Guidelines for diagnosis and treatment of endometriosis

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AUTHORS
These Recommendations have been written by a group of medical professionals (Drafters) identified by SIGO, AOGOI and AGUI Scientific Committees with the organizational support of the Confalonieri-Ragonese Foundation.

RECIPIENTS
These Recommendations are addressed to all professionals who deal with the diagnosis and treatment of the diseases covered by these guidelines.

METHODS
Writing medical Recommendations is a complex activity in terms of methods, and requires advanced technical skills, resources and time that companies usually are not able to provide. These recommendations are based on systematic reviews. Today, however, acquiring the critical skills required to assess the extent to which systematic reviews (or already existing Guidelines/recommendations produced in Italy or in other countries) are sufficiently valid from a scientific point of view to be taken into account for their application in Italy is the priority, and not writing new systematic reviews.

Based on these considerations, the production of these Recommendations included the following operational phases:
• Identification of expert drafters
• Identification of systematic reviews and the most recent guidelines published on the topic
• Formulation of clinical themes used to develop the guidelines
• Definition of recommendations by individual drafters through their response to the identified clinical themes
• Definition of the recommendations grading by the group of expert drafters

Specifically, the Quality Level and the strength of these recommendations were graded and expressed in Roman numerals (I to VI) and in letters (A to E). The Quality Level refers to the likelihood that a certain amount of knowledge derives from studies planned and conducted in such a way as to produce valid information without systematic errors, while the Strength of
Recommendation refers to the likelihood that the practical application of a recommendation will lead to an improvement in the health status of the target population to which the recommendation is addressed. The Level of Quality and Strength of Recommendations were defined according to the criteria suggested by the Methodological Manual of the National Guidelines System (table 1).

### Table 1.
Quality level and Strength of the Recommendations - Grading. From: ISS-PNLG 2002

<table>
<thead>
<tr>
<th>QUALITY LEVEL</th>
<th>DESCRIPTION</th>
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<tbody>
<tr>
<td>I</td>
<td>Evidence obtained from multiple randomised controlled trials and/or systematic reviews of randomised trials</td>
</tr>
<tr>
<td>II</td>
<td>Evidence obtained from a single randomised study of adequate design</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from non-randomised cohort studies with concurrent or historical controls or their meta-analysis</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from retrospective case-control studies or their meta-analyses</td>
</tr>
<tr>
<td>V</td>
<td>Evidence obtained from case studies (&lt;case series&gt;) without a control group</td>
</tr>
<tr>
<td>VI</td>
<td>Evidence based on the opinion of authoritative experts or expert committees as indicated in the guidelines or consensus conferences, or based on the opinions of the members of the working group responsible for these guidelines</td>
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<tr>
<th>STRENGTH OF THE RECOMMENDATION</th>
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<tbody>
<tr>
<td>A</td>
<td>The execution of that particular procedure or diagnostic test is strongly recommended. It indicates a particular recommendation supported by good quality scientific evidence, even if not necessarily type I or II</td>
</tr>
<tr>
<td>B</td>
<td>There are doubts about whether that particular procedure or surgery should always be recommended, but it is believed that its execution should be carefully taken into account</td>
</tr>
<tr>
<td>C</td>
<td>There is substantial uncertainty in favour of or against the recommendation to perform the procedure or surgery</td>
</tr>
<tr>
<td>D</td>
<td>The execution of the procedure is not recommended</td>
</tr>
<tr>
<td>E</td>
<td>The execution of the procedure is strongly discouraged</td>
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To develop these phases, an operational meeting was organised during the SIGO-AOGOI AGUI National Congress, followed by an exchange of material and comments via email. The Recommendations approved by a majority of the Group of Drafters have been revised by the Auditors appointed by the three Scientific Committees.

### BACKGROUND
In recent years, several scientific societies have produced consensus guidelines/documents or recommendations for the treatment of endometriosis. In Italy, guidelines were produced for the treatment of pelvic endometriosis in the late ‘90, using the Delphi’ method by the collaborative Group of Italian Endometriosis Study Group (GISE). Many recommendations/guidelines published are similar to each other and without any special changes over the years, an aspect that indicates the shortage of high-quality and innovative recent studies. However, the therapeutic scenario has in part changed in recent years, also following the introduction of new therapeutic diagnostic methodologies or molecules.

