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Reducing low-value care in endometriosis between limited evidence and unresolved issues: a proposal

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ABSTRACT: Quantification of benefits and harms of medical interventions should be based on high-quality evidence, which is not always the case in the endometriosis field. In many clinical circumstances, healthcare decisions in women with endometriosis are taken based on suboptimal evidence or on evidence of coexistence of benefits and harms that must be balanced. In these conditions, it is important to avoid or reduce the use of low-value care, i.e. interventions with defined harms and uncertain benefits, or whose effectiveness is comparable with less expensive alternatives. In particular, we suggest that: (i) non-surgical diagnosis based on symptoms, physical findings and transvaginal ultrasonography is possible in most women with symptomatic endometriosis. Thus, except in doubtful cases, laparoscopy should be intended for surgical treatment, not for diagnostic purposes: early diagnosis and diagnostic laparoscopy are not synonymous; (ii) future trials on new drugs for endometriosis should address those outcomes that are most important to patients, should be designed as superiority trials and should include a progestin or an estrogen-progestin as a comparator. Moreover, limitation of repetitive surgery for recurrent endometriosis is among the objectives of long-term medical treatment; (iii) indications for surgery should be the result of a balance between demonstrated benefits in terms of fertility enhancement and pain relief, specific risks associated with excision of different types of endometriotic lesions, cost-effectiveness and patient preference after detailed information; (iv) physicians, health professionals and policy makers should discriminate between screening for and diagnosis of endometriosis. Limited peritoneal foci, which are frequently observed also in asymptomatic women, regress or remain stable in about two thirds of cases. Therefore, the theoretical premises for a screening campaign are currently unclear; (v) physicians should develop the ability to effectively communicate quantitative information based on international guidelines and systematic literature reviews. This will assist a woman's understanding of the interaction between the evidence and her priorities, facilitating the transition towards value-based medicine.

Key words: endometriosis / infertility / pelvic pain / patient-centred medicine / low-value care

Introduction

Endometriosis is the presence of endometrial mucosa outside the uterine cavity. It develops during reproductive years mostly, although not exclusively, in the pelvis. According to the most credited hypothesis, viable endometrial fragments, detached from the uterine wall during menstruation, reach the pelvis via transtubal reflux. Most women have retrograde menstruation, but only some develop endometriosis, likely due to abnormalities in the peritoneal immune surveillance system resulting in ineffective clearance of menstrual debris. However, the tubal reflux hypothesis has not been definitively demonstrated, and alternative pathogenic theories have been postulated (Giudice, 2010; Hickey *et al.*, 2014; Vercellini *et al.*, 2014). In particular, the development of some extrapelvic endometriosis foci cannot be explained by retrograde menstruation and intra-abdominal dissemination of viable endometrial cells.

Independently of their origin, ectopic endometrial foci retain responsiveness to ovarian steroids. The repetitive, cyclic release of endometrial cells and molecules directly into the peritoneal cavity may trigger a

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chronic inflammatory response, resulting in scar tissue formation and adhesions between organs. Pelvic pain (e.g. dysmenorrhoea, non-menstrual chronic pelvic pain, deep dyspareunia, dyschezia, dysuria) and infertility, the symptoms most frequently associated with endometriosis, may thus originate from both ectopic inflammation and anatomical distortion (de Ziegler *et al.*, 2010; Giudice, 2010; Vercellini *et al.*, 2014).

In addition to inflammatory and mechanical nociception, other pain mechanisms have been recognized in patients with chronic symptoms, such as peripheral and central sensitization (Stratton and Berkley, 2011). Endometriotic infiltration may injure peripheral pelvic nerves, inducing hyperalgesia, which is the occurrence of excruciating pain when a non-painful stimulus is applied. Moreover, an abnormal modulation of nociceptive input resulting in increased intensity of the neural signal ascending to the cerebral cortex, may also lead to increased pain perception. Psychological and social factors in turn may modulate the final pain experience (Stratton and Berkley, 2011). The complexity of involved mechanisms and their interaction may explain the extreme clinical variability of symptoms in women with similar anatomical conditions.

It is a common clinical tenet that one woman out of 10 develops endometriosis. This estimate is derived from hospital-based studies, whereas population-based studies report estimates between 3 and 5% (Hickey *et al.*, 2014; Vercellini *et al.*, 2014). Indeed, the real population prevalence of either any endometriosis or clinically significant endometriosis is not known, since a laparoscopy would be required in all women to establish a diagnosis.

