


When more is not better: 10 ‘don’ts’ in endometriosis management. An *ETIC** position statement

ETIC Endometriosis Treatment Italian Club[†]

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ABSTRACT: A network of endometriosis experts from 16 Italian academic departments and teaching hospitals distributed all over the country made a critical appraisal of the available evidence and definition of 10 suggestions regarding measures to be de-implemented. Strong suggestions were made only when high-quality evidence was available. The aim was to select 10 low-value medical interventions, characterized by an unfavorable balance between potential benefits, potential harms, and costs, which should be discouraged in women with endometriosis. The following suggestions were agreed by all experts: do not suggest laparoscopy to detect and treat superficial peritoneal endometriosis in infertile women without pelvic pain symptoms; do not recommend controlled ovarian stimulation and IUI in infertile women with endometriosis at any stage; do not remove small ovarian endometriomas (diameter <4 cm) with the sole objective of improving the likelihood of conception in infertile patients scheduled for IVF; do not remove uncomplicated deep endometriotic lesions in asymptomatic women, and also in symptomatic women not seeking conception when medical treatment is effective and well tolerated; do not systematically request second-level diagnostic investigations in women with known or suspected non-subocclusive colorectal endometriosis or with symptoms responding to medical treatment; do not recommend repeated follow-up serum CA-125 (or other currently available biomarkers) measurements in women successfully using medical treatments for uncomplicated endometriosis in the absence of suspicious ovarian cysts; do not leave women undergoing surgery for ovarian endometriomas and not seeking immediate conception without post-operative long-term treatment with estrogen–progestins or progestins; do not perform laparoscopy in adolescent women (<20 years) with moderate–severe dysmenorrhea and clinically suspected early endometriosis without prior attempting to relieve symptoms with estrogen–progestins or progestins; do not prescribe drugs that cannot be used for prolonged periods of time because of safety or cost issues as first-line medical treatment, unless estrogen–progestins or progestins have been proven ineffective, not tolerated, or contraindicated; do not use robotic-assisted laparoscopic surgery for endometriosis outside research settings.

Our proposal is to better address medical and surgical approaches to endometriosis de-implementing low-value interventions, with the aim to prevent unnecessary morbidity, limit psychological distress, and reduce the burden of treatment avoiding medical overuse and allowing a more equitable distribution of healthcare resources.

Key words: endometriosis / low-value interventions / management / Endometriosis Treatment Italian Club / treatment burden

Introduction

Management of endometriosis is often dictated by personal convictions of physicians (and patients) and by local diagnostic–therapeutic paths and expertise (or lack of), rather than by robust evidence derived from adequately designed and conducted pragmatic, randomized, controlled trials (RCT) (Vercellini *et al.*, 2015). When developing the ESHRE guideline, the members of the committee noted that ‘One of the most striking experiences in writing this guideline was the notion that so many key questions could either not be answered or that only

little or low-quality data were available. Indeed, many issues could not be resolved based on the available literature.’ (Dunselman *et al.*, 2014).

As a consequence, diagnostic and treatment modalities for similar clinical conditions vary widely, exposing women with endometriosis to the risk of several potential harms, including those deriving from medical overuse. In fact, the general tendency to ‘do more’ in medicine has not spared the endometriosis field (Vercellini *et al.*, 2018a, 2018c). When managing women with endometriosis, any suggested medical intervention must be based on clear demonstration that the patient

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might benefit from it, and that the potential harms and the costs are proportional to the magnitude of the potential benefit.

For these reasons, the Endometriosis Treatment Italian Club (ETIC) has developed a process to jointly identify those diagnostic and therapeutic measures considered to be supported by low-quality evidence and whose application in women with endometriosis could lead to the following: an unjustified increase in the number of medical and surgical procedures; untoward effects and morbidity; a psychological impact including diagnostic labeling; and a burden of treatment including financial impact on individuals and families (Vercellini *et al.*, 2018a, 2018b).

The objectives of the resulting position paper were 2-fold. The first objective was the selection of a list of 10 low-value medical interventions that, owing to an unfavorable balance between potential benefits, potential harms, and costs, in general should be discouraged. The second objective was to define the uncertainties and potential downstream consequences of the 10 considered measures to be discussed when counseling women, with the objective of allowing them to make the decisions that most suit their priorities and preferences.

Methods

The ETIC network comprises numerous national endometriosis experts from 16 university departments and teaching hospitals distributed all over the country. The list of participating centers and experts is available at the end of this manuscript. All these regional referral centers provide expertise and treatment options in the medical, surgical, and ART areas. One of the aims of the ETIC network is to define and disseminate high-quality diagnostic and therapeutic standards to be adopted in various disease forms (Alabiso *et al.*, 2015 and 2016). In the present case, a steering committee circulated a first round of emails with the objective of defining the final list of medical interventions to be discouraged in women with endometriosis.

A provisional list was drafted and then jointly discussed during a 2-day binging meeting convened in Verona on 28 and 29 October 2016. On that occasion the list was refined, collectively selecting the final 10 priority points to be addressed. Participants were then asked to spontaneously self-propose themselves to be included in 10 sub-groups, each focused on one specific issue, with the objective of undertaking a comprehensive literature search on the assigned topic and of critically assessing the relevant available evidence. In addition to a comprehensive appraisal of the best available evidence, the guidelines of major scientific societies (College of Obstetricians and Gynecologists (ACOG), 2010; Leyland *et al.*, 2010; Practice Committee of the American Society for Reproductive Medicine, 2012, 2014; Dunselman *et al.*, 2014) and recommendations of internationally recognized professional associations (Johnson *et al.*, 2013; National Institute for Health and Care Excellence (NICE), 2017) were consulted to retrieve further information on the selected topics.

