopausal patients, because of the heterogeneity of the ultrasound appearance of endometriomas in postmenopausal patients (Tab. 9).

Table 4 Diagnostic performance of single variables and combination of variables with regard to discriminating between endometriomas and other types of adnexal masses

Rule	*Applicability**	*PPV*	*Sensitivity†*	*Specificity†*	*LR+ (95% CI)‡*	*LR− (95% CI)‡*	*FPR-M*
Rules based on decision tree							
Ground glass echogenicity (rule 1)	19.5% (686/3511)	75.8% (520/686)	72.9% (520/713)	94.1% (2632/2798)	12.3 (10.5–14.3)	0.29 (0.25–0.32)	6.0% (57/951)
Ground glass echogenicity + premenopausal (rule 2)	17.3% (609/3511)	83.4% (508/609)	71.2% (508/713)	96.4% (2697/2798)	19.7 (16.2–24.0)	0.30 (0.27–0.33)	2.4% (23/951)
Ground glass echogenicity + 1–4 locules + premenopausal (rule 3)	16.2% (568/3511)	86.8% (493/568)	69.1% (493/713)	97.3% (2723/2798)	25.8 (20.5–32.4)	0.32 (0.28–0.35)	1.5% (14/951)
Ground glass echogenicity + 1–4 locules but without papillary flow + premenopausal (rule 4)	15.6% (546/3511)	88.6% (484/546)	67.9% (484/713)	97.8% (2736/2798)	30.6 (23.9–39.4)	0.33 (0.29–0.36)	0.4% (4/951)
Other rules							
Ground glass echogenicity + 1–4 locules, no solid parts + premenopausal (rule A)	13.8% (486/3511)	90.1% (438/486)	61.4% (438/713)	98.3% (2750/2798)	35.8 (26.9–47.7)	0.39 (0.36–0.43)	0.2% (2/951)
Ground glass echogenicity + unilocular cyst (rule B)	11.8% (416/3511)	88.0% (366/416)	51.3% (366/713)	98.2% (2748/2798)	28.7 (21.7–38.1)	0.50 (0.46–0.53)	0.5% (5/951)
Ground glass echogenicity + unilocular cyst + premenopausal (rule C)	11.3% (398/3511)	90.5% (360/398)	50.5% (360/713)	98.6% (2760/2798)	37.2 (26.9–51.4)	0.50 (0.46–0.54)	0.2% (2/951)
Diagnostic algorithm of Guerriero *et al.*[16] § (rule G)	12.5% (439/3511)	86.6% (380/439)	53.3% (380/713)	97.9% (2739/2798)	25.3 (19.5–32.8)	0.48 (0.44–0.51)	0.7% (7/951)
Subjective impression (rule S)	18.6% (652/3511)	88.5% (577/652)	80.9% (577/713)	97.3% (2723/2798)	30.2 (24.1–37.9)	0.20 (0.17–0.23)	0.9% (9/951)

*Number and percentage of all tumors in which the variable/combination of variables was present. †Sensitivity and specificity with regard to endometrioma. ‡95% CIs were based on the Cox–Hinkley–Miettinen–Nurminen method[33]. §The algorithm is described in the methods section. FPR-M, number and percentage of malignant tumors with the feature present (false-positive malignant); LR+, positive likelihood ratio; LR−, negative likelihood ratio; PPV, positive predictive value with regard to endometrioma.

On the basis of the decision-tree analysis and the predefined criteria of the optimal rule, the authors found several rules as the optimal decision-tree rule: ‘premenopausal status, ground glass echogenicity, one to four locules and no papillations with detectable blood flow’ (Fig. 13).



(Van Holsbeke et al., 2010)

The differential diagnosis of endometriomas includes luteal cysts, cystadenomas, pyosalpinges, dermoids and ovarian cancers, because, in these masses, the cyst content (blood, mucus or pus) may display low-level echoes on ultrasound (Savelli, 2009). On TVS, an experienced sonologist should be able, in most cases, to distinguish between endometriomas and other types of adnexal mass by means of pattern recognition (Valentin, 2004). Moreover, power Doppler can be of help in showing the absence of flow within the cyst content when heterogeneous inner portions are found

due to intracystic hemorrhage or accumulation of the dense parts of the content (Guerriero et al., 1998). Endometriotic cysts are associated with scanty vascularization of the cyst wall, while non-endometriotic cysts, particularly luteal cysts and ovarian cancers, are characterized by rich vascularization of the wall and the presence of arterial flow within papillary projections with low resistance index and echogenic areas of the cyst.

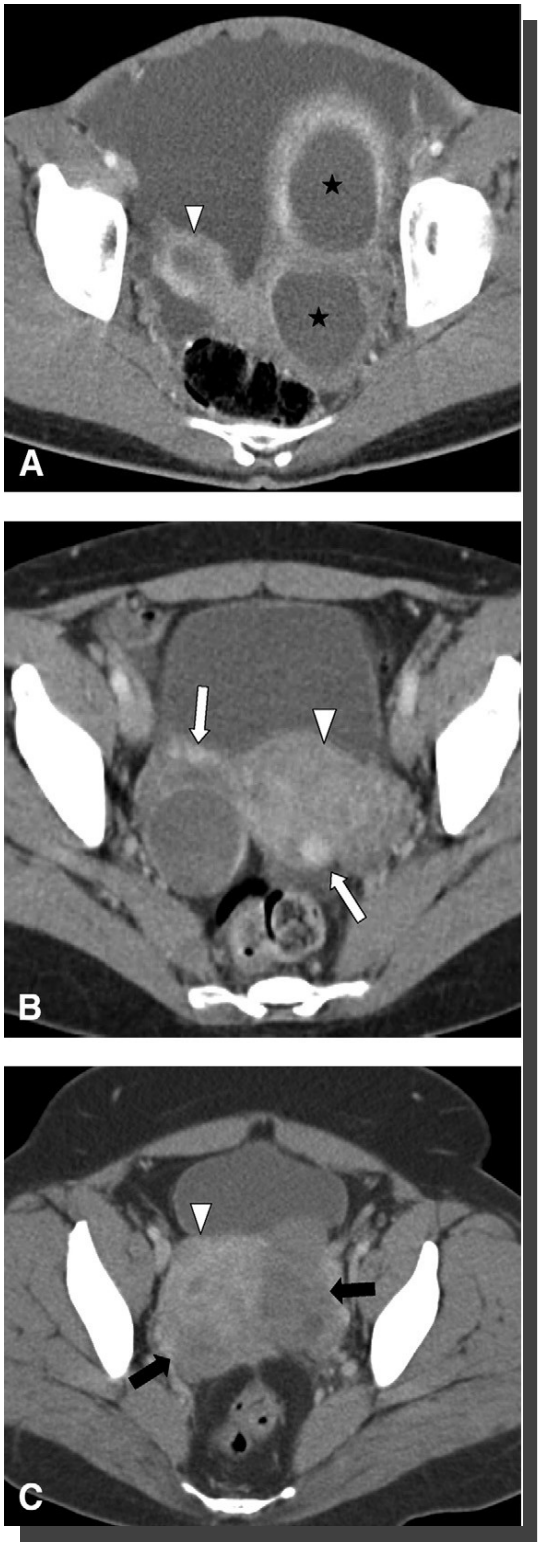
Another distinct feature of endometriomas is that they usually form adhesions. Thus, they can be found far from the true adnexal site (eg. attached to the pouch of Douglas), being fixed and painful when pressure is applied with the vaginal probe. These features may be revealed only if gentle pressure is exerted while visualizing the cyst on the screen (so-called 'sliding sign'). When endometriomas are bilateral, they can even be found adhering to each other behind or above the uterus (so-called 'kissing ovaries').

Computed Tomography

Because of the nonspecific imaging features of endometriosis at CT, CT is not the preferred imaging technique for the evaluation of a suspected endometrioma. Endometriomas generally appear as complex cystic pelvic masses, usually with high-density fluid components (HU-40 to 80) (Buy et

al., 1992). Sometimes endometriomas are seen as enhancing nodular deposits in the pelvis.

Adjacent reactive changes in the form of fibrosis, desmoplasia, and free fluid are more evident on CT (Fig. 14).