There are three recognized forms of pelvic endometriosis: superficial peritoneal implants, ovarian cysts (endometriomas) and deep lesions infiltrating the vagina, bowel, bladder and ureters. The rare extrapelvic manifestations are not considered here.

Our aim is to challenge some popular beliefs on endometriosis, and to raise awareness about alternative perspectives on specific controversial topics, including the appropriate application of laparoscopy in the diagnostic process, some unresolved issues regarding medical and surgical treatment, and the potential benefits and harms of screening. Moreover, we aim at introducing also in endometriosis management the concept of value, that is the balance between potential benefits, potential harms and cost of care (Colla, 2014; Korenstein, 2015). Quantification of benefits and harms should be based on high-quality evidence, which is not always the case in the endometriosis field. In many clinical circumstances, healthcare decisions in women with endometriosis are taken based on suboptimal evidence or on evidence of coexistence of benefits and harms that must be balanced. In these conditions, it is important to avoid or reduce the use of low-value care, defined as medical interventions (including tests and procedures) with defined harms and uncertain benefits, or whose effectiveness is comparable with less expensive alternatives. The views here expressed are at times personal and subjective; however, they are the result of extensive literature search and collective evaluation of the best available evidence in the area of endometriosis diagnosis and treatment, with priority given to systematic reviews and randomized, controlled trials.

The quality of the evidence (QoE) regarding each addressed issue has been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines. This system defines four quality categories (high; moderate; low; very low) that are applied to a body of evidence, not to individual studies, regarding both diagnostic tests and interventions (Schünemann *et al.*, 2008; Balshem *et al.*, 2011). Also the direction and strength of clinical suggestions have been classified according to the GRADE guidelines (Andrews *et al.* 2013a,b), separating them into strong and weak (strong-for; weak-for; weak-against; strong-against), taking into consideration estimates of effect for desirable and undesirable outcomes of interest, confidence in the estimates of effect, estimates of value and preferences, and resource use (Andrews *et al.* 2013a,b). Moreover, when interventions are promising, but supported by insufficient evidence and associated with appreciable harms or costs, and when further research (i) could likely reduce uncertainty regarding the effects of the interventions and (ii) is deemed good value for the anticipated costs, the suggestion 'only-in-research' has been indicated (Andrews *et al.* 2013a). At odds with the GRADE guidelines, we decided to use the term 'suggestion', and not 'recommendation', as issuing recommendations implies a pre-planned critical quantitative and qualitative analysis of the evidence by specifically convened societies' committees or large panels of experts with different professional profiles and competences.

Unresolved issues regarding diagnosis: diagnostic delay or diagnostic inexperience?

It is frequently reported that the delay between symptoms onset and final diagnosis of endometriosis is ~7 years (Rogers *et al.*, 2013). It is also maintained that laparoscopy with biopsy of lesions and histologic confirmation comprise the only accurate modality to make the diagnosis of endometriosis (Rogers *et al.*, 2013). However, surgery should not be considered the standard diagnostic modality, and a non-surgical diagnosis should be attempted before embarking on any operative procedure (weak-for suggestion). In fact, in addition to morbidity and costs, systematically performing a laparoscopy as a first-line diagnostic investigation, implies deciding for surgical treatment *a priori* in case lesions are found. This also deprives women of the possibility of choosing their preferred treatment.

Moreover, ovarian endometriomas are easily and reliably detected at transvaginal ultrasonography (Moore *et al.*, 2002) (QoE, moderate). Deep lesions can be diagnosed accurately at rectovaginal physical examination and transvaginal or transrectal ultrasonography (Hudelist *et al.*, 2011) (QoE, moderate). Thus, the only forms that cannot be identified without laparoscopy are peritoneal implants. However, when assessing the cause of dysmenorrhoea and pelvic pain, a presumptive diagnosis of peritoneal endometriosis implants can often be made without direct laparoscopic visualization, provided other causes of pain have been ruled out (Eskenazi *et al.*, 2001; QoE, low). In unclear cases, an empiric diagnostic trial with a gonadotrophin releasing-hormone (GnRH) agonist has been proposed before resorting to laparoscopy (Ling, 1999). However, although symptoms associated with endometriosis usually subside promptly during induced hypo-estrogenism, pain is also generally relieved in most women without endometriosis (The Practice Committee of the American Society for Reproductive Medicine, 2014). Thus, when a GnRH agonist is used as a clinical test, the only useful result is lack of pain relief, as women without endometriosis may not respond to a GnRH agonist, whereas this is highly unlikely for a patient with endometriosis. Thus, non-response to a GnRH agonist reduces the probability of endometriosis being the cause of symptoms (diagnosis of exclusion; Vercellini *et al.*, 2014) (QoE, very low).