Following the conclusion of the literature evaluation phase, the 10 sub-groups of experts were asked to draft a preliminary short report including also a summary description of the quality of the evidence and of the strength of the suggestions. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines were used to define the quality of the evidence regarding each addressed

issue. This system defines four quality categories (high, moderate, low, very low) that are applied to a body of evidence regarding both diagnostic tests and interventions (Schunemann *et al.*, 2008; Balshem *et al.*, 2011). The direction and strength of clinical suggestions have been also classified according to the GRADE guidelines (Andrews *et al.*, 2013a, 2013b), separating them into strong and weak. In the present case, obviously only the 'weak-against' and 'strong-against' definitions were taken into consideration, based on the estimates of effect for undesirable outcomes of interest, confidence in the estimates of effect, estimates of value, and resource use (Andrews *et al.*, 2013a, 2013b). 'Strong' statements were based on high-quality evidence against a specific intervention, whereas 'weak' statements were based on moderate- or low-quality evidence. Unlike the GRADE guidelines, we used the term 'suggestion', instead of 'recommendation', as issuing recommendations implies a pre-planned and registered critical quantitative, and not only qualitative (as here), systematic analysis of the evidence.

The 10 short reports were circulated by emails to all the members of the ETIC network, and then collectively examined during a second 2-day binging meeting that took place in Frascati (Rome) on 31 March and 1 April 2017. The controversial aspects were extensively addressed and a consensus was reached. All the ETIC members eventually agreed without caveat on the modifications to be implemented.

The 10 sub-groups of experts refined their short reports according to the shared conclusions that were agreed during the second joint meeting. The steering committee then further revised the text exclusively with the aim of ensuring a uniform style to the final assembled report. This was sent to all the ETIC members with a third round of emails and then definitively discussed, corrected, and approved during a third joint meeting convened in Catanzaro on 24–25 November 2017. This consensus process was developed with the financial support of a pharmaceutical company (IBSA Institut Biochimique SA, Lugano, Switzerland), which is not currently marketing drugs for the treatment of endometriosis.

Ethical approval

Institutional review board approval was not required for this manuscript, as only published and de-identified data were used to define the list of the considered 10 medical interventions to be discouraged in women with endometriosis.

The 10 'Don'ts' in Endometriosis Management

Do not suggest laparoscopy to detect and treat superficial peritoneal endometriosis in infertile women without pelvic pain symptoms (quality of the evidence, high; strong suggestion)

A first pivotal RCT conducted on infertile patients with stages I and II endometriosis demonstrated a significant improvement in the ongoing pregnancy rate and live birth rate in women who underwent diagnostic laparoscopy and ablation of lesions compared to those who received diagnostic only laparoscopy (Marcoux *et al.*, 1997). However, two

subsequent smaller RCTs failed to confirm these findings (Parazzini, 1999; Gad and Badroui, 2012). Noteworthy, the most recent study (Gad and Badroui, 2012) was presented at the International Federation of Gynecology and Obstetrics in Rome in 2012, but to date has not been published.

The first Cochrane meta-analysis on the issue included the Canadian and the Italian studies (Jacobson *et al.*, 2010), whereas the latest one (Duffy *et al.*, 2014) included the last study but excluded the Italian one (Parazzini, 1999) because women were allowed to use GnRH agonists for a few months after surgery. The combined odds ratio (OR) of ongoing pregnancy or live birth was 1.64 (95% CI, 1.05–2.57) and 1.94 (95% CI, 1.20–3.16) for the first and second meta-analyses, respectively. The number of infertile women that should undergo destruction of superficial peritoneal endometriosis to achieve an additional ongoing pregnancy compared with no treatment was 12 and 8, respectively. Therefore, since the prevalence of minimal or mild endometriosis among women with unexplained infertility is $\leq 50\%$, the number needed to benefit rises to more than 24 or 16, respectively. This compares unfavorably with the efficacy of IVF, whose rate of success is $\sim 25\%$ (corresponding to a number needed to be treated of four) (European IVF-Monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE) *et al.*, 2016).

Accordingly, guidelines issued by major international professional associations do not support routine laparoscopy for women with unexplained infertility (Practice Committee of the American Society for Reproductive Medicine, 2012; Dunselman *et al.*, 2014). This position is also endorsed in the National Institute for Health and Care Excellence (NICE) guideline that actually bases their recommendations on in-depth cost-beneficial analyses (National Institute for Health and Care Excellence (NICE), 2013). Finally, it is worthwhile underlining that this point is also included in the 'Choosing Wisely' initiative list for reproductive medicine (<http://www.choosingwisely.org/societies/american-society-for-reproductive-medicine/>). Conversely, surgery for suspected superficial peritoneal endometriosis can be considered when infertile women complain of moderate–severe pain and prefer to seek a conception without use of ART (Duffy *et al.*, 2014). The decision to offer surgery in women with infertility and pain is not the same as those without pain.

Do not recommend controlled ovarian stimulation and IUI in infertile women with endometriosis at any stage (quality of the evidence, moderate; weak suggestion)

Controlled ovarian stimulation (COS) and IUI to treat infertility associated with endometriosis at any stage should be discouraged for several reasons.