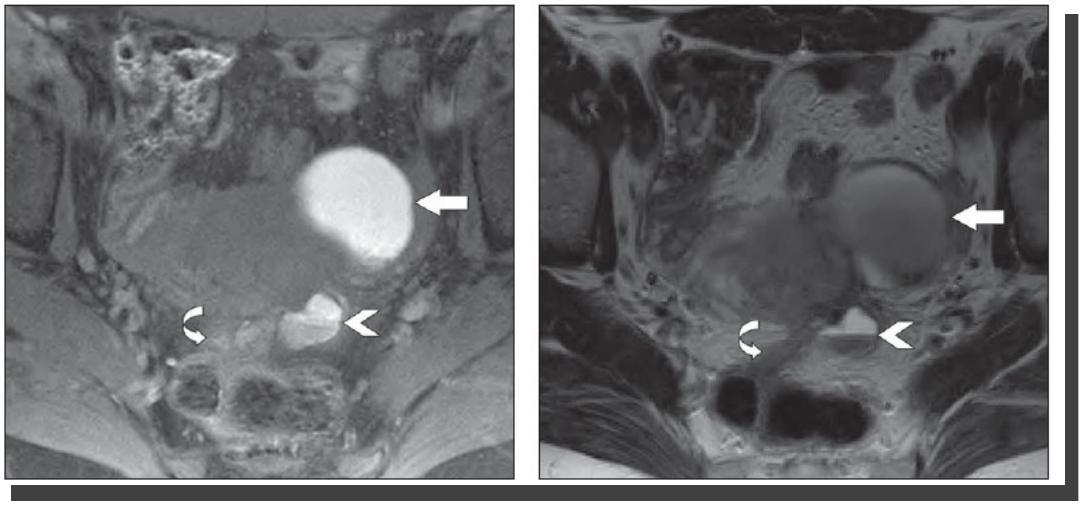


Contrast-enhanced CT scan appearances of bilateral ovarian and pelvic endometriosis in 3 different patients. (A) Thick-walled cystic left adnexal lesions (*) with ascites. (B) Enhancing nodular deposits along pouch of Douglas (arrows) associated with a right ovarian cyst. (C) Large, complex, heterogeneously enhancing soft tissue masses arising from both adnexae (black arrows). The uterus is indicated by arrowheads. (Soniavane et al., 2011)

For this reason, CT plays a greater role in the diagnosis of various complications of endometriosis and unusual sites of implantation.

Magnetic Resonance Imaging

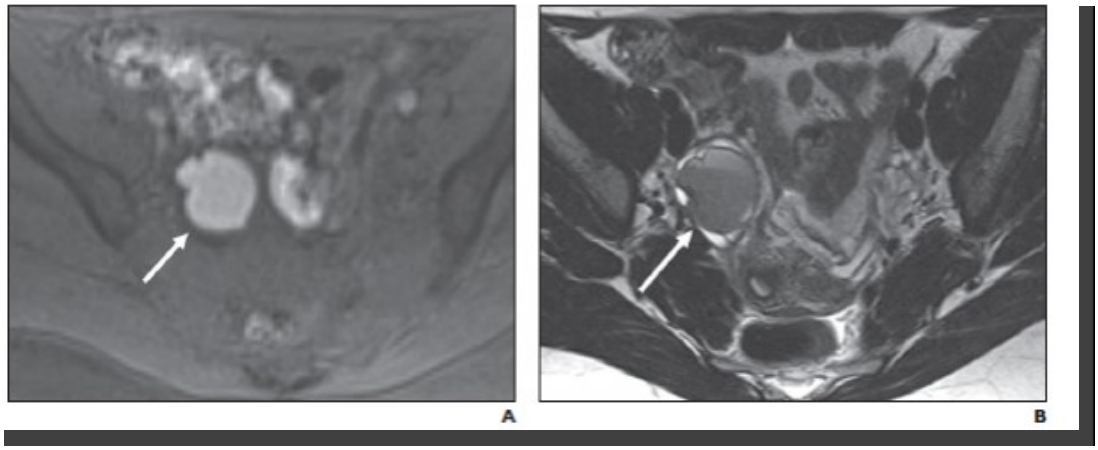
The multiplanar capability, high sensitivity for detection of blood products, and ability to identify sites of disease hidden by dense adhesions have made pelvic MRI the non-invasive imaging technique of choice for more accurate disease detection and staging (Choudhary et al., 2009) (Fig. 15).



A, Axial T1-weighted fat-suppressed image reveals left ovarian endometrioma that appears hyperintense (straight arrow), left uterosacral implant with hemorrhage–fluid level (arrowhead), and obliteration of posterior cul-de-sac (curved arrow). Mature cystic teratoma will also show high signal on T1-weighted images; however, in teratomas there is loss of signal on fat-suppressed sequences, unlike endometriomas, which remain hyperintense. B, Axial T2-weighted image shows shading in left ovarian endometrioma (straight arrow) as well as in left uterosacral implant (arrowhead). Note that adhesions in posterior cul-de-sac are of low signal intensity (curved arrow). Shading may range from faint dependent layering to markedly hypointense signal in lesion, depending on concentration of blood products. Endometriotic cysts usually also show peripheral rim of low signal intensity on T2-weighted images that represents hemosiderin or fibrous capsule. (Choudhary et al., 2009)

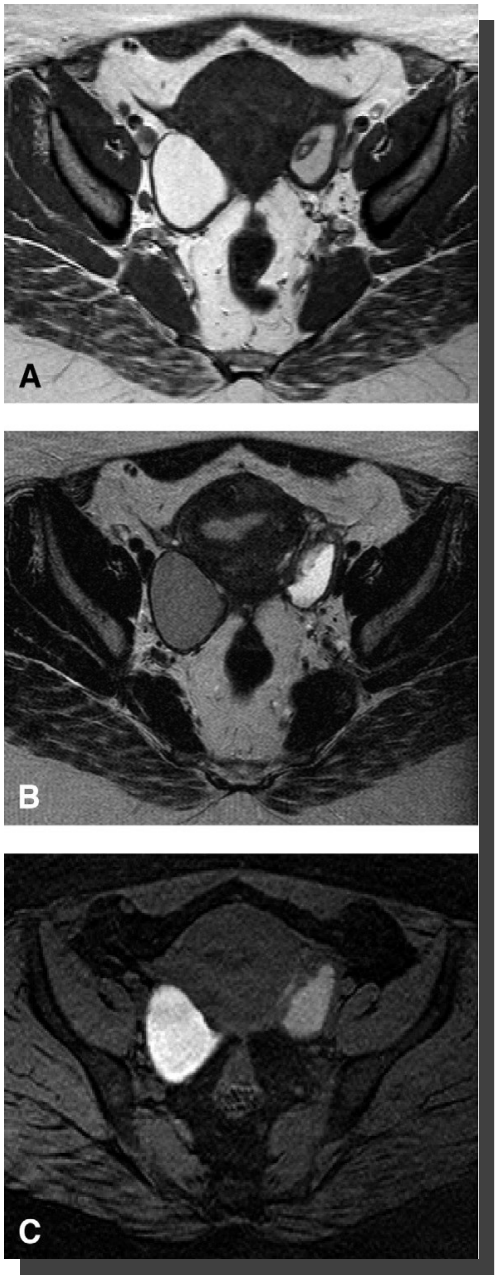
In a study by Togashi et al. (Togashi et al., 1991), MRI yielded an overall sensitivity, specificity, and accuracy of 90%, 98%, and 96%, respectively, for diagnosing endometriomas and in differentiating them from other gynecological masses.

The classic endometrioma shows shading, defined as a range of low-signal intensities on T2-weighted images and a corresponding high signal on T1-weighted images (Fig. 16).



MR appearance of endometrioma in 32-year-old woman. A, T1-weighted fat-suppressed image obtained during volumetric interpolated breath-hold examination shows high-signal-intensity lesion (arrow) within right adnexa compatible with blood-containing abnormality. B, T2-weighted image shows decrease in signal intensity of lesion (arrow); this finding is referred to as "shading" and is compatible with chronic blood. (Bennett et al., 2010)

This shading reflects the chronic nature of the endometrioma resulting from repeated episodes of hemorrhage accumulating over months and years with extremely high concentrations of iron, protein, and intracellular methemoglobin. Thirty percent of women also show concomitant tubal abnormalities such as hemato-salpinges (Fig. 17).



MR features of pathologically proven ovarian endometriomas. (A) T1W Transaxial image of pelvis shows bilateral adnexal complex cystic lesions with high signal intensity contents. (B) T2W transaxial image of pelvis showing shading effect in the right ovarian cyst and high signal intensity in left ovarian cyst. (C) T1W fat-suppressed image shows persistent high signal intensity in both ovarian cysts consistent with blood clots and proteinaceous contents. (Soniavane et al., 2011)

Fat saturation on T1-weighted images improves visualization of implants on peritoneal surfaces, although MR sensitivity for small implants remains limited (Gougoutas et al., 2000). Contrast enhanced sequences are useful for detection of microscopic endometrial implants associated with inflammatory reaction, as well as assessing for malignant change.

Moreover, MRI can be helpful in differentiating endometriomas from dermoids. Dermoids may also appear hyperintense on T1-weighted images but contain fat and, therefore, will decrease in signal intensity on fat-suppressed images or show chemical shift artifact.

Several clinical and imaging risk factors (Tanaka et al., 2010) have been reported as suggestive for malignant transformation, such as age of more than 40 years, large cyst size, lack of shading on MRI, and so on (Kobayashi et al., 2007). Investigators have also reported that patients with endometriotic cysts have decreased dysmenorrhea after malignant transformation occurs (JSOG, 2004). Of these findings, enhancement of mural nodules seems to be the most valuable imaging finding (Wu et al., 2004); however, benign conditions with this finding have been also reported (Kraft and Hughes, 2006; Onbas et al., 2007; Takeuchi et al., 2008) (Fig. 18).