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A laparoscopy for diagnostic reasons should be limited to specific situations, such as when a non-invasive approach has not lead to the identification of the cause of pain, when pain is not relieved by low-dose oral contraceptives or progestins, or when medical treatments cannot be used because the woman is trying to conceive (weak-for suggestion). Conceptually, the conviction that establishing a diagnosis in individual patients is limited to the gold standard of laparoscopy should be challenged, and the reported diagnostic delay may not only be due to lack of direct pelvic visualization. Early diagnosis and diagnostic laparoscopy are not synonymous. However, there is currently inadequate evidence demonstrating that a clinical diagnosis (i.e. not including laparoscopy) is effective and without unintended consequences. Therefore, a management approach not including systematic laparoscopy for diagnosis should be evaluated in a formal RCT.

General practitioners and gynaecologists play a fundamental role in the prevention of the diagnostic delay. In this regard, awareness of endometriosis as the most frequent cause of disabling dysmenorrhoea and pelvic pain symptoms should increase in the general medical and gynaecological settings. Once the presumptive diagnosis of endometriosis has been made, and in case initial treatment with oral contraceptives or progestins fails, or when a surgical procedure is deemed opportune, the woman should be referred to a centre of expertise, where she should be enabled to make, together with trained physicians, the final decision on which intervention best satisfies her needs as well as medical priorities.

Unresolved issues regarding medical treatment for endometriosis

Pharmacological treatment does not eradicate endometriosis, but rather suppresses it, thus usually relieving pain albeit temporarily (Vercellini *et al.*, 2011, 2014; QoE, high). Therefore, the objective of medical therapy is not definitive cure, but the achievement of long periods of remission of symptoms; pain relapse at drug discontinuation is expected and cannot be considered a demonstration of inefficacy, although it poses significant management challenges for patients and their healthcare providers.

Most hormonal therapies commonly prescribed to obtain pain relief have approximately the same efficacy (Leyland *et al.*, 2010; The American College of Obstetricians and Gynecologists, 2010; Brown and Farquhar, 2014; Dunselman *et al.*, 2014; The Practice Committee of the American Society for Reproductive Medicine, 2014; QoE, high). As medications may be needed for years or until seeking conception, it is important to take into consideration not only efficacy, but also long-term safety, tolerability and costs (Dunselman *et al.*, 2014) (strong-for suggestion). Progestins and low-dose, monophasic oral contraceptives offer the most favourable drug profile and are cost effective (Vercellini *et al.*, 2011; Dunselman *et al.*, 2014; QoE, moderate). However, medical therapy is not successful or not tolerated in ~20% of patients (Vercellini *et al.*, 2011). Moreover, for women with specific co-morbidities (e.g. migraine headaches with aura, depression), hormonal treatment may not be the best choice (QoE, high). When oral contraceptives and progestins are not effective in relieving pain symptoms or are not tolerated, the patient should be referred ideally to a tertiary care centre in order to select an alternative medical or surgical treatment.

Research on new drugs for endometriosis-related pain has been limited in recent years, and efforts have concentrated mostly on new delivery systems or combinations of existing formulations. Few studies have focused on drug development based on the pathophysiology of pain transmission, or distinct biochemical characteristics of peritoneal endometriosis versus endometrium within the uterus. Thus, hormonal manipulation still constitutes the only realistic modality to suppress disease and the inflammation that contributes to pain and perhaps infertility (QoE, high). Such an approach may be viewed as the result of our limited understanding of endometriosis pathogenesis, and thus information should also be sought by assessing the effects of hypothesis-driven experimental treatments, as this could ultimately lead to major improvements in disease management.