Firstly, IUI as a treatment for infertility is been questioned regardless of the indication. According to the latest NICE guideline (2017), the procedure is not cost-beneficial for the treatment of infertility. It can be considered only for conditions that cannot be defined as proper infertility, such as HIV discordance, semen donation, and sexual disturbances (Royal College of Obstetricians and Gynaecologists, 2013). Secondly, the use of IUI for endometriosis-related infertility is not supported by scientific evidence. The procedure was initially advocated based on low quality studies (Deaton *et al.*, 1990; Fedele

et al., 1992; Nulsen *et al.*, 1993; Omland *et al.*, 1998; Tummon *et al.*, 1997; Werbrouck *et al.*, 2006). To note, in some of these studies, there was no attempt to differentiate women with unexplained infertility and those with endometriosis stages I and II, while, in others, endometriosis was considered together with other causes of infertility, such as mild male factor or ovulatory dysfunctions. Interestingly, a recent comparative non-randomized study failed to show any difference between COS and IUI, and expectant management (Gandhi *et al.*, 2014). Moreover, the results of a systematic review and meta-analysis conducted by Hughes (1997) suggest that IUI effectiveness is halved in women with early endometriosis. Overall, first-cycle chance of pregnancy with IVF is significantly higher than the cumulative pregnancy rate that can be obtained after six IUI cycles (Dmowski *et al.*, 2002). This is somehow not surprising as the procedure lacks a biological rationale; IVF, but not IUI, can be expected to overcome the detrimental effects of a pelvic inflammatory milieu.

Lastly, the risk of endometriosis recurrence appears to be increased by IUI (Van der Houwen *et al.*, 2014) and was reported to be higher than after IVF (D'Hooghe *et al.*, 2006). Robust explanations for this surprising finding are, however, lacking and further evidence is needed (Somigliana *et al.*, 2017).

The use of COS–IUI for endometriosis-associated infertility should not be recommended because, according to the available evidence, the procedure is debatable *per se*, the effect size appears negligible and the procedure may expose women to an increased risk of disease recurrence.

Do not remove small ovarian endometriomas (diameter <4 cm) with the sole objective of improving the likelihood of conception in infertile patients scheduled for IVF (quality of the evidence, high; strong suggestion)

Ovarian endometriosis has been suggested to perturb ovarian responsiveness to hyper-stimulation and to interfere with folliculogenesis (Sanchez *et al.*, 2014). Maneschi *et al.* (1993) firstly hypothesize that endometriomas could impair ovarian function. This seems unquestionable for large cysts (Coccia *et al.*, 2014; Ferrero *et al.*, 2017), but may occur also in the case of small (<4 cm) endometriomas (Benaglia *et al.*, 2009). Interestingly, serum anti-Müllerian hormone (AMH) was shown to be slightly lower in women with ovarian endometriomas, particularly in case of bilateral lesions (Somigliana *et al.*, 2014; Goodman *et al.*, 2016).

On the other hand, after surgery for ovarian endometriotic cysts serum AMH levels are decreased (Raffi *et al.*, 2012; Somigliana *et al.*, 2012), spontaneous ovulation is reduced (Loh *et al.*, 1999; Candiani *et al.*, 2005; Horikawa *et al.*, 2008), and the response to ovarian hyper-stimulation is lowered (Gupta *et al.*, 2006; Somigliana *et al.*, 2011), particularly in case of recurrent ovarian endometriomas (Ferrero *et al.*, 2015). Ovarian responsiveness is crucial for the success of IVF (Polyzos and Sunkara, 2015) and, according to Sugita *et al.* (2013), the decrease in ovarian reserve may not be limited to the immediate post-operative period because of removal of ovarian cortex but may be progressive with time based on different pathogenic mechanisms.

When women with endometriomas were randomized to surgery or expectant management before IVF, a reduced ovarian responsiveness was observed in the former group (Demiroglu *et al.*, 2006). No significant difference emerged in pregnancy rates, but the study was underpowered for this outcome. Larger RCTs are lacking but may be now considered ethically questionable. In fact, according to the results of systematic literature reviews, surgical excision of small endometriomas before IVF is associated with a need for higher amounts of gonadotrophins, lower peripheral estrogens levels, reduced number of follicles, and lower number of oocytes retrieved, but no effect on the chances of pregnancy (Brink Laursen *et al.*, 2017; Tao *et al.*, 2017; Nickkho-Amiry *et al.*, 2018). Excision of small endometriomas before IVF is particularly discouraged in case of repetitive surgery or bilateral cysts. However, surgery remains mandatory in the presence of non-reassuring sonographic findings and can be considered in women with moderate to severe pelvic pain. How to manage women carrying asymptomatic endometriomas >4 cm should be clarified. In fact, for large endometriomas there is a high risk of cyst puncture and rupture during the oocyte retrieval. Evidence on new, more conservative, surgical techniques (that avoid the removal of the cyst wall such as laser vaporization) is still insufficient to draw suggestions (Candiani *et al.*, 2018).

Do not remove uncomplicated deep endometriotic lesions in asymptomatic women, and also in symptomatic women not seeking conception when medical treatment is effective and well tolerated (quality of the evidence, moderate; weak suggestion)

'Endometriosis should not be treated just because it's there' (Thomas, 1993). This is even truer when extirpative surgery is associated with major intra- and post-operative complications and when progression is unlikely. Complications occur in 3–10% of patients undergoing deep endometriosis removal and include (but are not limited to) incidental bowel, bladder, and ureteral injury, neurogenic bowel and bladder dysfunction and, in case of colorectal resection, anastomotic dehiscence, and rectovaginal fistula formation (Vercellini *et al.*, 2009a; Lebovic, 2016). Noteworthy is the fact that deep invasive endometriosis does not progress in more than 9 out of 10 affected women (Fedele *et al.*, 2004). Therefore, removal of uncomplicated (i.e. not causing ureteral or bowel stenosis) deep lesions in women without symptoms, or when symptoms can be effectively handled with medical therapy, appears unjustified, especially when conception is not an issue.