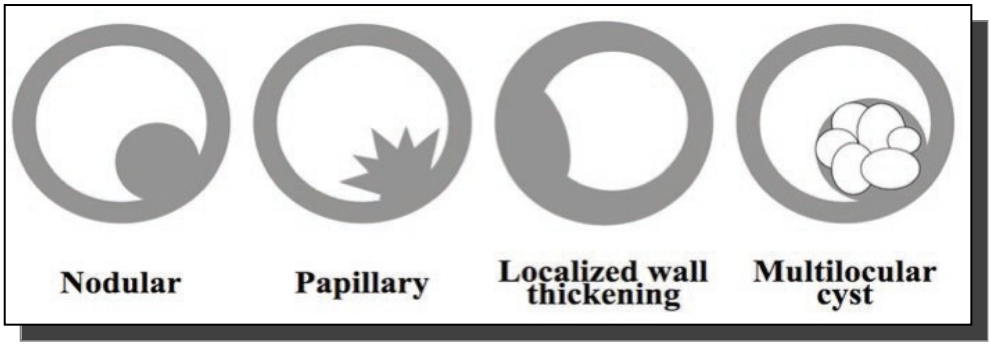


Illustration shows morphologic classification of protruded cyst wall. We classified morphologic pattern of protruded cyst wall into four types: nodular, papillary, localized wall thickening, and multilocular cyst. (Tanaka et al., 2010)

Principle of Treatment

The principal objective in treating endometriosis is symptom relief management (Chwalisz et al., 2002). In addition to relieving pain, the goals of treatment for patients with endometriosis are to prevent or delay disease progression by reducing endometriotic implants through surgical treatment or medically induced atrophy of the implants (Rice, 2002; Valle et al., 2003). Because neither medical nor surgical treatments have been proven to improve fertility rates substantially in women with endometriosis in its early stages, the focus of treatment is on the relief of pain symptoms (Chwalisz et al., 2002; Shaw, 2003). Because of the chronic nature of this disease, long-term or repeated courses of medical therapy are required to control these symptoms (Schweppe, 2001).

In the past, endometriosis was treated primarily by surgery; and in fact, surgery—alone or in combination with medical therapy— remains a common treatment method for all stages of endometriosis (Viganò et al., 2003).

In a 12 month trial (n = 39), more women reported improvement in symptoms after excisional surgery (80%) than after receiving placebo (32%) (Abbott et al., 2004). Nevertheless, surgery is an invasive therapeutic option that is far from ideal, because 20% of cases do not respond (Abbott et al., 2004), and the recurrence rate is high after surgery (Milingos et al., 2003). Although data directly comparing the results of

surgical and medical treatment are scarce, the available evidence suggests that surgery does not provide any greater relief of pain symptoms than does medical therapy (Winkel, 2000).

Although estimates vary, an independent, randomized, controlled clinical trial reported that 51% of women experienced a recurrence of symptoms sufficient to require additional medication for pain within 1 year of surgery (Hornstein et al., 1997). Other reports have indicated that 7–30% of patients experience recurrence of pain symptoms within 3 years of laparoscopic surgery, an estimate that increases to 40–50% at 5 years after surgery (Valle et al., 2003). Studies of laser surgical treatment also suggest increasing recurrence of symptoms with time (e.g. recurrence occurred in 23% of patients at 1 year and 31% of patients at 2 years in one study cohort of 106 patients) (Shaw, 2003). These rates are roughly comparable with those following medical therapy: a long-term follow-up study of GnRH analogue therapy reported recurrence rates of 28% at 2 years and 53% at 5 years after cessation of therapy (Waller and Shaw, 1993).

For this reason, medical therapies that can be administered for only a few months due to safety concerns or poor tolerability are not ideal for women with symptomatic endometriosis (Vercellini et al., 2003a). In addition, repeated surgical procedures for recurring pain increases morbidity, as well as physician and patient frustration (Vercellini et al., 2000). Thus, chronic pain symptoms and the effects of poorly tolerated, ongoing, or repeated

treatment courses can contribute to poor quality of life for women with endometriosis, disrupting job performance, social relationships, or sexual functioning (ESHRE Capri Workshop Group, 2001; Marques et al., 2004).

Medical Therapy

Medical treatment of endometriosis-associated pain is generally effective, with little difference in efficacy observed among the different types of agents used; however, the adverse-event profiles of the various drug regimens can differ markedly (Child et al., 2001). Therapies that have been used include non-steroidal anti-inflammatory agents (as first-line therapy for mild symptoms), androgenic agents (danazol), GnRH analogues, estrogen/ progestin combined oral contraceptives (COCs) and progestins (Tab. 10) (Rice, 2002).

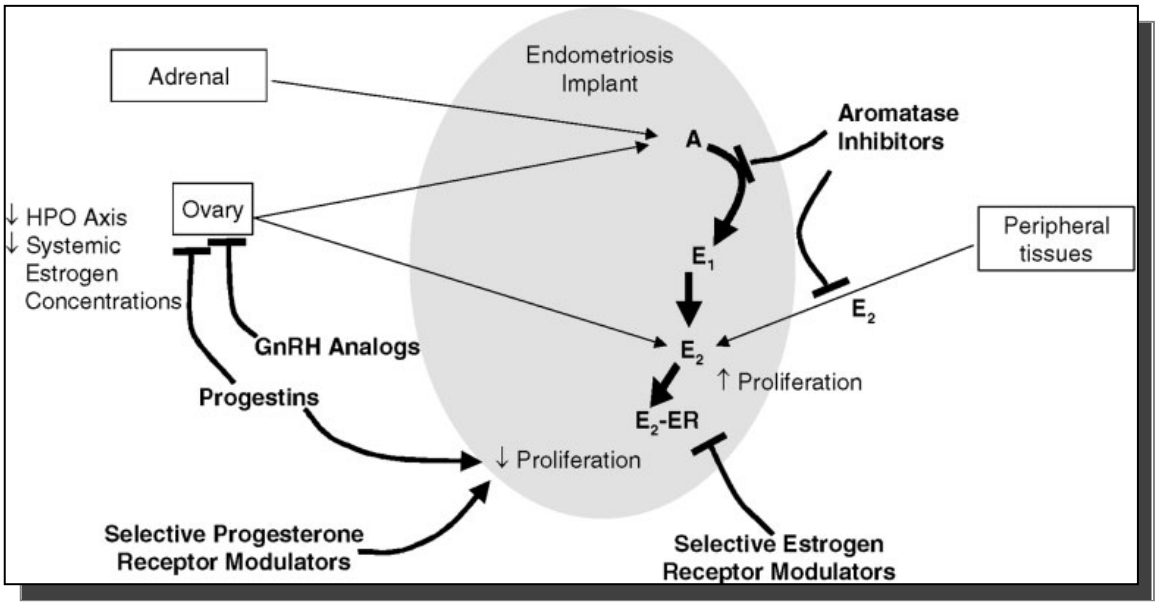
Table I. Agents for the pharmacologic management of endometriosis-associated pain (Overton *et al.*, 1994; Gestrinone Italian Study Group, 1996; Vercellini *et al.*, 1997; Rice, 2002; Valle *et al.*, 2003; Donnez *et al.*, 2004; Crosignani *et al.*, 2005; Schlaff *et al.*, in press)

Agent	Dose	Route	Dosing frequency	Common side effects
Combined oral contraceptives	30–35 µg ethinyl estradiol, plus progestin	Oral	Daily (cyclic or continuous)	Irregular bleeding, weight gain, bloating, breast tension and headache
Androgen				
Danazol	400–800 mg	Oral	Daily (duration limited to 6 months by side effects)	Androgenic/anabolic (weight gain, fluid retention, breast atrophy, acne, oily skin, hot flashes and hirsutism)
GnRH agonists			(Duration limited to 6 months due to BMD effects)	
Leuprolide	1 mg/day	SC injection	Daily	Hypoestrogenic (hot flashes, vaginal dryness, emotional lability, loss of libido and BMD decline)
Leuprolide depot	3.75 mg	IM injection	Monthly	
	11.75 mg	IM injection	Every 3 months	
Triptorelin	3 mg	IM injection	Monthly	
Triptorelin depot	11.25 mg	IM injection	Every 3 months	
Goserelin	3.6 mg	SC implant	Monthly	
Buserelin	300–400 µg	Intranasal	Tid	
Nafarelin	200–400 µg	Intranasal	Bid	
Progestins				
Dydrogesterone	60 mg	Oral	12 days per cycle*	
Gestrinone	2.5–5 mg	Oral	Daily/twice weekly	
Megestrol acetate	40 mg	Oral	Daily	Irregular bleeding, weight gain, bloating and edema
Norethindrone acetate	5 mg†	Oral	Daily	
MPA	30 mg	Oral	Daily	
DMPA-IM 150‡	150 mg	IM injection	Every 3 months	
DMPA-SC 104‡	104 mg	SC injection	Every 3 months	

BMD, bone mineral density; DMPA, depot medroxyprogesterone acetate; IM, intramuscular; MPA, medroxyprogesterone acetate; SC, subcutaneous.
*During the luteal phase.
†Starting dose, with gradual dose escalation.
‡Also with transient BMD decline.