Objective of this document is to provide Italian gynecologists a useful tool in clinical practice, based on updated evidences.

### SECTION 1: OVARIAN ENDOMETRIOSIS

#### 1.1 Diagnosis

**1.1.1 Role of ultrasound**

Transvaginal ultrasound (TV) should be the first diagnostic approach in case of ovarian endometriosis. The diagnostic accuracy of transvaginal ultrasonography for the diagnosis of ovarian endometriosis is very high.

The diagnostic accuracy of transvaginal ultrasonography for the diagnosis of ovarian endometriosis is very high.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of evidence</th>
<th>Strength of recommendation</th>
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</thead>
<tbody>
<tr>
<td>Transvaginal ultrasound (TV) should be the first diagnostic approach in case of (suspected) ovarian endometriosis</td>
<td>V</td>
<td>A</td>
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</tbody>
</table>

**1.1.2 Diagnostic Criteria**

A “typical” endometrioma usually appears at ultrasound as a unilocular or, less frequently, multilocular (with a low number of locules) cyst, with a homogeneous low-level echogenicity (ground glass) of the fluid content and regular walls with poor vascularization [1,2]. Some endometriomas can contain scarcely vascularized internal septa or can present as a fluid-dense cysts with an internal hyperechogenic level and a poor pericystic vascular pattern. Color/power Doppler analysis of endometriotic cysts is useful in the differential diagnosis with other histotypes of adnexal masses [2,3]. Endometriomas with atypical appearance may present hyperechogenic internal content due
to blood clots or fibrin deposits lying adjacent to the cyst wall. Such content will show no vascularisation at Doppler examination.

Ovarian endometriosis is frequently associated with pelvic adhesions and deep infiltrating lesions. The percentage of this association varies from 20 to 80%. When both ovaries present adhesions they may tend to prolapse in the pouch of Douglas and adhere posteriorly to the uterine wall showing the typical so-called “kissing ovaries” ultrasonographic sign, possibly associated with concomitant posterior infiltrating endometriosis (20%) and tubal involvement (90%)\(^4\). A detailed ultrasonographic evaluation of pelvic adhesions, deep pelvic lesions and adenomyosis is of outmost importance in patients with ovarian endometriosis\(^5\).

The sonographic appearance of endometriomas may vary depending on the hormonal status of the patient. Post-menopausal endometriomas more frequently appear as solid or multilocular-solid cysts with anechoic fluid content or with mixed echogenicity fluid content, sometimes mimicking borderline or malignant neoplasia\(^6\).

The ultrasound pattern of endometriomas may transform also during pregnancy. In pregnant patients the typical endometrioma can undergo a decidualization process and appear as a unilocular- or multilocular-solid cyst, due to the presence of internal papillae, with a regular and smooth surface and often vascularized at Power Doppler examination. In these cases, knowledge of the presence of the endometrioma before pregnancy can facilitate a correct diagnosis and minimize the risk of unnecessary surgery\(^7\). Borderline and malignant tumors arising from endometriomas are rare (more often endometrial or clear cell trimas): in these cases they show typical sonographic features of non-benign adnexal pathology such as cysts with vascu larized internal papillar or solid tissue. Patients with an endometrioma that also present associated risk factors (e.s. familiar hystory of malignancy, menopause, infertility, long term persistent cysts) should undergo careful US follow-up with surgical removal and histologic evaluation when suspicious findings arise\(^8\).

1.2 Medical Therapy
The objectives of medical therapy in case of ovarian lesion are:

- treatment of the ovarian lesion before or instead of surgery
- reduction of risk recurrence after surgery
- pain control

### Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of evidence</th>
<th>Strength of recommendation</th>
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<tbody>
<tr>
<td>Color/power Doppler evaluation of endometriosis cysts may be useful in the differential diagnosis with other types of adnexal conditions</td>
<td>V</td>
<td>B</td>
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</tbody>
</table>
1.2.1 Medical therapy vs surgery

The treatment of endometrioma depends mainly by the symptoms and the patient’s desire of pregnancy. Options include waiting, medical or surgical therapy, and assisted reproduction techniques (ART).