The management of deep endometriosis should be individualized considering clinical presentation, symptom severity, disease extent and location, reproductive desire, patient age, medication side effects, surgical complication rates, risk of recurrence, costs, and patient preference (Lebovic, 2016). We believe that deep endometriosis is rarely asymptomatic but can be treated effectively and safely with hormonal drugs in at least two-thirds of cases (Vercellini *et al.*, 2016, 2017). Maximization of medical treatment use is supported also by the American Society for Reproductive Medicine (Practice Committee of the American Society for Reproductive Medicine, 2014). Surgery is mandatory in case of hydronephrosis and sub-occlusive bowel stenosis (complicated deep endometriosis) and in highly symptomatic

women wishing a natural conception and declining IVF (Dunselman *et al.*, 2014).

Most guidelines recognize the benefits of surgery on deep lesions related pain, but also recommend to treat this subset of patients in tertiary care and referral centers of expertise adopting a multidisciplinary approach including urologists and colorectal surgeons (Leyland *et al.*, 2010; Brown and Farquhar, 2014; Dunselmann *et al.*, 2014). In particular, intestinal and pain complaints improved substantially in most women (71–93%) who underwent colorectal resection for bowel endometriosis (Seracchioli *et al.*, 2007; Wills *et al.*, 2008; De Cicco *et al.*, 2011). However, inappropriate or non-radical surgery may incompletely relieve or even worsen bowel symptoms (Berlanda *et al.*, 2016). Medications used for deep endometriosis are symptomatic, do not cure the disease, and may be associated with untoward effects and adverse events.

The final decision on whether to undertake long-term medical therapy or complex surgery must be shared with the patient after a complete, detailed, and unbiased sharing of information.

Do not systematically request second-level diagnostic investigations in women with known or suspected non-subocclusive colorectal endometriosis or with symptoms responding to medical treatment (quality of the evidence, low; weak suggestion)

Transvaginal sonography (TVS) has been demonstrated to be accurate and reliable in the identification and follow-up of deep endometriosis infiltrating the bowel. According to a systematic review and meta-analysis, the sensitivity and specificity of TVS in detecting rectosigmoid endometriosis were 91% and 98%, respectively (Hudelist *et al.*, 2011). Several authors observed a diagnostic accuracy of TVS similar to that of MRI in the detection of deep bowel endometriosis (Bazot *et al.*, 2007; Exacoustos *et al.*, 2017; Maiorana *et al.*, 2011; Medeiros *et al.*, 2015). Accordingly, MRI should be suggested as a complementary investigation only in selected women with doubtful TVS findings (Exacoustos *et al.* 2014).

Enhanced ultrasonographic techniques, such as rectal water contrast and/or sonovaginography, have also been proposed to improve the accuracy of TVS. However, in a systematic review and meta-analysis, the pooled sensitivity, specificity, positive and negative likelihood ratios of TVS in detecting deep endometriosis infiltrating the rectosigmoid were 91% (95% CI, 85–94%), 97% (95% CI, 95–98%), 33% (95% CI, 19–59%), and 0.10% (95% CI, 0.06–0.16%), respectively, without statistically significant differences between TVS and enhanced TVS (Guerriero *et al.*, 2016). Finally, Savelli *et al.* (2011) compared double-contrast barium enema (DCBE) and TVS for the detection of bowel lesions, and reported a sensitivity of, respectively, 43% versus 91%, a negative predictive value of 6% versus 29%, and an overall accuracy of 45% versus 91%. Furthermore, TVS showed a better agreement with histology than DCBE (Cohen's K, 0.413 versus 0.04).

Considering the demonstrated high overall accuracy, TVS should be considered the first-line imaging technique for the detection and follow-up of non-sub-occlusive bowel endometriosis. (College of Obstetricians and Gynecologists (ACOG) 2010; Leyland *et al.*, 2010; Dunselman *et al.*, 2014; Guerriero *et al.*, 2016). Conversely, in women

with sub-occlusive symptoms, second-line assessments, such as DCBE, multi-detector computerized tomography enema or MRI with rectal contrast, can be proposed to investigate the presence and degree of stenosis of the rectosigmoid junction and sigma. Colonoscopy and rectosigmoidoscopy should be recommended in selected cases for the evaluation of mucosal involvement and for the exclusion of primary intestinal malignancies.

The presence of non-subocclusive endometriotic bowel infiltration does not justify *per se* major intestinal procedures. Therefore, additional invasive and expensive diagnostic tests do not seem justified. The clinician should be guided by a patient's symptoms and, unless a malignant lesion is suspected or a surgical procedure planned, the results of second-level diagnostic investigations would not change the management anyway but would add discomfort and anxiety. This suggestion may only be questioned in context of insufficient expertise with TVS.

Do not recommend repeated follow-up serum CA-125 (or other currently available biomarkers) measurements in women successfully using medical treatments for uncomplicated endometriosis in the absence of suspicious ovarian cysts (quality of the evidence, low; weak suggestion)

According to the ESHRE guideline, clinicians are recommended not to use peripheral biomarkers, including CA-125, in plasma, urine or serum and/or biomarkers in endometrial tissue, menstrual or uterine fluids to diagnose endometriosis (Dunselman *et al.*, 2014). None of the available biomarkers consistently met the criteria for a replacement or triage diagnostic test (Nisenblat *et al.*, 2016) either for detecting pelvic endometriosis or for differentiating ovarian endometrioma from other benign ovarian masses.