(Crosignani et al., 2006)

It has been understood for some time that endometriotic tissue is hormonally sensitive, and that symptoms of endometriosis usually improve during pregnancy or after menopause. Currently available medical therapies for endometriosis act by attempting to mimic periods during which a woman does not menstruate: menopause (GnRH analogues), amenorrhoea (chronic anovulation with danazol) or pregnancy [oral contraceptives (Ocs) or progestins] (Child et al., 2001) (Fig. 19).



Investigational agents for the treatment of endometriosis-associated pain: mechanisms of aromatase inhibitors, anti-estrogens (selective estrogen receptor modulators) and selective progesterone receptor modulators. This schematic depicts the mechanisms of several new investigational agents for the treatment of endometriosis in relation to existing therapies in common use. GnRH analogues decrease the activity of endometrial implants by inhibiting the hypothalamic-pituitaryovarian (HPO) axis and blocking ovarian function, thereby greatly reducing systemic estrogen levels (inducing artificial menopause). Progestins both suppress HPO function and have antiproliferative effects directly on endometrial tissue (eutopic and endometriotic implants). The new agents attempt to more specifically target endometriotic implants. Aromatase P450, which is up-regulated in endometriotic implants, is a key enzyme in the biosynthesis of estrogen. Therefore, aromatase inhibitors decrease estrogen concentrations in the implants. Selective estrogen receptor modulators (SERMs) antagonize the effects of estrogen in the implants, thus reducing the growth and proliferation of implants. Selective progesterone receptor modulators (SPRMs), which can act as either agonists or antagonists of progesterone receptors in various tissues, have antiproliferative effects on endometrial growth (similar to progestins, but acting by differing mechanisms). However, SPRMs selectively suppress endometrial growth without inhibiting ovarian estrogen production. A, androstenedione; E1, estrone; E2, estradiol; E2–ER, estradiolbound estrogen receptors (Chwalisz et al., 2002; Olive, 2002; Viganò et al., 2003; Bulun et al., 2004).

Although the use of NSAIDs for pain relief seems logical, their effectiveness has not been studied well or compared with other treatments. For empiric medical therapy, OCPs and medroxyprogesterone acetate have apparent therapeutic equivalence and should be used as first-line therapies (Prentice et al., 2000). Many sources support the empiric use of GnRHas for treatment of the pain associated with endometriosis (Prentice et al., 1999); however, a systematic review found them to be no more effective than OCPs or progestogens (Moore et al., 1997) (Tab. 11).

Medical Treatment for Endometriosis: Summary of Studies

Study	*Population/setting*	*Outcomes*	*Comment*
Combined OCPs compared with goserelin (Zoladex)[A1]	Women of reproductive age, surgically diagnosed/ primary and secondary health care settings	Pain relief, side effects	No significant difference in pain six months posttreatment; significantly more side effects with goserelin
Progestogens and anti-progestogens[A2,A3]	Premenopausal women, laparoscopically diagnosed/ primary and secondary health care settings	Pain relief, resolution of endometriotic implants, side effects, compliance	Equivalent to other medical therapies for pain (e.g., danazol [Danocrine]), therefore likely effective; scant good data
GnRHas compared with placebo[A4]	Premenopausal women, laparoscopically diagnosed, between 18 and 50 years of age/ gynecologic outpatient clinics	Pain relief and side effects	More effective than placebo; high dropout rates in placebo group
GnRHas compared with other medical treatments[A4,A5]	Premenopausal women, laparoscopically diagnosed, between 18 and 50 years of age/ gynecologic outpatient clinics	Pain relief and side effects	Similar effectiveness as other medical treatments (OCPs, gestrinone, danazol); gestrinone possibly more effective; OCPs less effective for dysmenorrhea
GnRHas compared with GnRHas plus add-back therapy[A4]	Premenopausal women, laparoscopically diagnosed, between 18 and 50 years of age/ gynecologic outpatient clinics	Pain relief and side effects	Similar effectiveness; fewer side effects with add-back hormone therapy
Danazol[A6]	Women of reproductive age, surgically confirmed diagnosis/ settings not specified (systematic review)	Subjective symptom relief, objective disease improvement, side effects, compliance, disease recurrence	Significantly more effective than placebo after six months' therapy but with significant side effects (e.g., weight gain, acne)
Preoperative hormonal suppression for endometriosis surgery compared with surgery alone[A7]	Various populations/settings not specified (systematic review of 11 studies)	Pain relief, disease recurrence, pregnancy rates, adverse effects	Significant reduction in objective disease extent scores, but insufficient evidence to support use; no evidence of decreased disease recurrence or improved pregnancy rates
Hormonal suppression after endometriosis surgery compared with surgery alone[A7]	Various populations/settings not specified (systematic review of 11 studies)	Pain relief, disease recurrence, pregnancy rates	No benefit; insufficient evidence. No evidence of decreased recurrence or improved pregnancy rates
Ovulation suppression for endometriosis-associated subfertility compared with placebo, no treatment, or danazol[A8]	Women with visually diagnosed disease who did not conceive after at least 12 months of unprotected intercourse/settings not specified (systematic review)	Pregnancy, adverse outcomes	Not beneficial for improvement of subfertility; multiple side effects
Levonorgestrel-releasing intrauterine system (Mirena) for dysmenorrhea after surgery[A9]	Parous women with moderate to severe dysmenorrhea who were undergoing surgery/tertiary care referral center	Pain relief one year after surgery	10 percent recurrence of moderate to severe dysmenorrhea in treatment group compared with 45 percent in control group

OCPs = oral contraceptive pills; GnRHas = gonadotropin-releasing hormone analogues.

Information from references:

A1: Moore J, Kennedy S, Prentice A. Modern combined oral contraceptives for pain associated with endometriosis. Cochrane Database Syst Rev 1997;(4):CD001019.

A2: Prentice A, Deary AJ, Bland E. Progestagens and anti-progestagens for pain associated with endometriosis. Cochrane Database Syst Rev 2000;(2):CD002122.

A3: Vercellini P, Cortesi I, Crosignani PG. Progestins for symptomatic endometriosis: a critical analysis of the evidence. Fertil Steril 1997;68:393-401.

A4: Prentice A, Deary AJ, Goldbeck-Wood S, Farquhar C, Smith SK. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. Cochrane Database Syst Rev 1999;(2):CD000346.

A5: Vercellini P, Trespidi L, Colombo A, Vendola N, Marchini M, Crosignani PG. A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. Fertil Steril 1993;60:75-9.

A6: Selak V, Farquhar C, Prentice A, Singla A. Danazol for pelvic pain associated with endometriosis. Cochrane Database Syst Rev 2001;(4):CD000068.

A7: Yap C, Furness S, Farquhar C. Pre and post operative medical therapy for endometriosis surgery. Cochrane Database Syst Rev 2004;(3):CD003678.

A8: Hughes E, Fedorkow D, Collins J, Vandekerckhove P. Ovulation suppression for endometriosis. Cochrane Database Syst Rev 2003;(3):CD000155.

A9: Vercellini P, Frontino G, De Giorgi O, Aimi G, Zaina B, Crosignani PG. Comparison of a levonorgestrel-releasing intrauterine device versus expectant management after conservative surgery for symptomatic endometriosis: a pilot study. Fertil Steril 2003;80:305-9.

(Mounsey et al., 2006)

Furthermore, GnRHas can have hypoestrogenic side effects (Vercellini et al., 1993). These side effects may be alleviated somewhat with add-back therapy (i.e., replacement of hormones blocked by the action of GnRHas) without diminishing the effect of the GnRHa; however, the optimal method of add-back therapy has not been established (Moore et al., 1997). One small study found the levonorgestrel releasing intrauterine system (Mirena) to be effective in postoperative treatment for dysmenorrhea (Vercellini et al., 2003).

Unlike surgery, these methods of treatment are non-invasive and are not operator dependent. However, a disadvantage for women desiring pregnancy in the near term is that conception is generally not possible during medical therapy; indeed, many of these agents are also used as effective contraceptives. Therefore, before choosing therapy, health care providers should consider an individual woman's family plans and fertility status (Child et al., 2001).

Conservative Treatment

Treatment options of ovarian endometriosis include expectant management, medical treatment, and surgery. Laparoscopic cystectomy to remove ovarian endometriomas is an effective procedure; however, in the

presence of pelvic adhesions or advanced stage disease it can be difficult to visualize anatomic structures, leading to suboptimal resection, frequent cyst recurrence, and surgical complications.

Ultrasound-guided aspiration of ovarian endometriomas was proposed in 1991 as an alternative for patients who decline surgery or in whom surgery is contraindicated (Aboulghar et al., 1991). Studies have reported varying rates of recurrence after simple aspiration. To reduce recurrence, some investigators have combined aspiration with in situ injection of a sclerosing agent, for example, tetracycline (Aloulghar et al., 1993), methotrexate (MTX) (Mesogitis et al., 2000), recombinant interleukin-2 (Acien et al., 2003), or ethanol (Noma and Yoshida, 2001). Noma and Yoshida (Noma and Yoshida, 2001) reported that ethanol instillation into the cyst cavity for >10 minutes was most effective at reducing the recurrence rate.