Yap and Collaborators (1) in a review of the literature considered the role of medical treatment pre-and post-surgery according to cyst size, pain and infertility. With regard to pre-operative therapy, two studies were included: in both of them there was a difference in the size of the endometrioma of 1-2 cm between the treated vs untreated group, but there was no evidence of a clinical benefit of therapy.

Muzii et al. (2), in a recent meta-analysis on the efficacy of combined oral contraceptives (COC), administered cyclically versus non-cyclically, showed no significant reduction in endometrioma before surgical treatment on post-operative outcome. The efficacy of progestins in ovarian endometriosis has been object of several studies (3-5).

A randomized multicenter study evaluated the efficacy of administration of dienogest in 187 women, with a statistically significant reduction in the size of the cysts (6). In consideration of side effects, therapy with GnRH agonists or with danazol (equally effective) should be considered as second-line treatment (6-9). Medical therapy is symptomatic and not cytoreductive (10, 11).

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<tr>
<th>Recommendation</th>
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<tr>
<td>Medical treatment of ovarian endometrioma (endometrioma) can be considered in case of lesions of limited size, but we have no data that allow us to consider such treatment as effective in the long period</td>
<td>V</td>
<td>B</td>
</tr>
<tr>
<td>Medical treatment with progestins alone (Ia) or with estrogens (Ila) may be considered in patients with pain and awaiting for surgery with the goal of controlling pain but not of improve surgical outcomes</td>
<td>I</td>
<td>A</td>
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1.2.2 Medical therapy to lower the risk of recurrence of ovarian lesion after surgery

The risk of recurrence of the ovarian lesion after surgery is about 10% per year for the first five years (1). In consideration of the impact of surgery on the ovarian function, it is necessary to improve clinical strategies aimed to prevent repeated surgery, especially in young and not searching pregnancy patients (2,3).

Medical therapy after surgery for endometriosis has the objective of reducing the risk of long-term relapses, defined as recurrence of symptomatology or lesion after 12/24 months after surgery. There is some evidence that post-surgical combined oral contraceptive (COC) use lower the risk of recurrences of ovarian endometriosis. In a randomized controlled prospective study women who underwent laparoscopic enucleation of endometrioma were allocated to: no treatment, treatment with low doses monophasic COC for 24 months in cyclic or continuous regimen.
The 2-year recurrence rate was significantly lower in treated patients (cyclic regimen: 14.7%, continuing regimen: 8.2%, no treatment 29%). In cases of recurrence in treated patients with both regimens of administration, size and growth of the lesions were significantly lower than among the untreated patients. There were no significant differences between the continuous and cyclic regimes (4).

The similar efficacy of cyclic and continuous regimen in the prevention of recurrence of ovarian endometriosis is confirmed by another randomized prospective study, which reports, however, more side effects among patients treated with continuous regimen (5).

A controlled randomized study has analyzed the COC’s efficacy in the prevention of relapses with different progestin formulation. The three regimens tested with different progestins (desogestrel, gestodene and dienogest), showed no significant difference (26.5%, 31.8%, 20.5%). The recurrence rate of untreated patients (74.7%) was significantly higher than in any COC treatment group (6). Ota et al. (7) showed in a retrospective cohort study that the recurrence rate is significantly lower in patients with ovarian endometriosis treated with dienogest for five years after surgery, than in untreated patients (69% vs. 4%; OR = 0.09; 95% CI = 0.03 – 0.26; P < 0.0001) In this study anemia occurred in 4% due to metrorrhagia directly after administration, metrorrhagia including spotting was observed in 20% at 1 year and decreases in bone mineral density and depression were observed in 4 and 2.6%, respectively, in the dienogest group: these conditions did not require treatment interruptions.