The use of CA-125 measurements to monitor the course of endometriosis during medical treatments is sometimes used in clinical practice, but this practice is not supported by robust data. Fedele *et al.* (1988) evaluated the accuracy of serum CA-125 measurements in detecting endometriosis recurrence diagnosed at follow-up laparoscopy and failed to highlight significant benefits. The reliability of a positive (> 35 U/mL) or negative CA-125 test was compared with that of presence/absence of pain symptoms, and of abnormal/normal findings at gynecologic examination. Sensitivity and specificity of serum CA-125 measurements in the diagnosis of endometriosis recurrence were 15% and 100%, respectively. On the other hand, sensitivity and specificity of pain relapse were 71% and 80%, respectively, and those of abnormal physical examination were 82% and 41% (Fedele *et al.*, 1988).

The value of serum CA-125 variations as a modality to monitor the response to medical therapy are controversial, with some studies suggesting a good predictive value for disease progression (Nagamani *et al.*, 1992; Garzetti *et al.*, 1994; Ozaksit *et al.*, 1995) and recurrence (Chen *et al.*, 1998), and others failing to observe useful correlations (Marana *et al.*, 1990; Lanzone *et al.*, 1991; Ozaksit *et al.*, 1995). No data are available on CA-125 monitoring during use of estrogen-progestin pills or progestins.

Therefore, the follow-up of women with uncomplicated disease forms (without bowel stenosis or obstructive uropathy) and without suspicious adnexal masses should be based on history, physical examination, and ultrasonography. The addition of 'routine' serial biomarkers' serum level determinations does not consistently improve endometriosis management, but inevitably increases costs and the overall burden of treatment. Such an approach might theoretically benefit a small minority of patients, but in practice most women would not be helped, and some would be harmed. In fact, the detection of serum CA-125 levels >35 U/mL may generate anxiety and would inevitably trigger a cascade of further testing and investigations and might even result in the performance of needless laparoscopies.

Do not leave women undergoing surgery for ovarian endometriomas and not seeking immediate conception without post-operative long-term treatment with estrogen-progestins or progestins (quality of the evidence, high; strong suggestion)

A cyst recurrence rate of ~10% per year has been reported after surgery for ovarian endometriomas (Chapron *et al.*, 2002; Koga *et al.*, 2006; Liu *et al.*, 2007; Guo, 2009; Koga *et al.*, 2015). Women who underwent repeat surgery were more likely to need assisted conception and reported more irregular menstrual cycles associated with FSH concentrations ≥ 14 UI/ml (Fedele *et al.*, 2006; Gelbaya and Nardo, 2011). Second-line surgery determines cumulative damage to the ovarian reserve and is followed by a reduced likelihood of natural conception (Vercellini *et al.*, 2009c). Therefore, every effort should be put in place to prevent repeat ovarian procedures.

As endometriomas appear to develop from ovarian follicles and corpora lutea (Vercellini *et al.*, 2009b), inhibition of ovulation with oral contraceptives (OCs) or progestins should decrease the risk of cyst recurrence (Seracchioli *et al.*, 2009). Indeed, based on a meta-analysis of comparative studies, the pooled OR of post-operative endometrioma recurrence was 0.12 (95% CI: 0.05–0.29) in long-term OC users compared with never OC users (Vercellini *et al.*, 2013). In RCTs and systematic reviews, no significant differences were detected between cyclic and continuous OC use in terms of cyst recurrence rate (Muzii *et al.*, 2011, 2016; Seracchioli *et al.*, 2009, 2010). As expected, better results were observed with continuous use when the considered outcome was dysmenorrhea (Muzii *et al.*, 2016).

The protective effect of OCs rapidly vanishes after drug withdrawal (Vercellini *et al.*, 2008). Once ovulations re-initiate, women are exposed each month to a low but consistent risk of endometrioma recurrence. Such a risk is justified in women seeking a natural pregnancy, otherwise tertiary prevention is recommended particularly in patients wishing a conception in the future, unless OCs and progestins are contraindicated or not tolerated. The use of OCs for long periods of time after surgery to reduce lesion and pain recurrences is suggested also by international guidelines (Leyland *et al.*, 2010; Dunselman *et al.*, 2014; National Institute for Health and Care Excellence (NICE), 2017).

Do not perform laparoscopy in adolescent women (<20 years) with moderate–severe dysmenorrhea and clinically suspected early endometriosis without prior attempting to relieve symptoms with estrogen–progestins or progestins (quality of the evidence, low; weak suggestion)

Endometriosis is the most common cause of secondary dysmenorrhea in adolescent women (Harel, 2012), and the prevalence of visually confirmed endometriosis in this patient population is over 60% (Janssen *et al.*, 2013). Most adolescent women with endometriosis have early-stage disease, and the most common lesions are small clear or red vesicles and thin pelvic adhesions between the ovaries and the peritoneum (Vercellini *et al.*, 1989; Laufer *et al.*, 2003; Leyland *et al.*, 2010; Brosens *et al.*, 2013). These limited forms cannot be detected at TVS or MRI and can be definitively diagnosed only at laparoscopy.