Sclerotherapy (Hsieh et al., 2009) was originally used to treat tuberculosis pneumonitis and is currently used by medical oncologists to treat malignant pleural effusion.

The cellular mechanisms involved in the sclerotherapy of ovarian cysts are not fully known, but it seems that epithelial cells lining the cyst wall play an essential role (Kafali et al., 2003). When adequate contact between the sclerosing agent and the cyst wall is achieved, the activation of the coagulation cascade and the production of mediators for inflammation and fibrosis by epithelial lining cells lead to cyst wall adherence.

Various agents have been used for sclerotherapy. In 1993 Aboulghar et al. (Aboulghar et al., 1993) reported the efficacy of tetracycline as a means of avoiding surgery in patients with ovarian endometriomas. These findings were supported by the work of AbdRabbo and Atta in 1995 (AbdRabbo and Atta, 1995), and by Chang et al. in 1997 (Chang et al., 1997). Fish and Sher (Fish and Sher, 2004) showed that sclerotherapy of ovarian endometriomas with 5% tetracycline before IVF can achieve a resolution rate of 75% and a pregnancy rate (PR) of 57%. In 2000, Mesogitis et al. (Mesogitis et al., 2000) reported a recurrence rate of 5%–20% of ovarian endometriomas after aspiration and injection of MTX.

Many investigators believe that endometriosis is an autoimmune disease and immunomodulators, such as interferons or interleukins (IL), might enhance the cytotoxic activity of macrophages and natural killer (NK) cells to suppress the endometrial activity. In 2003 Acien et al. (Acien et al., 2003) reported that the time until recurrences was significantly longer when recombinant interleukin-2 (rIL-2) was used, although the rates of recurrence of with or without rIL-2 were similar.

Sclerotherapy with ethanol infusion and removal was reported by Noma and Yoshida (Noma and Yoshida, 2001) to have a recurrence rate of 14.9%. The study also demonstrated that instillation for R10 minutes was related to a recurrence rate of 9.1% versus 62.5% if the ethanol was left in the cyst cavity for <10 minutes.

The reported incidence of recurrence ranges from 9.1%–66.7% in various studies (Acien et al., 2003; Fish and Sher, 2004; Mittal et al., 1999; Giorlandino et al., 1993; Kafali et al., 2003). Parazzini et al. (Parazzini et al., 2005) indicated that the recurrence rate of endometriosis tends to be higher in cases with advanced stage of the disease at first diagnosis (Aboulghar et al., 1993). Different concentrations of ethanol as sclerosing agent might influence efficacy, but there is no definite evidence.

Moreover, Chang et al. (Chang et al., 1997) demonstrates that reduction of cystic size and preservation of ovarian tissue increases folliculogenesis, as highlighted by the increased number of antral follicles.

The presence of ovarian endometrioma and endometriosis is a well-documented finding in infertile patients. The mechanical effect of the mass of an endometrioma on the ovarian blood supply may result in poor ovarian response. Another possible cause suggested for poor follicular growth is that mechanical pressure allows no space for the follicles to reach 18 mm in diameter (Molloy et al., 1987). In addition, the presence of a mass made the oocyte retrieval more difficult and in some cases, it made the ovary inaccessible. The ectopic endometrial tissues impair the normal intraovarian mechanisms of follicle and oocyte maturation, which in turn may affect the quality of the oocytes retrieved. This does not seem to influence their capacity to be fertilized and cleave, but, instead, results in

functionally abnormal embryos with a defective implantation capacity (Dicker et al., 1991).

Sclerotherapy may help to preserve primordial follicles in a population already at risk for decreased ovarian reserve (Fish and Sher, 2004).

Complications of ethanol sclerotherapy have been rare with the absence of particularly severe complications. Most cases of alcohol intoxication can be prevented by infusing into the cyst less than 100 ml of ethanol and by adequately washing with physiological saline. Rare cases of alcohol intoxication can be readily controlled by intravenous infusion of lactate Ringer solution. Postoperative pelvic pain was minimal, requiring only a low dose of analgesic. Post-operative vaginal bleeding was also minimal and required no special treatment.

Ethanol sclerotherapy is indicated for almost all ovarian endometriomas such as severe endometriosis and for recurrence of ovarian endometriomas after cystectomy.

It is not indicated for cases of endometrioma having two or more cysts because of high recurrence rate with the classical approach.

Ultrasound-guided drainage of endometriomas is considered safe and noninvasive, but complications including abscess and adhesion formation may occur. The tissue trauma associated with transvaginal drainage or leakage of cyst contents during aspiration or inadvertent rupture may result in adhesion formation.

As histological diagnosis cannot be made in transvaginal puncture, differential diagnosis to exclude malignant neoplasm is important. Therefore, careful preoperative diagnosis is indicated.

With TVS most endometrial cysts can be differentiated from malignant tumors (i.e., benign cysts have simple structure, smooth border, septal thickness <3 mm, and absence of solid or inner papillary projections). Color Doppler blood flow analysis can be performed if there is suspicion of malignancy (i.e., cyst size >10 cm, thick cyst wall, papillary projections or multilocular). Depending on the pulsatile index, resistance index, and CA-125 level, highly suspicious cases may be treated with laparoscopy or laparotomy. If solid parts and irregular walls of the cysts suggest malignancy, transvaginal puncture should not be selected.

If the content of the cysts cannot be well elucidated by ultrasonography, MRI capable of ascertaining the content is useful in diagnosis (Nishimura et al., 1987).

Invasive Treatment

There is a general consensus that laparoscopy is the gold standard for the diagnosis of endometriosis (Tab. 12).

Surgical Treatment for Endometriosis: Summary of Studies

Study	*Population*	*Outcomes*	*Comment*
Systematic review of LUNA[B1]	Women with endometriosis and dysmenorrhea	Pain relief	LUNA with ablation was not superior to ablation alone.
Systematic review that included one study of laparoscopic surgery and LUNA compared with no treatment[B2]	Women with endometriosis and pelvic pain	Increased pain relief at six months	LUNA was used with ablation, so benefit cannot be determined.
Systematic review of presacral neurectomy with ablation compared with ablation alone[B1]	Women with endometriosis and dysmenorrhea	No overall difference in pain relief	Women with midline abdominal pain had a significant decrease in pain.
Systematic review of two RCTs that evaluated fertility rates after laparoscopic ablation of endometrial deposits[B3]	Infertile women 39 years of age with minimal or mild endometriosis	Increase in ongoing pregnancy and live birth rates	Both studies had methodologic flaws.

LUNA = laparoscopic uterine nerve ablation; RCT = randomized controlled trial.

Information from references:

B1: Proctor ML, Farquhar CM, Sinclair OJ, Johnson NP. Surgical interruption of pelvic nerve pathways for primary and secondary dysmenorrhoea. Cochrane Database Syst Rev 2005;(4):CD001896.

B2: Jacobson TZ, Barlow DH, Garry R, Koninckx P. Laparoscopic surgery for pelvic pain associated with endometriosis. Cochrane Database Syst Rev 2001;(2):CD001300.

B3: Jacobson TZ, Barlow DH, Koninckx PR, Olive D, Farquhar C. Laparoscopic surgery for subfertility associated with endometriosis. Cochrane Database Syst Rev 2002;(4):CD001398.

(Mounsey et al., 2006)

It allows direct visualization of the lesions and histological confirmation (Farquhar, 2007; Bulun, 2009).

Surgical treatment for endometriosis requires considerable experience and expertise on the part of the surgeon, and therefore results are likely to be operator dependent (Winkel, 2000). In addition to differences in skill level and experience of surgeons, the wide variability in the appearance of endometriotic lesions can make them difficult to recognize. For example, subperitoneal, small or microscopic lesions may not be seen during

laparoscopic procedures. Deep lesions (type III) can be particularly difficult to identify and are most likely to occur in patients with mild or minimal endometriosis. These and other factors may provide an explanation for why surgery does not improve pain in some patients.

Regarding the surgical technique, there is debate as to which technique should be chosen, between laparoscopic excision (the so-called 'stripping' technique) on one hand, and fenestration and ablation or coagulation of the cyst wall on the other hand. A recent meta-analysis reports that laparoscopic excision is associated with better outcomes in terms of postoperative pregnancy rates and pain recurrences when compared with the ablation technique (Hart et al., 2005). Some authors (Brosens et al., 1996; Donnez et al., 1996), however, have questioned the stripping technique, since it can be associated with removal of ovarian tissue together with the wall of ovarian endometriomas, with loss of follicles and diminished ovarian reserve. Consistently with this hypothesis, premature ovarian failure in young patients submitted to laparoscopic excision of endometriomas has been reported (Busacca et al., 2006; Di Prospero and Micucci, 2009).

Histology studies have been published, reporting the possibility that a rim of normal appearing ovary is inadvertently removed along with the endometrioma wall, using the stripping technique. In one study (Muzii et al., 2005), different parts of the whole cyst wall were thoroughly examined,

demonstrating that, for most of the surface of the cyst specimen, the ovarian tissue inadvertently removed is thin and with only scanty primordial follicles, or with no follicles at all. Only near the hilus is the ovarian tissue removed thicker and with normal histological features.