A central issue in the investigation of new drugs or devices for endometriosis is the frequent dichotomy between interventional trial outcomes required for registration, and those that matter to patients. As an example, the Food and Drug Administration requires comparison with placebo and with a GnRH agonist (considered as the standard treatment) despite the fact that women with endometriosis likely have little interest in superiority over a placebo, as they would not take a placebo for their symptoms, and because it has already been repeatedly demonstrated that any drug is better than placebo for pain relief (Vercellini *et al.*, 2011; Brown and Farquhar 2014; QoE, high). In addition, affected women might not care about non-inferiority with a GnRH agonist, because the latter rarely constitutes first choice long-term treatment. Generally, what is likely most relevant to patients is whether, compared with medications in current use, a new drug is more effective for their pain control, is associated with less metabolic effects, is better tolerated, and whether the benefits justify additional costs. Defining patient preferences is essential in new drug development and is currently under-researched, despite regulatory requirements.

Moreover, in a survey on the patterns of publication of interventional clinical trials on endometriosis that were registered at ClinicalTrials.gov (Guo and Evers, 2013), 71 trials were identified, of which 49% were completed and 21% were either stopped or inactive in the past 2 years, whereas the remaining 30% were ongoing. Among the 35 completed trials, 25 (71%) were sponsored by industry, and results were published of only 11 (31%; 5 industry-sponsored, and 6 non-industry-sponsored). Results of trials sponsored by industry were nearly four times less likely to be published compared with non-industry-sponsored trials, despite their having larger sample sizes and more rapid completion compared with the latter, likely due to unfavourable or inconclusive results in terms of safety, efficacy or both (Guo and Evers, 2013). This is disappointing since such information may be of value to the greater community. In fact, knowing that a hypothesis-driven compound is not effective may be as informative as a positive result in terms of understanding the pathogenic mechanisms of the disease and also help guide subsequent therapeutic target design and trials.

Unresolved issues regarding surgical treatment for endometriosis

Endometriomas are by far the most frequent benign ovarian cysts and they are often detected at transvaginal ultrasonography in symptomatic

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and asymptomatic women (Moore *et al.*, 2002). Surgical removal of endometriomas may increase the likelihood of conception in infertile women (Vercellini *et al.*, 2009a; De Ziegler *et al.*, 2010; Brown and Farquhar, 2014; QoE, low), although it can diminish ovarian reserve (Raffi *et al.*, 2012; QoE, moderate). The absence of randomized trials complicates clinical decision-making. Surgery is indicated when endometriomas are large and associated with pain (strong-for suggestion), but what to do with small cysts is debateable (e.g. expectant management or surgery or *in vitro* fertilization) (Leyland *et al.*, 2010; The American College of Obstetricians and Gynecologists, 2010; Dunselman *et al.*, 2014; The Practice Committee of the American Society for Reproductive Medicine, 2014). In women not seeking pregnancy, the use of an oral contraceptive to inhibit growth of the cyst (Harada *et al.*, 2008) should be considered as an option for treatment (weak-for suggestion).

When performed by expert surgeons, extirpation of deep lesions infiltrating the rectum and vagina, combined with colorectal resection, generally relieves pain, but is associated with severe complications in 5–10% of the cases, the most frequent being bladder denervation and rectovaginal fistula formation (Vercellini *et al.*, 2009b; De Cicco *et al.*, 2011) (QoE, low). However, major advantages of surgery over alternative treatments for deep infiltrative disease have not been consistently demonstrated, thereby raising the issue of potentially avoiding these serious complications by choosing other therapies. For example, progestins are effective for pain relief in two thirds of affected patients (Vercellini *et al.*, 2011), and *in vitro* fertilization constitutes a safer and not inferior option in case of infertility (Vercellini *et al.*, 2009a; QoE, low). Thus, extirpative surgery of rectovaginal lesions with rectal resection should be performed when hormonal medications are ineffective or not tolerated (Vercellini *et al.*, 2009b, 2014; weak-for suggestion). Highly symptomatic women who prefer to conceive naturally may also benefit from surgery (Vercellini *et al.*, 2009a; Dunselman *et al.*, 2014; QoE, low). In fact, progestins should not be used here, given their anti-ovulatory effect. Removal of rectovaginal plaques in the absence of severe symptoms warrants further consideration because, without medical therapy, these remain stable in more than 90% of patients (Fedele *et al.*, 2004; QoE, low). Ultimately the decision is between the patient, her partner, and the healthcare team as to which route to pursue.