1.2.3 Medical therapy in the control of pain

In case of pain, medical therapy of patients with ovarian endometriosis is similar to that of patients with superficial or deep endometriosis. In presence of pain symptomatology, progestins alone or, in particular in case of contraceptive needs, in association with estrogen, should be considered as first choice treatment (1).

Controlled randomized studies have compared the use of GnRH agonists vs progestins alone or COC in the treatment of pain associated with endometriosis: a higher frequency of side effects in the GnRH group was reported. Regidor et al. (2) compared Linestrenolo with Leuprorelina: In the Linestrenolo group there was a reduction of dysmenorrhoea in 50% of patients and chronic pelvic pain in 59% of cases after 6 months of treatment, vs 85 and 69%. In the Leuprorelina group respectively. Strowitzki et al. (3) compared the use of dienogest vs monthly Leuprorelina and showed a similar reduction in pain symptomatology in the two groups and greater tolerability of the Dienogest. Guzik et al. (4) compared a COC-based ethinyl estradiol-norestisterone (35 mg/1 mg per day) vs Leuprorelina 11.25 mg every 2 weeks and norestisterone 5 mg day). In both groups a
reduction in pain was observed. Systematic reviews of controlled randomized trials \((5,6)\) concluded that GnRH treatments, COC and progestins are equally effective in the control of pain associated with endometriosis. Studies have shown that dienogest (2 mg/day) is an effective (in comparison with placebo) therapy for the control of pain in patients with endometriosis. Desonorgestrel has shown similar results as GnRH analogues in pelvic pain control and in all other endometriosis-related symptoms. There are no studies comparing desonorgestrel with other progestin or oestrogens formulations as a first-line therapy in the control of pain symptomatology associated with endometriosis.

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<th>Recommendation</th>
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<tr>
<td>Progestins alone or COC are the most efficacious treatments</td>
<td>III</td>
<td>A</td>
</tr>
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</table>

3) Strowitzki T., Marr J., Gerlinger C. et al. Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis; a 24-week, randomized, multicentre, open-label trial. Hum Reprod 2010;25:633-41.

1.2.4 Medical therapy in adolescents
Lacking specific data guidelines for adult women should be considered.
COC (cyclic or continuous use) associated with non-steroidal anti-inflammatory drugs are indicated as first line treatment. If the first-line therapies do not work, taking into account age and side effects, all the therapies available for endometriosis in adults can be used in adolescents as second-line therapies. Clinicians should use GnRH-agonists cautiously, since teenagers may not have reached the maximum bone density \((1)\).

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<th>Recommendation</th>
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<tr>
<td>In adolescents, the treatment of choice are COCs</td>
<td>VI</td>
<td>B</td>
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1.3 Surgical Therapy
1.3.1 Role of surgical therapy in the treatment of endometrioma
Surgical treatment of endometrioma is indicated if symptoms are or become not responder to medical therapy, or the endometrioma increases in volume or is greater than 3 cm in diameter in infertile patients \((1,2)\).

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<th>Recommendation</th>
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<tr>
<td>Surgery should be considered in symptomatic women Or if endometrioma increases in volume or is greater than 3 cm in diameter in infertile patients</td>
<td>VI</td>
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1.3.2 Surgical modalities in the treatment of endometrioma.
Laparoscopy is the gold standard for the treatment...
of endometriosis, due to faster recovery, better post-operative outcome and reduced hospital costs. Ovarian cystectomy compared to laser vaporization or coagulation of the cystic bed, lowers the number of recurrences and is associated with an increase rate of spontaneous pregnancies in the short and long term. Laser vaporization techniques are currently under evaluation in clinical studies with the aim of making the procedure reproducible and safe for the ovarian tissue. A further application of the CO2 Laser involves the combined use of the excisional and the ablative surgery: a large part of the cystic capsule of the endometrioma is stripped followed by vaporization of the remaining part of the capsule. The combined technique respects the vascularization of the ovarian parenchyma, guarantees a greater preservation of the volume and the follicular count, compared to cystectomy. In addition, an increase in the rate of spontaneous pregnancies and a reduction in recurrences have been reported. The damage of ovarian parenchyma is inversely related to the experience of the surgeon. Surgically treated patients showed an increase of 50% of spontaneous pregnancy 1-2 years after surgery. However, it has been shown that the rate of spontaneous ovulation decreases following laparoscopic cystectomy in infertile women with unilateral endometrioma during a natural cycle. Surgical treatment is not recommended in teenagers and young women who are searching pregnancy and are asymptomatic. In view of the reduction of the ovarian reserve and the increased risk of premature ovarian failure, especially in patients with bilateral endometrium, several