Recently, several authors (Muzii and Panici, 2010) have been described a combined surgical technique, with the stripping technique applied for most of the endometrioma wall, and the ablation technique applied on the final part of the procedure, near the hilus: the preliminary data appear promising. In fact, since the excision technique is associated with better results in terms of subsequent fertility and pain recurrence, this technique is performed for most surgical procedures (Fig. 20). When approaching the hilus, where excision has been demonstrated to be maximally dangerous for the ovary, an ablation technique is used, in order to avoid damage to the tissue (Fig. 21).

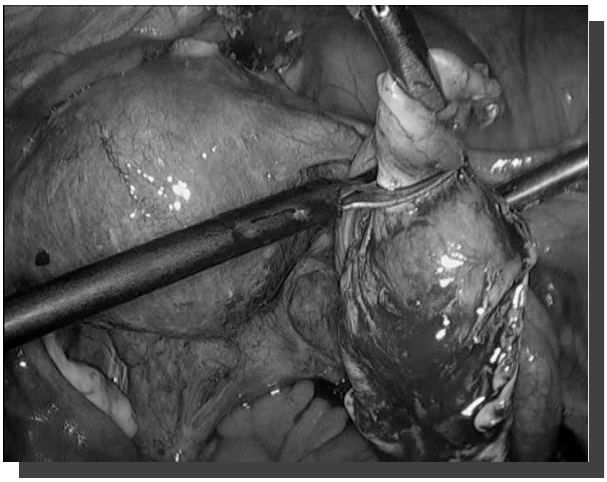
Assessment of the accuracy of laparoscopy for diagnosing endometriosis (De Almeida et al., 2008) has demonstrated that it is highly precise in ruling out the disease, thereby informing therapeutic decisions (Wykes et al., 2004). Recent studies have shown that endometriosis is principally diagnosed by laparoscopy combined with histopathological examination, although a negative result does not rule out the possibility of the disease (Kennedy et al., 2005) (Tab. 13).

Table 2. Laparoscopic and histopathological findings (n = 976)

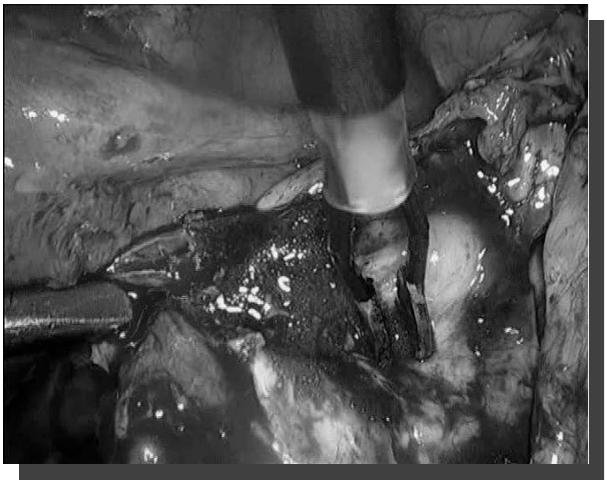
Surgical diagnosis (laparoscopy)	Histopathological confirmation		Total
	Positive	Negative	
Positive	337 (34.52%)	131 (13.42%)	**468 (48.15%)**
Negative	8 (0.81%)	500 (51.22%)	**508 (52.04%)**
Total	**345 (35.34%)**	**631 (64.65%)**	**976 (100%)**

(Wykes et al., 2004)

The results obtained suggest that laparoscopy alone is of limited efficacy. Therefore, it needs to be combined with histopathological examination in order to achieve diagnostic confirmation of endometriosis.



The endometrioma wall is excised with the stripping technique up to the hilus. When the hilus is reached, the stripping technique is stopped, and the excised part of the cyst (above) is cut with cold scissors from the remaining part, that is left on the remaining ovarian parenchyma (below). (Muzii and Panici, 2010)



The remaining part of the endometriotic cyst is exposed for coagulation. Bipolar coagulation forceps are applied to the part of the cyst wall adherent to the ovarian hilus. (Muzii and Panici, 2010)

EXPERIMENTAL SECTION

Endometriosis is a chronic and complex pathological condition that arises from the anomalous presence of implants of functional endometrial glands and stroma outside of the uterus in anatomical sites such as ovaries, tubes, peritoneum, vagina, intestines and ureters (Woodward et al., 2001; Arumgam and Li, 1997; Schenken, 1999). The main clinical characteristics are pelvic pain and infertility (Arumgam and Li, 1997). The condition affects 10% of fertile European women, usually aged between 25 and 29 years, and can have considerable psychological and socioeconomic implications, since it is the cause of 30%–40% of infertility and is characterised by a high rate of recurrence (Eskenazi and Warner, 1997). In general, the radical therapeutic approach is surgical, either laparotomy or laparoscopy (Langerbrekke et al., 2008; Hart et al., 2008; Winkel and Scialli, 2001). Although aggressive surgery is considered the treatment of choice for endometrioma and its recurrence, patients' young age and desire for pregnancy call for a conservative procedure that is adequately supported by pre- and postoperative hormone treatment. This requires finding therapeutic techniques alternative to surgery.

Deferring pregnancy, medical treatment with hormone therapy and ultrasound (US)-guided aspiration of the endometrial cysts have, to date, made up the main alternative treatment options (Winkel and Scialli, 2001;

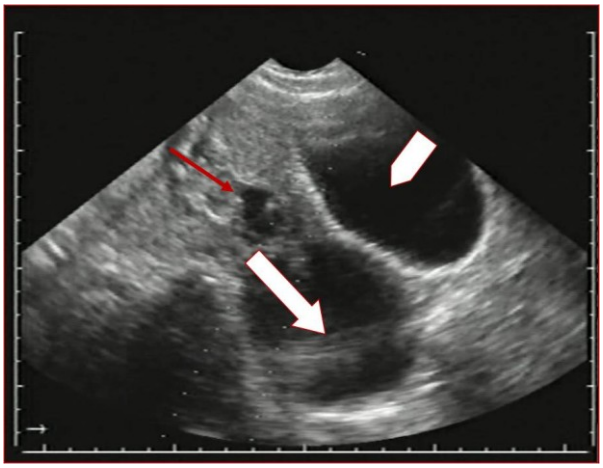
Hsieh et al., 2009; CFPC, 2006; Chapron et al., 2002; Lessey, 2000; Dodson and Haney, 1991). Recent studies have demonstrated the high rate of short- and long-term recurrence associated with these approaches, which runs counter to their noninvasiveness and simplicity (Namnoum et al., 1995). Recently we have demonstrated the efficacy of US-guided sclerotherapy with ethanol following cyst aspiration in the conservative treatment of endometroid cysts, reporting a recurrence rate of about 8% following this technique (Gatta et al., 2010).

Aim of this study is to propose a modified approach to ovarian endometriosis in order to improve the safety of US-guided aspiration and ethanol sclerotherapy decreasing the incidence of recurrence and other complications. This treatment could be improve results of conservative therapy of endometrioid cysts, preserving follicologenesis and so pregnancy attendance in patients with ovarian endometrioma.

Materials and Methods

Between 2008 and 2011, 140 patients with a diagnosis of ovarian endometrial cysts were enrolled and underwent US-guided aspiration and ethanol sclerotherapy of a total of 183 endometriomas. Mean patient age was 26.3 [standard deviation (SD) 6.1; range 16–45) years. Sixty-six patients (47%) had already undergone surgery for other endometrial cysts; twelve (8%) had undergone pelvic surgery for conditions other than endometriosis; nine (6%) were treated during the first trimester of pregnancy. The inclusion criteria were endometrial cysts between 2 and 8 cm, refusal to undergo surgical treatment and contraindications to laparoscopy or laparotomy (adhesions, pregnancy, high anaesthesia risk).

All selected patients (n=140) were randomly included in two different groups (n=70 for each) accordingly to a different interventistic protocol (see below) and underwent aspiration and ethanol sclerotherapy. In total, 183 cysts were aspirated and treated with ethanol sclerotherapy – 70 with the transabdominal approach (virgo intacta, cranially displaced ovaries) and 113 with the transvaginal approach. The treatment of pregnant women has been performed with a trans-abdominal approach in five cases and with transvaginal one in the other four patients. The procedure was carried out in the 10th week of gestation; all the lesion had a size bigger than 6 cm (Fig. 22).