However, in adolescent women with moderate–severe dysmenorrhea, early endometriosis must always be suspected, independently of direct visualization. Therefore, a non-surgical diagnosis must be pursued and medical treatment started, even when TVS is negative and physical findings are inconclusive. Provided pain symptoms are effectively relieved, a delay in visual diagnosis is not a great concern, given that peritoneal lesions have not been shown to progress in the vast majority of women, and that the hormonal treatments used to alleviate symptoms generally coincide with those used to prevent disease progression or post-operative lesion recurrence (Evers, 2013; Vercellini *et al.*, 2015, 2018b). In addition, no convincing evidence is available supporting the notion that early surgical treatment of limited peritoneal implants modifies the natural history of endometriosis, as well as the outcomes that matter to women, that is, pain, pregnancy, and risk of future surgery (Templeman, 2012; Janssen *et al.*, 2013; Saridogan, 2017).

When endometriosis is suspected in adolescent women, non-steroidal anti-inflammatory drugs and very low-dose OCs should be started without delay (American College of Obstetricians and Gynecologists (ACOG), 2005; Laufer, 2008; Saridogan, 2017; Zannoni *et al.*, 2016), similar to what is generally suggested in adult women (American College of Obstetricians and Gynecologists (ACOG), 2010; Leyland *et al.*, 2010; Dunselman *et al.*, 2014; Practice Committee of the American Society for Reproductive Medicine, 2014; National Institute for Health and Care Excellence (NICE), 2017). A response to OCs further supports the hypothesis of early endometriosis. In such a case, the use of low-dose OCs may be continued indefinitely also with the aim of limiting disease progression (Zannoni *et al.*, 2016). When OCs used cyclically do not relieve dysmenorrhea, they may be used continuously (Harel, 2012; Laufer, 2008; Altshuler and Hillard, 2014). In this case, patients should be informed that OCs must be stopped for 4–7 days if erratic bleeding occurs (tailored cycling). Laparoscopy should be offered to adolescent women not responding to medical therapy (Janssen *et al.*, 2013; Dunselman *et al.*, 2014), or when follow-up pelvic examination and TVS or transrectal sonography suggest endometriosis progression. If laparoscopy is eventually chosen, these young patients must be informed that surgery cannot be expected to provide a definitive cure (Laufer *et al.*, 2003; American College of Obstetricians and Gynecologists (ACOG) 2005; Zannoni *et al.*, 2016).

Do not prescribe drugs that cannot be used for prolonged periods of time because of safety or cost issues as first-line medical treatment, unless estrogen–progestins or progestins have been proven ineffective, not tolerated, or contraindicated (quality of the evidence, high; strong suggestion)

Currently used medical treatments for endometriosis include estrogen–progestins, progestins, and GnRH agonists (Dunselman *et al.*, 2014). Despite the demonstrated efficacy of these drugs in controlling endometriosis-related symptoms, none of them is curative and symptoms usually recur after therapy withdrawal. Most women affected by endometriosis should take medications even for years, discontinuing them only in case they wish to conceive. Consequently, physicians should tailor medical treatment for endometriosis considering patients' preferences and aiming at long-term adherence, thus choosing agents combining good efficacy and good tolerability (Vercellini *et al.*, 2016).

Among the available options, hormonal contraceptives and progestins demonstrated the most favorable safety/efficacy/tolerability/-cost profile (American College of Obstetricians and Gynecologists (ACOG), 2010; Leyland *et al.*, 2010; Dunselman *et al.*, 2014; Practice Committee of the American Society for Reproductive Medicine, 2014; National Institute for Health and Care Excellence (NICE), 2017) and are, therefore, suitable for long-term use. Progestins can be used in women with metabolic or cardiovascular contraindications to estrogen–progestins and limit the risk of post-operative dysmenorrhea recurrence also when released locally via an intrauterine system (Strowitzki *et al.*, 2010; Brown *et al.*, 2012; Petraglia *et al.*, 2012; Abou-Setta *et al.*, 2013).

The metabolic impact and the incidence and type of untoward effects of different progestins should be considered in relation to specific patient characteristics. As an example, progestins with androgenic properties are not suitable for women with acne and seborrhea. The cost of different medications should also be taken into account, as this is a determinant of long-term treatment adherence (Vercellini *et al.*, 2018a, 2018b). Despite their excellent efficacy on pelvic pain symptoms (Brown *et al.*, 2010), GnRH agonists may not be considered as the first-line treatment option. The profound hypo-estrogenism induced by GnRH agonists prevents their use for prolonged periods, particularly in younger women who may not have reached their peak bone density (Bedaiwy *et al.*, 2017). The association of GnRH agonists with hormonal add-back therapy prevents bone loss without decreasing their efficacy (Surrey *et al.*, 2010). However, this approach is associated with even higher costs and an additional therapeutic burden.

According to systematic literature reviews and meta-analyses, as well as recommendations of major international scientific societies, no major differences exist between available medications for endometriosis in terms of efficacy on pain (American College of Obstetricians and Gynecologists (ACOG), 2010; Leyland *et al.*, 2010; Dunselman *et al.*, 2014; Practice Committee of the American Society for Reproductive Medicine, 2014; National Institute for Health and Care Excellence (NICE), 2017). However, the issue deserves further studies (Brown *et al.*, 2010). At present, the safest, better tolerated, and

least expensive pharmacologic solution should be initially chosen to treat endometriosis-related symptoms, stepping up to costlier or less safe medications only in women unresponsive, intolerant, or with contraindications to combined hormonal contraceptives or progestins. This stepped-care approach should be maintained even when GnRH antagonists will soon become available.