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<tbody>
<tr>
<td>Ovarian cystectomy when compared to laser vaporization or coagulation of the cystic bed, lowers the number of recurrences</td>
<td>II</td>
<td>A</td>
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</tbody>
</table>


1.3.3 Effect of surgery on ovarian reserve
Recent studies have shown that the laparoscopic stripping technique is associated with a reduction of the ovarian reserve, as documented by a reduction in the levels of postoperative Antimullerian hormone (AMH). Otherwise it has been suggested that AMH is lowered independently by the type of surgical procedure used. The clinical consequences of surgical impairment are limited in cases of unilateral endometrioma. On the contrary, the damage can become clinically relevant in cases of bilateral endometriomas. in this case a higher frequency of premature ovarian failure has been observed. Surgical treatment is not recommended in teens and young women who are searching pregnancy and are asymptomatic. In view of the reduction of the ovarian reserve and the increased risk of premature ovarian failure, especially in patients with bilateral endometrium, several
cryopreservation techniques are currently available\(^{(5)}\).

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<th>Recommendation</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>No evidences are available on the comparative effect of different surgical techniques on ovarian reserve after surgery</td>
<td>V</td>
<td>A</td>
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</table>


1.4 Approach to the infertile patient

1.4.1 Endometrioma as cause of infertility
Endometrioma may be a cause of infertility. The impact of endometrioma and its surgical treatment have been the subject of a recent meta analysis including 30 retrospectives and 3 randomized studies\(^{(5)}\).
Women with endometrioma admitted to IVF/ICSI have shown a clinical outcome similar to that observed in women without endometrioma, but showed a lower mean number of oocyte retrieved.

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<th>Recommendation</th>
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<tbody>
<tr>
<td>Endometrioma should be always considered in the diagnostic work up of infertility</td>
<td>III</td>
<td>A</td>
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</table>


1.4.2 Surgical treatment before ART
According to the guidelines of the European Society of Human Reproduction and Embryology\(^{(3)}\), the surgical treatment of endometrium > 3 cm in diameter improves fertility better than simple drainage or only coagulation of the cyst. The conservative treatment of the pseudocapsule may be associated with a substantial risk of recurrence\(^{(3)}\). Endometriosis is a recurrent disease, thus the timing of management of the infertile patient should take into account future pregnancies. It is necessary to personalize each treatment taking into account other woman’s characteristics such as age. Moreover, the presence of endometrioma during the IVF/ICSI treatment may be associated with difficulties in the recovery of the oocytes, contamination of the follicular fluid, potential progression of disease, complications in case of pregnancy. Nevertheless, the presence of endometrioma does not represent a contraindication to IVF/ICSI treatment.

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<tr>
<th>Recommendation</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>Surgical treatment should take into account woman’s characteristics such as age</td>
<td>VI</td>
<td>C</td>
</tr>
<tr>
<td>The presence of endometrioma does not represent a contraindication to IVF/ICSI treatment</td>
<td>VI</td>
<td>C</td>
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SECTION 2: PERITONEAL ENDOMETRIOSIS

2.1 Diagnosis

2.1.1 Role of ultrasound and other imaging techniques
Ultrasound is recognized as the most common diagnostic approach and first line imaging technique also for the evaluation of peritoneal endometriosis. MRI is useful when performed by expert operators and should be requested in specific cases that may benefit from further diagnostic investigations, considering it is...

burdened by high costs.