It is frequently maintained that a single operative laparoscopy could be a better option than taking medications for years. This is based on the assumption that complete excision of endometriotic lesions results in definitive cure. However, post-operative symptom persistence is frequent (Vercellini *et al.*, 2009b) and pain recurs in 40–50% of women (Guo, 2009; QoE, low). Therefore, in many cases the real alternative is not between medical-only and surgical-only treatment, but rather between medical-only treatment and surgery combined with post-operative medical treatment. In fact, according to the results of systematic reviews, post-operative medical treatment is associated with a reduction in risk of symptoms' and lesions' recurrence compared with surgery alone (Seracchioli *et al.*, 2009; Vercellini *et al.*, 2013).

Endometriosis should not be surgically treated just because it is present. The need for surgery is indisputable in cases of ureteral obstruction, bowel stenosis associated with sub-occlusive symptoms, and adnexal mass of doubtful nature (strong-for suggestion). For everything else there are alternatives, although surgery may turn out to be the best choice in several cases, including symptomatic women who do not desire future conceptions, in whom definitive surgery (hysterectomy with or without oophorectomy) may be offered as an alternative to prolonged periods of suppressive medical therapy (Leyland *et al.*, 2010; The American College of Obstetricians and Gynecologists, 2010; Dunselman *et al.*, 2014; The Practice Committee of the American Society for Reproductive Medicine, 2014; weak-for suggestion).

Not all endometriosis forms are equal: early lesions and the potential for overtreatment

A histologic diagnosis of endometriosis is not always synonymous with clinical disease. In particular, the causal association between limited peritoneal lesions and infertility has been questioned (Parazzini, 1999). In order to justify laparoscopy when superficial endometriosis is suspected, the outcome should be improvement of symptoms or relief from infertility as a consequence of physical destruction of peritoneal lesions. However, the results of the only two available randomized, controlled trials on surgical treatment of minimal–mild endometriosis in infertility patients demonstrated limited benefit (Marcoux *et al.*, 1997; Parazzini, 1999) and, based on data pooling, it has been calculated that a laparoscopy should be performed in 25 women to achieve one additional pregnancy (Vercellini *et al.*, 2009a; The American College of Obstetricians and Gynecologists, 2010; QoE, high).

With regard to pain, limited forms of endometriosis generally respond well to hormonal therapy, whereas symptom relief is frequently only partial or temporary after surgery without post-operative medical treatment (Vercellini *et al.*, 2009b; QoE, low). Thus, in the first instance, symptomatic women with a clinical presentation suggestive of endometriosis, but with no evidence of endometriomas or deep infiltrative lesions and who are not seeking immediate conception, might benefit more from a medical approach such as an oral contraceptive or a progestin (Leyland *et al.*, 2010; The American College of Obstetricians and Gynecologists, 2010; Dunselman *et al.*, 2014; The Practice Committee of the American Society for Reproductive Medicine, 2014). Surgery should be limited to women who decline pharmacological treatment, and to those in whom medications are not effective, not tolerated, or contraindicated (weak-for suggestion).

While destruction of early lesions may prevent disease progression, data from laparoscopies repeated 6 months apart in the context of randomized studies, consistently demonstrated that, without treatment, peritoneal implants also regress or remain stable in more than 70% of women (Evers, 2013; Table I; QoE, high). In addition, early endometriosis is a frequent finding even in parous, asymptomatic women, and the reported prevalence in laparoscopic tubal sterilization series published in the last 30 years ranges from 3 to 44% (Kresch *et al.*, 1984; Liu and Hitchcock, 1986; Moen, 1987; Kirshon *et al.*, 1989; Trimbos *et al.*, 1990; Mahmood and Templeton 1991; Moen and Muus, 1991; Rawson, 1991; Sangi-Haghpeykar and Poindexter, 1995; Balasch *et al.*, 1996; Moen and Stokstad, 2002; Barbosa *et al.*, 2009; Table II; QoE, moderate). The high variability of estimates could be related to the retrospective (Sangi-Haghpeykar and Poindexter, 1995) versus prospective (Liu and Hitchcock, 1986; Rawson, 1991; Balasch *et al.*, 1996) study design, surgeons' awareness of the protean presentation of superficial implants, and motivation for active search and reporting of small lesions. In fact, in most cases, minimal and mild forms were observed. It seems unlikely that these incidentally discovered asymptomatic,

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Table I Natural course of endometriosis between first- and second-look laparoscopy in untreated patients.