Donna di 29 anni, alla XV settimana di gravidanza: cavità uterina (freccia sottile); vescica (punta di freccia); cisti endometriosica del diametro di 6,5cm (freccia spessa)

We identified, located and characterised all endometrial cysts with a US study done with suprapubic, endovaginal or endorectal insonation (with adequate preparation) in virgo intacta patients, thirteen of whom had already undergone pelvic magnetic resonance (MR) imaging in another centre, which confirmed the US diagnosis of ovarian endometriosis, and who therefore came to our centre for the interventional procedure (Carbognin et al., 2006). The main US features for the characterisation of endometrial cysts are the following:

– hypoanechoic masses with fine, low-level internal echoes located prevalently in the inferior portion;

– hypoechoic masses with diffuse, fine, low-level internal echoes;

– multilocular hypoanechoic masses with internal septations;

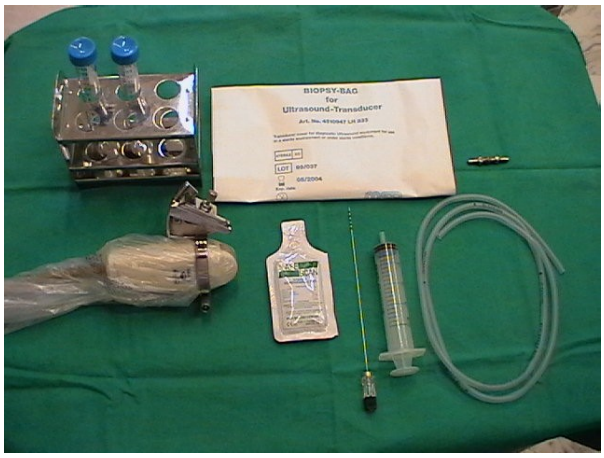
– multilocular hypoechoic masses with internal septations;

– in rare cases, anechoic masses with fine diffuse internal echoes (early-phase endometrioma).

Presumably malignant lesions were excluded with the support of colour Doppler, power Doppler, high-flow or contrast-enhanced US (Guerriero et al., 1996), as well as extemporaneous cytological examination of the cystic aspirate. Two carcinogenic antigens (CA) were assayed (Guerriero et al., 1996): CA 125 and CA 19.9 (the former as a nonspecific marker for endometriosis and the latter to rule out the presence of ovarian malignancy). Moreover, HE4 (a protease inhibitor recently identified as marker for ovarian carcinoma; Li et al., 2009) and the ROMA Index (a more sensitive algorithm for risk of malignancy; Moore et al., 2009) were also evaluated. All patients gave written informed consent and underwent the procedure after consultation with the radiologist. The procedure was performed in the presence of anaesthesiological assistance but without the use of a local anaesthetic: the possible passage of ethanol into the pelvic cavity can cause sharp pain that requires the prompt administration of analgesics, particularly in pregnant women (paracetamol by mouth, intramuscular ketorolac). Patients received antibiotic prophylaxis 24 h prior to the procedure, as well as appropriate bowel preparation. In cases of transabdominal approach, patients received an antibiotic with high urinary concentration and/or a urinary disinfectant. In cases of transvaginal approach, vaginal disinfection was performed with iodine lavage (at the

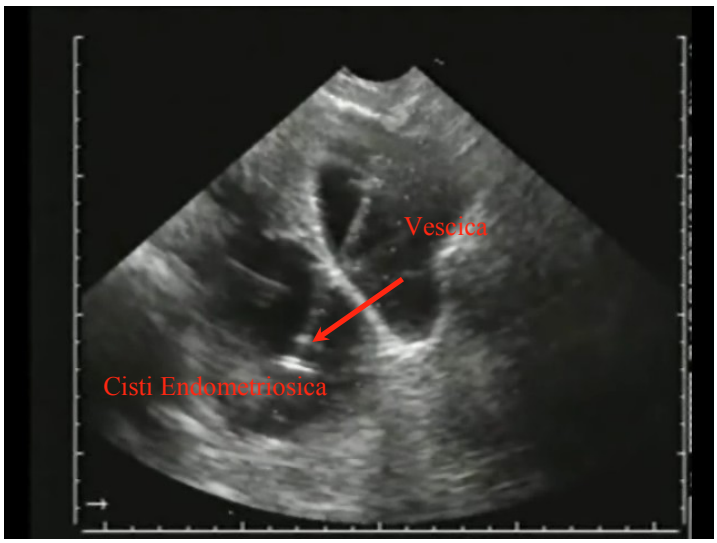
time of the procedure, vaginal disinfection is carried out with iodine swabs).

Prior to the procedure, patients underwent US study with a Toshiba SSA 250A system with 3.75 MHz convex transducers, 6 MHz microconvex transducers and 3,5 MHz sector probe with biopsy needle guides. The following single-use materials required for the procedure were positioned on the service trolley: sterile gel, sterile transducer sheaths, needle-guide attachments and a set comprising tubular connector for syringes with cone-tipped catheter, phial of sterile ethanol, saline solution and 18- to 20-gauge needles with echogenic tip (Fig. 23).



In cases of US-guided transvaginal access, the patient was placed in the gynaecological position, whereas in cases of US-guided or US-assisted transabdominal access, the patient was positioned supine with a full urinary bladder. The cystic mass was reached either by transvaginal or

transabdominal approach – in the latter case with the puncture of the anterior and posterior wall of the bladder (Fig. 24).



Donna di 29 anni, alla XV settimana di gravidanza: punta dell'ago (freccia)

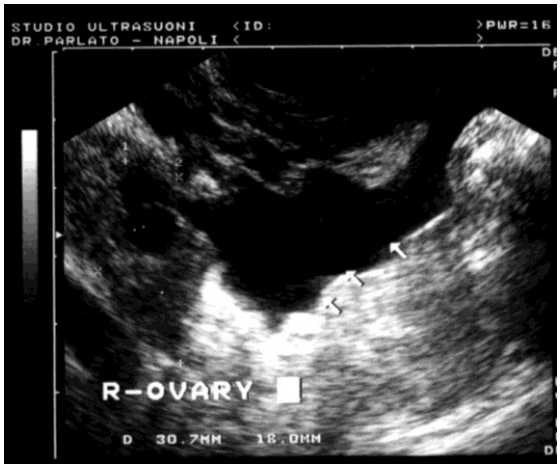
As far as the first group of patients (n=70), the needle was inserted into the mass and the contents aspirated. When dense, the contents needed to be diluted with isotonic lukewarm saline solution and then aspirated. This should be repeated until all the blood material was removed. The ethanol was then injected to completely fill the cyst and left within the cyst for 10 min before being aspirated. Finally, 95% ethanol equivalent to 10% of the total volume of the cyst was injected into the cyst, where it remained.

As far as the interventistic procedure adopted in the second group of patients (n=70), several differences were followed: cystic content was diluted with hypertonic (not isotonic like in the first group) lukewarm saline solution and then aspirated in order to induce a major osmotic stress on the wall of endometriotic cyst. Moreover, in the final step, a solution of 45° pre-warmed ethanol, antibiotic, and 5% polivinilpirrolidone iodio was

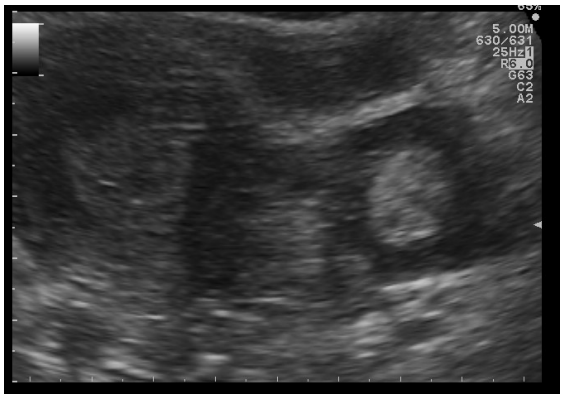
injected into the cyst (not only a 95% ethanol as in the first group), where it remained in order to avoid infective complications following this procedure. US follow-up was performed at 12–24 h to evaluate possible early bleeding and then at 3, 15 days and 3, 6, 12 and 24 months to detect any late complications and/or recurrence and to evaluate the residual ovarian function.

Results

The first US follow-up was performed in both the groups at 12–24 h. There were no signs of bloody effusion, either at the level of the anatomical site treated with sclerotic solution or within the surrounding tissue. In the 3 days following the interventistic procedures, a small amount of effusion in the recto-uterine pouch was found in thirteen women (seven treated with the classical approach and six with the modified one) (Fig. 25).



An intracystic abscess was found in two patients of the first group (Fig. 26).



At 15 days from the procedure, US study showed in both the groups similar findings to the study done at 12–24 h in terms of post-procedure complications, although the appearance and organisation of a finely hypoechoic tissue was appreciable replacing the original endometrial cyst. This hypoechoic finding was compatible with the outcomes of ethanol sclerotherapy. After 3–6 months, US follow-up showed in all patients the absence of local recurrence and disease in the remaining anatomical sites that could be explored with US. The study also showed the disappearance of the intraovarian hypoechoic finding seen at 15 days as the outcome of ethanol sclerotherapy. US follow-up at 12 months showed six cases of recurrence at the site of previous ethanol sclerotherapy in the first group of treatment and none in the second group. In five of the six unsuccessful cases, ethanol sclerotherapy was repeated with the modified approach and success was gained in all cases, showing complete regression of ovarian recurrences at short- and long-term follow-up. Only one case, where the maximum transverse diameter of the cyst was bigger than 10 cm, surgery was preferred. Also the surgical laparoscopic treatment failed with recurrence detected at 12 months of follow-up: this recurrence has been early and successful treated through sclerotherapy and modified approach. At 24 months from aspiration and ethanol sclerotherapy, thirty-two women had become pregnant (fourteen belonged to the first group, and eighteen to

the second one), and they all successfully brought the pregnancy to term (Table 14).