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<th>Recommendation</th>
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<tbody>
<tr>
<td>Ultrasound examination should be the first line diagnostic technique in the diagnosis of peritoneal endometriosis</td>
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<td>A</td>
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</table>

2.1.2 Sonographic Diagnostic Criteria for peritoneal/superficial endometriosis

The presence of peritoneal/superficial endometriotic disease with associated adhesions should always be evaluated in patients with complaints of cyclic/chronic pelvic pain. The US “sliding sign” allows to identify with high accuracy the obliteration of the Douglas pouch due to severe posterior adherences (1), that in turn can be associated with the presence of deep infiltrating endometriosis of the posterior compartment.

This simple maneuver can easily be performed by operators with different levels of expertise and should be routinely carried out when scanning patients with symptoms and a clinical history possibly related to pelvic endometriosis. Moreover, pain complained by patients during ultrasonographic examination in specific anatomic sites can guide in the detection of deep infiltrating lesions.

2.1.3 Sonographic Diagnostic Criteria for tubal endometriosis

Endometriotic tubal involvement is usually superficial, resulting in adhesions that can cause anatomic distortion, functional impairment and ectasia of the tubes. When tubal occlusion occurs typical sonographic signs of hydrosalpinx can be observed: a tubular unilocular mass with thickened walls, incomplete septa and a fluid anechoic content or a dense content (ground glass) similar to endometrioma (haemato-salpinx).

2.1.4 Ultrasound evaluation in case of pelvic endometriosis infiltrating

Sonographic criteria for the diagnosis and mapping of deep pelvic endometriotic lesions were recently published by a consensus of experts (2). A correct diagnosis is crucial for adequate clinical and/or surgical management of patients. Diagnostic accuracy of ultrasound performed by expert operators varies from 70 to 90% depending on the specific anatomic location (2,3). An accurate evaluation of the extension of deep pelvic endometriosis is based on the identification, description and measurement of infiltrating lesions in the anterior, lateral and posterior compartments (4,5).

The typical sonographic features of postero-lateral deep infiltrating endometriotic lesions are the following: solid hypoechic tissue with irregular margins and poor or no vascularization which alters the normal sonographic appearance of the involved anatomical site. Bladder and vaginal nodules can show a slight increase of the vascularisation when compared to typical postero-lateral lesions (5,9).--For deep infiltrating nodules of the anterior, lateral and posterior paracervical areas it is of outmost importance to verify the extension of the lesion and its distance from the intra-pelvic distal tract of the ipsilateral ureter in order to evaluate urinary tract involvement. In case of doubt or difficult ureteral direct visualization, evaluation of pyelectasis can be easily obtained with trans-abdominal ultrasound in order to identify patients requiring urgent surgical approach (5).

The sonographic evaluation of deep pelvic endometriosis requires specific skills and a high level of expertise arising from adequate training and strict cooperation with pelvic surgeons, which are usually achieved in dedicated tertiary centers.

In order to reduce potential diagnostic delay, even less experienced operator should be able to at least suspect pelvic endometriosis and identify the presence of infiltrating lesions, eventually referring affected patients to dedicated sonographic or MRI operators for further and more accurate investigation.


2.2 Medical Therapy

2.2.1 Medical therapy in the prevention and therapy of pain syndrome.

Medical treatment has a role in controlling pain and avoiding the progression of injuries. Studies have shown that medical therapies are effective only during their use and the symptoms often recur after the stop of treatment (1).

In women with rectal-vaginal endometriosis, a review of the literature has shown that the effect of medical treatment in terms of pain reduction is substantial (2). In the presence of pain symptomatology, the use of paracetamol, NSAIDs may be associated to hormonal treatments (3,4).


2.3 Surgical Therapy

2.3.1 The aims of surgical treatment

A conservative approach aimed at restoring normal anatomical conditions with preservation of visceral innervation (nerve sparing techniques) must be the basis of the surgical strategy. Due to the high diagnostic accuracy of imaging techniques, the role of laparoscopy for purely diagnostic purposes is at present extremely limited (1) and histological evidence is not currently needed for treatments planning. The surgical approach should be whenever possible conservative and modulated according to patient’s age and desire of pregnancy. Non-conservative surgical treatment should be considered only in cases of pain refractory to any medical and surgical treatment in perimenopausal patients whit no childbearing desire. When surgery is the treatment of choice, it should be appropriately planned and performed by expert operators in order to avoid unnecessary and potentially damaging repeated procedures.