Do not use robotic-assisted laparoscopic surgery for endometriosis outside research settings (quality of the evidence, moderate; weak suggestion)

Robotic-assisted surgery (RAS) is one of the latest innovations in the field of minimally invasive surgery. It already has many applications in cardiac, abdominal, and urological surgery, and it has been evaluated also for possible use in gynecological surgery.

Several RCTs have been designed in order to compare robotic-assisted surgery and conventional laparoscopic techniques (or, when feasible, a vaginal approach) in terms of effectiveness and safety in patients with benign or malignant gynecological conditions. According to a Cochrane review (Liu *et al.*, 2014), robotic surgery, despite some advantages (i.e. it enables three-dimensional visualization of the surgical field, reduces or eliminates wrist motions, allows the surgeon to be seated, and shortens the learning curve), was not shown to provide better clinical outcomes compared with conventional laparoscopic surgery. In particular, the risk of conversion to laparotomy and of intraoperative complications was not reduced. RAS seems to be associated with a moderately shorter hospitalization time, but on the other hand, it has longer operating times and it is much more expensive. The additional cost includes not only the cost of the instrument itself, but also maintenance and the need for a specially trained staff. The results of the first RCT comparing RAS and conventional laparoscopy for endometriosis excision (Soto *et al.*, 2017) confirm the findings of previous observational studies (Berlanda *et al.*, 2017). In fact, no significant differences were observed between the two surgical approaches in terms of operative time, complications, and clinical outcomes at 1-year follow-up.

The American College of Obstetricians and Gynaecologists discourages the routine use of RAS for gynecological benign disorders (<https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/Choosing-Wisely>). In particular, no evidence is available supporting the routine use of RAS in patients with endometriosis, and such an approach outside research settings should be avoided. This recommendation is currently robust.

It should not be ruled out that, in case of future cost reduction and an increase in the number of trained personnel, RAS might be implemented in standard practice for particularly challenging and long-lasting procedures. In particular, this may become valid in some particular settings such as those with less laparoscopic expertise. To note, Lim *et al.* (2016) recently reported the rate of conversion was lower with robotic surgery when referring to a general community-based sample of gynecologic surgeons. However, even if the systematic adoption of RAS would possibly benefit surgeons, the magnitude of the effect on patient outcomes would likely remain limited, and the costs unjustified (Vercellini *et al.*, 2018a, 2018b).

Discussion

Medical overuse constitutes one of the main problems of modern medicine (Morgan *et al.*, 2016) and several initiatives have been launched by major medical journals and professional medical associations to counteract this growing and widespread phenomenon (<http://www.choosingwisely.org>; <https://jamanetwork.com/collections/44045/less-is-more>; <https://www.bmj.com/too-much-medicine>). Broadly defined, medical overuse may be considered as a combination of overtesting/overdiagnosis with overtreatment that results in an unfavorable balance between incremental benefits, risk of harms, and cost of healthcare interventions (Moynihan *et al.*, 2012; Colla, 2014). Several downsides are associated with unnecessary, or excessive, or disproportionately expensive medical measures, from both an individual and collective perspective.

Individual people may incur needless harms without net benefits, bear the psychological impact of disease labeling, or carry an avoidable supplementary burden of treatment in addition to the burden of illness (Grady and Redberg 2010; Moynihan *et al.*, 2012; Tran *et al.*, 2015). From a societal point of view, the implementation of diagnostic and therapeutic measures that do not translate into consistent and substantial improvements in health outcomes, is implicitly inequitable toward other patients (Oliver, 2017). Moreover, considering that generally the healthcare resources are finite, adopting unjustifiably expensive technologies displaces resources in other similar patients, with a net decrease in population health (Paulden, 2017).

Several drivers of overmedicalization have been recognized (Grady and Redberg, 2010; Greenberg and Green, 2014). Both patients and physicians may believe that detecting early disease and treating even smaller abnormalities improve outcomes. Although this has not been definitively demonstrated in women with endometriosis, such an approach fits into the more general cultural belief that in medicine more is better. Moreover, it may be simpler to order a test or indicate a surgical procedure rather than take the time to explain why it would be better to avoid those measures. This attitude is facilitated by the glamor of advanced new technology, or when gynecologists have insufficient knowledge or confidence in managing women with endometriosis. This last aspect is frequently linked with defensive medicine, especially considering that underdiagnosis, but not overdiagnosis, is generally legally prosecuted. Finally, medical overuse may be prompted by commercial and professional vested interests, or whenever payment systems incentives reward more tests and treatments. In this regard, the use of diagnostic and therapeutic measures that have been proven beneficial in a high-risk population may be expanded to lower-risk groups in which the potential benefit does not outweigh the risk of harm (Grady and Redberg, 2010). In fact, interventions show safety and effectiveness features that depend on the characteristics of the population to whom it is offered. Extrapolation of the evidence derived from application of medical measures to specific clinical sub-groups is inappropriate and may be encouraged by financial incentives (Elshaug *et al.*, 2013).

The initiative of the ETIC group is specifically aimed at limiting medical overuse in women with known or suspected endometriosis. The 10 measures to be avoided have been selected through the development of a pre-planned methodological approach. Interestingly, all the statements made achieved complete agreement among

participants, without the expression of cautionary detail to be considered when evaluating or interpreting both the definition of the statement or its strength. The present position paper is the expression of a nation-wide network of experts providing high-quality care in all fields of endometriosis management. Therefore, the resulting document is unlikely to be skewed toward a particular management approach. Moreover, each suggestion is based on a critical appraisal of the best available data and the quality of the evidence was graded according to an internationally adopted system. On the other hand, it has to be recognized that a possible limitation of this paper could be the potential influences coming from our country in terms of local costs and availability of different procedures (all participants were Italian). Moreover, the selection of the 10 points was based on expert opinion rather than a robust scientific approach and we cannot exclude that other excluded points could be similarly (or more) important.