Patients	Age (mean)	N cysts (mean)	Previous Surgery for CE	Pelvic Pain	Pregnancy	Complications following 3 days	Recurrences following 2 years
Scleroterapy by "classic" approach							
70	25.4 (range 16–44)	1.2 (range 1-2)	30	54	14	7 (Douglas Fluid) 2 (intracystic Abscess)	6
Scleroterapy by "modified" approach							
70	27.2 (range 17-45)	1.4 (range 1-2)	36	52	18	6 (Douglas Fluid) 0 (intracystic Abscess)	0

Discussion

Although surgical resection of endometrioma still remains the reference standard, it should be noted that the invasive approach to endometrial cysts is a radical operation that is not without risks associated with the procedure itself, which – given its invasiveness – can damage part of the healthy adnexa containing the oocytes (Langerbrekke et al., 2008; Hart et al., 2008; Winkel and Scialli, 2001). The surgical approach, whether laparoscopic or laparotomic, can induce formation of synechiae, which in turn can cause infertility by obstructing the physiological release of oocytes by the ovaries and limiting the patency of the uterine tubes. Postsurgical adhesions can also be a frequent cause of pelvic pain and can lead to costiveness or intestinal occlusion/subocclusion arising from obstruction of the small bowel loops.

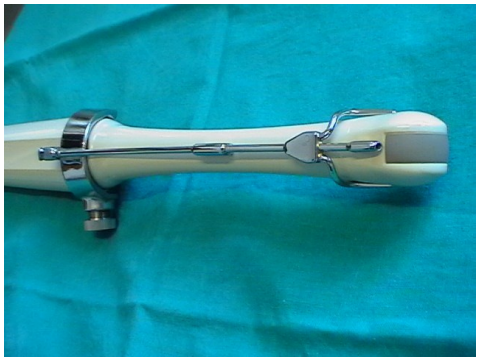
Finally, although it is a minimally invasive surgical technique, laparoscopic treatment that involves stripping endometriotic lesions from the ovary has been associated with a significant risk for premature ovarian failure (POF) (Di Prospero and Micucci, 2009), corresponding to a rate of 2.4%, and to early onset (Busacca et al., 2006) and late onset (Di Prospero and Micucci, 2008) of POF after the treatment.

The literature reports a recurrence rate of endometrial cysts after conservative laparotomy or laparoscopy that varies between 0.5% and 52%, and important studies report a recurrence rate with the need of repeated

surgery in 23% of cases (Langerbrekke et al., 2008; Hart et al., 2008). In addition, the possibility of refusal to undergo surgery by a large number of young patients is neither negligible nor infrequent due to the significant psychological pressure created by the disease, which can of course lead to infertility. Pharmacological treatment that acts on the hormonal front, and percutaneous puncture with aspiration of the endometrial cyst, have over the years shown a high rate of recurrence (around 50%) (Winkel and Scialli, 2001). Moreover, a disadvantage for women desiring pregnancy in the near term is that conception is generally not possible during medical therapy; indeed, many of these agents are also used as effective contraceptives. Finally, the approach with laser and radiofrequency ablation has proved to be excessively aggressive, with damage to the healthy adnexal parenchyma (Winkel and Scialli, 2001; Hsieh et al., 2009; Chapron et al., 2002).

We propose a modified sclerotherapy technique with a solution of 95° pre-warmed ethanol, antibiotic, and 5% polivinilpirrolidone iodio following aspiration of the endometrial cyst contents under US guidance as a valid alternative for treating endometriomas (Hsieh et al., 2009; Messalli et al., 2003). We used two different approaches – trans-abdominal and transvaginal (Patel et al., 1999; Volpi et al., 1995). The trans-abdominal approach is characterised by puncturing the anterior and posterior walls of the urinary bladder under US guidance (US-assisted procedure), which on

the one hand avoids the risk of intestinal perforation, while on the other hand exposes the patient to the risk of both inflammations and infections (Fig. 24). In our study, this approach was preferred in 70 patients with virgo intacta and/or cranially displaced ovaries. To avoid the risk of post-procedural inflammatory processes, all patients underwent antibiotic prophylaxis that was continued in the days following the procedure. In the US-assisted approach (Patel et al., 1999), US scans are done to visualise the correct position of the cystic mass into which a large-diameter needle with an echogenic tip was inserted and through which the cyst contents were aspirated and the ethanol introduced. The correct placement of the needle with respect to the US transducer is fundamental in that only by following the course of the echogenic tip along the entire needle track can the laceration of adjacent vascular and nerve structures be avoided. The transvaginal approach (Volpi et al., 1995; Jan, 1994) involves the use of a dedicated US transducer with a needle guide (US-guided procedure) (Fig. 27), which allows the certainty of visualising the needle throughout the procedure.



The large-diameter needle punctures the vaginal wall to firstly perform aspiration and subsequently sclerotherapy of the endometrioma. This technique can induce slipping of the needle along its course through the vaginal canal, vaginal wall or in the adnexa. A not infrequent complication is ethanol leakage into the vagina with the production of intense burning due to direct contact of the chemical agent with the vaginal mucosa. Lastly, unlike the transabdominal approach, the transvaginal approach is characterised by the possible formation of synechiae, which can obstruct oocyte passage and uterine tube patency.

The aim of needle aspiration is emptying the cyst contents of the endometrioma to prepare it for subsequent ethanol sclerotherapy. Whether US-assisted or US-guided, it is in itself a simple and inexpensive procedure that can be performed as a day-hospital procedure and has virtually no associated significant complications (moderate and transient pain, rapidly reabsorbed haematomas). Only in two cases in our series treated with the classical approach (Group 1) we detected an intracystic abscess (Fig. 26). The patients presented low-grade late-afternoon fever (about 37.5°C) that progressed in the space of a week into fever with early afternoon and late-afternoon peaks (38.0–38.5°), with pain at the treatment site. The diagnosis was performed with an endovaginal US study that demonstrated distension of the treated cystic mass, with low-level internal echoes tending to slight hyperechogenicity. The abscess was promptly aspirated and drained, and

the cavity was lavaged with saline solution at 37°C mixed with an equal proportion of 10% povidone–iodine solution. After repeated washings, a broad-spectrum antibiotic was injected into the cavity. Treatment with 10% ethanol for 10 min is thought to achieve its therapeutic mechanism thanks to ethanol's ability to induce sclerosis of the microvascular structures, thus blocking the onset of neoangiogenesis and preserving the ovarian tissue in its role of folliculogenesis (Noma and Yoshida, 2001). The dilution of cyst content during the aspiration phase with hypertonic lukewarm saline solution contributed to osmotic stress the ectopic endometrial tissue in order to decrease the variable recurrence rate that characterise this procedure. The tool consisting in to remain a solution of 95° pre-warmed ethanol, antibiotic, and 5% polivinilpirrolidone iodio within the ovarian endometrioma has revealed crucial to avoid/limit infective complications following this interventistic procedure. The rate of recurrence in our study obtained with the classical technique (Group 1) was in agreement with findings reported in the international literature also by our group and lower than rates reported for aspiration alone or ethanol sclerotherapy alone (Gatta et al., 2010; Hsieh et al., 2009; Messalli et al., 2003; Giorlandino et al., 1993; Mittal et al., 1999; Chang et al., 1997; Noma and Yoshida, 2001). The results achieved with the modified technique (Group 2) are really promising, especially for the reduced/absent incidence of recurrence and

other complications and mainly for the preserved follicologenesis and pregnancy attendance in patients with ovarian endometrioma.

Conclusions

Despite the efforts of the scientific community to increase the efficacy of the methods used to treat endometriosis, various limitations remain, thus making it difficult to reach a definitive solution. In particular, the rate of recurrence and other complications, and mainly the effects on a possible pregnant status affects and limits any kind of treatment.

Sclerotherapy with 95° ethanol following aspiration of the endometrioma is a valid alternative to surgery. The technique is simple if performed by expert operators and overcomes the main disadvantages and possible complications associated with surgery. It is also more economical than surgery and can produce complete and rapid disease resolution. The possibility of choosing between a transabdominal and a transvaginal approach, between an US-guided and US-assisted approach, allows treatment to be personalised with a low rate of procedure-related complications in the short and long term. Recurrences, which are associated more with the natural history of the disease rather than the interventional procedure used, can be newly treated with the same procedure, thus avoiding – especially in young women – invasive and

aggressive surgery. Moreover, it's now clear that the timing of ethanol instillation (Noma and Yoshida, 2001), the concentration of sclerosing agent and the stage of disease at first diagnosis (Parazzini et al., 2005) may affect the long-term efficacy of this procedure.

Here, we reported a modified technique in which no recurrence neither infective complication was detected in 24 months of follow-up. The results achieved with this protocol are really promising, considered both the reduced/absent incidence of recurrence and other complications, but mainly, the parenchymal preservation and follicologenesis as highlighted by the pregnancy occurred in the patients treated with this technique.

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