Indications to surgical treatment for pelvic endometriosis are:

- symptomatic superficial/or infiltrating lesions in patient not responsive or with contraindications to hormonal medical therapy (symptoms and/or disease progression).
• functional organ damage (bowel subocclusion/occlusion, urinary tract impairment with renal function compromission).

There is no reliable data showing superiority of excision compared to the ablation of lesions in the surgical treatment of peritoneal endometriosis (2). However, the excisional technique allows histological diagnosis and removal of deep lesions which, to a simple inspection, could erroneously appear as superficial. For these reasons, it is considered that surgical excision of the endometriosis should be chosen when possible (3). A “patient-centered” approach should represent the cornerstone in the management of patients with endometriosis disease.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of evidence</th>
<th>Strength of recommendation</th>
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<tbody>
<tr>
<td>A conservative approach and nerve sparing must be the basis of the surgical strategy</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>Repeated surgeries should be avoided</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>Excisional technique should be preferred</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>Adequate counsaling about therapeutic surgical options should be always offered to the patient</td>
<td>VI</td>
<td>B</td>
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2.3.2 Surgical technique

Several findings (1) show the superiority of laparoscopy vs laparotomy in the treatment of pelvic endometriosis, provided that the surgical procedure is performed in highly specialized centers for endoscopic pelvic surgery by operators with high level of experience in the treatment of endometriosis (“High volume surgeons”). Preferably procedures should be carried out by surgeons with proven experience in the laparoscopic treatment of extragenital conditions, such as urological or colorectal surgical procedures (“pelvic surgeon”). Otherwise the treatment can be carried out by a multidisciplinary team (gynecologist, general surgeon, urologist), but in any case with proven experience in the treatment of severe pelvic endometriosis.

2.4 Approach to the infertile patient

2.4.1 Superficial and deep endometriosis as a cause of infertility

Deep endometriosis has a marked influence on the outcome of ART (1). Clinical pregnancy rate (CPR) is reduced, being also related mainly to patient’s age, serum value of AMH and presence of adenomyosis (2). A complete evaluation of the couple should always be offered, taking into account not only endometriosis as a cause of infertility, but also of possible concomitant pathologies (e.g. male infertility).

There is still no clear scientific evidence of the association between miscarriage rate and deep endometriosis \(^2\).

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<tr>
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<tbody>
<tr>
<td>There is no indication to surgical treatment to improve fertility</td>
<td>VI</td>
<td>B</td>
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<tr>
<td>In case of surgery, if spontaneous conception does not occur after 6 months, a IVP/ICSI should be recommended</td>
<td>IV</td>
<td>B</td>
</tr>
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SECTION 3: ENDOMETRIOSIS IN ATYPICAL SITES

3.1 Endometriosis of the abdominal wall, inguinal canal, umbilicus
Endometriosis in these locations can be viewed with high frequency linear probes. Endometriosis appears as hypoechoic areas that interrupt the normal sonographic contour of the tissues. These hypoechoic nodules have irregular margins and poor vascularity and are painful to palpation especially during menses. At the umbilical level, endometriosis may show cystic appearance with fluid dense content.

3.2 Endometriosis in other sites
The presence of endometriosis in other sites should be suspected on a clinical basis. Ultrasound examination is often not useful in case of deep abdominal (diaphragm) lesions and is non-diagnostic for thoracic and cranial lesions. The ultrasound examination does not appear to be diagnostic in case of endometriosis involving nervous structures.

3.2.1 Bowel deep endometriosis
The infiltrating endometriosis nodule appears as a hypoechoic, usually oblong thickening of the intestinal muscle. The intestinal walls are generally visualized with TV approach up to the proximal sigma/distal descending colon, in conditions of adequate acoustic window. Intestinal nodules should be measured in the three orthogonal diameters, including the depth of infiltration (anteroposterior diameter). Furthermore, the percentage of circumference involved, the degree of stenosis, the distance of the caudal boundary of the nodule from the margin of the anus can be evaluated \(^1\).