Source, year	Number of patients	Regression	No change	Progression
Thomas and Cooke, 1987	17	9	0	8
Telimaa *et al.*, 1987	12	1	8	3
Mahmood and Templeton, 1990	11	3	1	7
Overton *et al.*, 1994	15	8	3	4
Sutton *et al.*, 1994	24	7	10	7
Harrison and Barry-Kinsella, 2000	43	27	12	4
Abbott *et al.*, 2004	18	4	6	8
Total	140	59 (42%)	40 (29%)	41 (29%)

Data from published randomized controlled trials.
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Table II Prevalence of pelvic endometriosis at laparoscopy performed in women undergoing tubal sterilization (Literature data, 1984–2009).[a]

Source	Year	Number undergoing tubal sterilization	Number with endometriosis	%	(95% CI)[b]
Barbosa *et al.*	2009	80	13	16	(10–26)
Moen and Stokstad	2002	196	39	20	(15–26)
Balash *et al.*	1996	30	13	43	(25–63)
Sangi-Haghpeykar and Poindexter	1995	3384	126	4	(3–4)
Mahmood and Templeton	1991	598	36	6	(4–8)
Moen and Muus	1991	208	40	19	(14–25)
Rawson	1991	77	34	44	(33–56)
Trimbos *et al.*	1990	200	6	3	(1–6)
Kirshon *et al.*	1989	566	42	7	(5–10)
Moen	1987	108	19	18	(11–26)
Liu and Hitchcock	1986	75	32	43	(31–55)
Kresch *et al.*	1984	50	NR	15	(—)

CI, confidence interval; NR, not reported.
[a]Based on PubMed search (medical subject heading terms, 'endometriosis AND tubal sterilization'; search period, 1984–2014), review of related citations in PubMed, and review of reference lists of retrieved articles. Only articles written in English were considered.
[b]Calculated according to a binomial distribution model and based on figures reported in individual studies.

limited endometriosis forms, will become symptomatic later (Moen and Stokstad, 2002; QoE, low). Interestingly, endometriosis was detected also in 16% of 101 women during the first trimester of pregnancy (Moen and Muus, 1991). In this context, uncertainties arise on the precise clinical significance of early endometriosis. Furthermore, while the gene expression profile of eutopic endometrium in symptomatic women with minimal–mild disease differs from that of normal, asymptomatic women without endometriosis (Tamaresis *et al.*, 2014), whether there are differences in asymptomatic women with minimal–mild disease remains to be determined.

Thus, women with the same histological diagnosis are not necessarily affected by the same clinical entity. Indeed, some investigators suggest considering only the ovarian and deep forms as 'definite disease' (Holt and Weiss, 2000). Including also superficial peritoneal lesions independently of symptoms can greatly inflate the boundaries of endometriosis as a disease (weak-against suggestion).

Diagnosis versus screening: potential harms from overdiagnosis

Endometriosis does not seem to satisfy the characteristics required for organizing a screening campaign, i.e. testing asymptomatic individuals (Somigliana *et al.*, 2010), as discriminating between self-limiting lesions and those that will evolve to overt disease is currently not possible (Evers, 2013; QoE, low). Moreover, no data are available that show that early treatment of the condition prevents progression to the full-blown clinical picture. In addition, there is no consensus on the optimal management of small lesions (Brown and Farquhar, 2014; Dunselman *et al.*, 2014). This means that, at the individual level, some women may benefit from a population screening test, but others would be harmed, whereas for the majority the net balance between benefits and harms

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would be currently not possible to determine (only-in-research suggestion).

Finding a new biomarker to detect early endometriosis is deemed a priority by some investigators (Rogers *et al.*, 2013). Intense research is under way to develop non- or low-invasive diagnostic tests for endometriosis implants in symptomatic women (May *et al.*, 2010). The risk here is that such biomarkers could be misused in women without pain symptoms or to estimate the fertility potential in those who are not even actively trying to conceive (Somigliana *et al.*, 2010). Thus, a test originally developed as a diagnostic tool could be transformed into a screening test, with the inherent risks associated with potential overdiagnosis. In fact, minimal–mild endometriosis in asymptomatic women could become to be viewed as a pre-disease, in case of an increased biomarker, but because the natural history of limited peritoneal implants cannot be predicted in the individual woman, it is currently uncertain if a positive test result would change clinical management when pain symptoms or infertility are not an issue (only-in-research suggestion).