The quality of the evidence supporting the considered points was estimated high for four topics, moderate for three, and low for three. The suggestion was considered strong-against for four issues and weak-against for the remaining six. Strong suggestions were made only when high-quality-against evidence (RCTs or systematic reviews with meta-analyses) was available. Although 3 of the 10 suggestions (the fifth, sixth, and eighth) are based on low-quality evidence, all the experts agreed that overtreatment and overdiagnosis is extremely frequent in the respective circumstances, thus a statement was deemed justified despite paucity of data derived from adequately designed studies. Performance of any diagnostic measure should be based on the principle that management changes in relation to the different possible test results. In the best scenario, treatment for the above conditions would unlikely change, thus the reason for ordering uncomfortable and/or costly investigations is unclear. In the worst scenario, needless and potentially harmful procedures would be indicated that might not improve clinical outcomes.

Different diagnostic and therapeutic strategies associated with highly variable management costs can be adopted in women with endometriosis. To maximize the benefit from a given sum of money, or minimize the resources required for a pre-defined benefit, low-value diagnostic and treatment interventions, and those whose effectiveness is comparable with less expensive alternatives, should be recognized based on the available evidence, and de-implemented (Vercellini *et al.*, 2015, 2018a, 2018b). This appears particularly important when considering that the disease may cause symptoms for decades. The present list is certainly not exhaustive and other relevant interventions may have been disregarded. However, we focused on the topics that all the participants judged to be most pertinent. We plan to update, modify, or integrate this position paper as soon as further robust evidence on the considered points accumulates.

Many people equate decreasing the volume of care to rationing. However, rationing implies that the care being withheld is beneficial and is being withdrawn exclusively to save money (Grady and Redberg, 2010). The issue here is completely different and is related to, first, the avoidance of those procedure that have not been demonstrated to be associated with improved outcomes and, second, use of the money saved by de-adopting measures associated with harms or psychological distress to improve the health of the largest possible number of patients. Indeed, several stakeholders may profit from overdiagnosis

and overtreatment of endometriosis. Industry influence, hospital revenues, competing interests, self-referrals, and fee-for-service payment systems, in addition to healthcare providers' insufficient knowledge of economic evaluation, may impact on the financial burden of disease management shouldered by families and health services. According to LeFevre (2013), 'every dollar spent on health care is someone's income stream. In any move to do less, there will be efforts from those who lose income to push back. [...] We should be able to buy more health for the money we spend'.

Affordability also is a determinant of patients' adherence, and some women with endometriosis might forego care when faced with highly expensive treatments (Vercellini *et al.*, 2018a, 2018b). Therapeutic individualism, especially when unsupported by good-quality evidence, carries an implicit risk of overmedicalization and is hardly acceptable, particularly in the context of fixed-budget public health systems designed to provide collective coverage to the many (Oliver, 2017). Resources wasted on unnecessary measures can be much better spent treating those patients with severe or refractory endometriosis forms that need continuous medical assistance.

In addition to prevention of unnecessary medical procedures and limitation of outcome-unrelated costs of disease management, the reduction of the burden of treatment for women with endometriosis is a further objective of the present list of 10 diagnostic and therapeutic interventions to be de-implemented. The burden of treatment has been defined as the challenges associated with everything patients have to do to take care of themselves (Tran *et al.*, 2015). In the case of endometriosis, women have to deal with drug management, self-monitoring, diagnostic measures such as laboratory tests, imaging investigations, and endoscopic examinations, visits to the gynecologist, repeated surgical procedures, lifestyle changes, and administrative tasks to access and co-ordinate care. Hidden costs should also be considered, as the expenses of getting to clinic appointments, taking time off work, and paying for all or some of the treatments may constitute a problem (Mair and May, 2014). The quality of life for women with endometriosis, already worsened owing to the burden of disease, may be further deteriorated by an excessive burden of treatment. Modifying management with the objective of reducing the burden of treatment has the potential to improve outcomes (Spencer-Bonilla *et al.*, 2017). Adopting the ETIC suggestion list might contribute to promoting a minimally-disruptive management of endometriosis.

The evidence in support of several aspects of endometriosis management is suboptimal. In addition to explanatory trials of efficacy, designed mainly for registration purposes with highly selected participants, pragmatic trials of effectiveness conducted on the general population of endometriosis patients in routine practice settings are badly needed to inform women's choices (Haynes, 1999). Moreover, cost-effectiveness studies might facilitate divestment from interventions associated with excessive opportunity costs, where the expected health gains do not exceed the value of the expected health losses (Paulden, 2017). Along this line, more attention should be given to initiatives designed to increase cost-consciousness in endometriosis management, as this could favor a more equitable distribution of healthcare resources among patients with different clinical conditions. Providing high-value care, avoiding medical overuse, and reducing the burden of treatment should be the main goals of

physicians caring for women with endometriosis. In the absence of sufficiently robust data supporting the performance of specific diagnostic and treatment interventions, the priority remains 'first, do no harm'.

Authors' roles

P.V. and E.S.: conception and design of the study, preparation of part of the first draft of the manuscript; all authors: critical appraisal of the evidence, writing of the 10 short reports relative to the 10 topics, critical revision of the article for important intellectual content, and approval of the final version of the manuscript.

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