3.2.2 Bladder endometriosis
Ureteral endometriosis may be a consequence of an intrinsic localization of the disease (endometriosis that infiltrates the muscle) or be caused by a peri-ureteral nodule with ureteral involvement. Both the localizations can cause hydrourereteronefrosis. In the evaluation of infiltrating endometriosis of the anterior/lateral/posterior parametrium it is appropriate to verify the relationship of the lesion with the intrapelvic tract of the ipsilateral ureter in order to identify a possible involvement. In case of doubt, pyelectasis should be verified through trans-abdominal route for the identification of patients with functional impairment of the urinary tract.


3.3 Medical terapy

3.3.1 Medical therapy in different location.
In the case of urinary endometriosis and, in particular, in case of symptoms related to bladder endometriosis, there is evidence on the efficacy of progestins (dienogest) \(^1\) or GnRH analogues \(^2\). A prospective study of 500 women who underwent...
surgical treatment for intestinal endometiosis showed a low percentage of recurrence (7.8% in 2-6 years). The percentage of recurrence of disease was lower in women who undergo progestin therapy after surgery (1%) or who had suspended it for a pregnancy (2%). In women who stopped treatment without getting pregnant, the recurrence rate was 20% (3). After surgery the goal of hormonal therapy is to prevent the recurrence of the disease and to prevent and treat the painful symptomatology (4).

Although most of the evidence regarding the role of medical therapy in preventing recurrences after surgery focuses on ovarian endometriosis, hormonal treatment should be considered also in case of deep infiltrating endometriosis. There is no definitive evidence on the superiority of a drug on the prevention of recurrences, but the limitation must be made on the basis of the possibility of long-term adhesion and side effects, taking into account also woman’s preferences.

3.4 Surgical Therapy
3.4.1 Surgical Therapy in different location

Indications to surgery are:
- failure of and/or controindications to medical therapy
- functional organ damage (Bowel subocclusion/occlusion, urinary tract impairment with renal function compromise)

Surgical techniques for the treatment of Bowel endometriosis include excision of the endometriotic infiltrating lesion by nodulectomy (shaving or discoid resection) or by segmental resection.

There are no guidelines to determine in which cases segmental resection should be performed. Instead of conservative techniques, many operators base their choice on the anatomic localization of the disease and clinical symptoms. Whenever possible, nodulectomy should be the procedures of choice (1,2). However, there are some cases in which shaving or discoid resection are not feasible and segmental resection should be performed (3,4): multiple nodules, single nodule with longitudinal diameter greater than 3 cm and/or single nodule with deep infiltration of muscularis layer. In such cases, in fact, nodulectomy techniques could be unsatisfactory in terms of risk of excessive residual disease and an higher rate of complications.

Laparoscopic segmental Bowel resection is a safe and feasible technique with low complication rate when performed by expert operators with proper preoperative indications (4,5). The risk of peri and postoperative complications is greater in the case of low or ultra-low anastomosis compared to the level of the anal verge and in case of simultaneous opening of the vaginal wall. The use of a transient ileum or Colostomy protection is discretionary. Concerning ureteral endometriosis, it is generally accepted that an intrinsic localization of the disease requires ureteral resection with reanastomoses or bladder reimplantation, whereas in the case of extrinsic involvement usually ureterolysis can be feasible (6). Ureteral endometriosis can be silent but even in asymptomatic cases can lead to the loss of renal function (7), so if diagnosed it requires surgical approach. In case of bladder endometriosis the main indications for surgery are pain and urinary symptoms refractory to medical therapy (8).

The standard surgical treatment for bladder endometriosis is segmentary bladder resection. Laparoscopic shaving procedures are feasible only for superficial peritoneal disease. Cystoscopic treatment must be avoided.

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<tbody>
<tr>
<td>Long term hormonal treatment is useful in pain control and disease progression</td>
<td>I</td>
<td>A</td>
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<tr>
<td>Progestins are the first line treatment</td>
<td>I</td>
<td>A</td>
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