The potential benefits of screening for early asymptomatic endometriosis are unclear, whereas diagnostic labelling is a real harm as the emotional burden of becoming a 'patient' is not without consequences. It might be difficult to convince worried well women that a 'biomarker positive' condition, whose progression is unlikely in the absence of symptoms, is different from active disease that could result in chronic pain and infertility. Moreover, a diagnosis of endometriosis would inevitably imply long-term monitoring, further testing, periodic investigations and possibly unnecessary treatments. In addition to personal inconvenience, in the asymptomatic population this could readily translate into avoidable risks, harms and costs.

In spite of the above considerations, it is difficult to speculate on the benefits or harms associated with the implementation of a minimally invasive diagnostic test until it is available and its characteristics are understood. Whatever the clinical utility of such a test, a definitive minimally invasive test might hypothetically help to address many of the currently unanswered questions, including issues of progression and variability in symptoms and disease presentation for limited endometriosis forms, as well as response to treatments and recurrence of lesions in the setting of symptoms reappearance. However, the condition for investigating a novel biomarker should not be the mere presence of asymptomatic, superficial, peritoneal lesions alone.

Opportunities to improve the value of care for women with endometriosis

The individual and societal costs of endometriosis are high, as the disease is frequent, chronic, recurring and sometimes disabling. It is associated with significant quality of life implications and limitations of fertility (Rogers *et al.*, 2013; Hickey *et al.*, 2014). Endometriosis affects mainly young women aiming at a normal sexual life and reproductive potential. This constitutes a particularly vulnerable group that may be highly motivated to prevent the feared consequences of the disorder in all possible ways. Moreover, the inherent financial incentives in current fee-for-services models adopted in many countries may act as an obstacle towards delivery of high-value care, e.g. when surgeons' financial rewards are procedure-based instead of outcome-based (Schroeder and Frist, 2013).

Physicians should refer to major guidelines on the management of endometriosis (Table III), and try to achieve the optimal diagnostic and treatment standards at the lowest possible risk of harm, personal implications and financial costs. In the calculation of costs, expenses associated with additional visits for pain, issues due to compromised quality of life and, in the case of medical therapy, management of drug side effects, should be considered.

Based on the best available evidence and within the context of international guidelines, we make the following suggestions to increase value and reduce resource misuse:

(i) For the investigation of ovarian cysts of presumed endometriotic nature, in the absence of evidence of superiority, transvaginal ultrasonography should be used, limiting other approaches, e.g. magnetic resonance imaging, to exceptional circumstances (Moore *et al.*, 2002; Hudelist *et al.*, 2011; weak-for suggestion).

(ii) For pelvic pain, with other aetiologies ruled out, low-cost progestins and continuous low-dose monophasic oral contraceptives, with the addition of non-steroidal anti-inflammatory drugs when required, should be preferred to more costly or less safe medical alternatives (Leyland *et al.*, 2010; The American College of Obstetricians and Gynecologists, 2010; Dunselman *et al.*, 2014; strong-for suggestion).

(iii) Cost-effectiveness estimates of any procedure for pain mitigation or fertility enhancement should be part of the overall balance leading to a surgical indication (weak-for suggestion).

(iv) Laparoscopy should be preferred to robotic surgery, which greatly inflates the costs without demonstrated benefit (Steege and Einarsson, 2014; Wright *et al.*, 2014; weak-for suggestion). In general, before introduction into clinical practice, novel surgical techniques should undergo the same kind of rigorous evaluation via randomized, controlled trials as medical therapies.

(v) Prolonged post-operative use of oral contraceptives (or other safe and effective medications that inhibit ovulation, including progestins) should be encouraged, if tolerated, to reduce the high endometrioma recurrence risk (Vercellini *et al.*, 2013) and the moderately increased ovarian cancer risk (Modugno *et al.*, 2004; strong-for suggestion).

(vi) When feasible, medical therapy should be preferred to surgery, also with the objective of limiting serial procedures (The Practice Committee of the American Society for Reproductive Medicine, 2014; Abrao *et al.* 2015; weak-for suggestion).

(vii) In referral centres, multidisciplinary teams (including gynaecologists, reproductive endocrinologists, colorectal, general, and urologic surgeons, pain specialists, radiologists, physical therapists, health-focused psychologists and sexologists) should be created for women with disabling endometriosis-associated symptoms and infertility; this would allow taking into account also the different biologic, psychological and socio-environmental factors that may affect pain experience (Stratton and Berkley, 2011) and infertility management in women with the disease (weak-for suggestion).

Conclusion: towards patient-centred care and value-based medicine in endometriosis

In most clinical presentations of endometriosis there are multiple therapeutic options, and different women may choose differently. Each woman knows what is most important for her, and which level of

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Table III Synthesis of available guidelines for the diagnosis and treatment of pelvic pain associated with endometriosis developed by major international scientific societies.

Source	American College of Obstetricians and Gynaecologists	Society of Obstetricians and Gynaecologists of Canada	European Society for Human Reproduction and Embriology[a]	American Society for Reproductive Medicine
Year	2010	2010	2014	2014
COIs of panel members	Not declared	Not declared	Declared; 9/14 members (64%) with COIs. All costs for guideline development covered by the society	Declared. Only members without COIs included in the panel
Non-surgical diagnosis	TVUS for ovarian cysts and deep infiltrative lesions (technique of choice); MRI only for rectovaginal and bladder endometriosis when TVUS equivocal	TVUS; rectovaginal examination for deep infiltrative lesions; rectal US, colonoscopy, cystoscopy, and MRI in women with bowel or bladder lesions. When H&P or TVUS positive, LPS indicated for therapeutic, not diagnostic, purposes	H&P; TVUS for ovarian cysts and bowel lesions. Additional investigations in selected circumstances	Not clearly defined
Diagnostic laparoscopy	For definitive diagnosis. Biopsy not always mandatory but recommended if visual findings doubtful	Gold standard for diagnosis; biopsy recommended. Not always required before treatment in patients with pelvic pain	Gold standard for diagnosis; biopsy recommended. Not always required before treatment in patients with symptoms and signs suggestive of endometriosis	Recommended before initiating medications associated with important side effects. Biopsy not always mandatory
Empiric medical therapy	Cyclic or continuous OCs. If failure, second-line suppressive medications or diagnostic LPS	Cyclic or continuous OCs. If failure, second-line suppressive medications or LPS for diagnosis and treatment	OCs or progestins after other causes of pelvic pain are excluded. If failure, LPS for definitive diagnosis and treatment	Indicated in women with presumed superficial peritoneal lesions
Recommended first-line medical treatment in women with a diagnosis of endometriosis	OCs and progestins	OCs and progestins	No specific medication indicated	No specific medication indicated
Indication for surgery	Ovarian endometriomas >3 cm if no previous diagnosis of endometriosis	Failure of medical treatment; ovarian endometriomas >3 cm; ovarian cyst of uncertain origin; severe infiltrative disease of bowel, bladder, ureter	All endometriosis forms. Unclear if surgery recommended as first-line treatment or only after failure of medical therapy	'Large' endometriomas or deep lesions that fails to respond to medical treatment
Post-operative medical treatment	Long-term cyclic or continuous OCs or levonorgestrel-releasing intrauterine system	Long-term cyclic or continuous OCs	Long-term OCs or levonorgestrel-releasing intrauterine system	Long-term medical therapy recommended. No specific medication indicated
Definitive surgery	Hysterectomy with conservation of ovaries, if normal, and removal of endometriotic lesions	Bilateral salpingo-oophorectomy $\pm$ hysterectomy and excision of all endometriotic lesions. Alternatively, hysterectomy with ovarian preservation	Hysterectomy with bilateral salpingo-oophorectomy and removal of all endometriotic lesions	Hysterectomy $\pm$ bilateral salpingo-oophorectomy when other therapies have failed

COIs, conflicts of interest; TVUS, transvaginal ultrasonography; MRI, magnetic resonance imaging; US, ultrasonography; H&P, history and physical examination; LPS, laparoscopy; OCs, oral contraceptives.
[a]The Royal College of Obstetricians and Gynaecologists guideline no. 24 (The investigation and management of endometriosis; October 2006) has now been archived as the ESHRE has produced a comprehensive guideline on the same topic (https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg24/; 11 October 2014, date last accessed).

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risk she is willing to accept when faced with diverse treatment strategies. It is the duty of the caring gynaecologists, primary care physicians, reproductive endocrinologists and other healthcare providers, to inform patients in depth, explaining clearly the pros and cons of all therapeutic options, not only those she/he is willing or capable of offering. The effect of any intervention must be described in absolute terms, using crude percentages and defining the benefit as the difference from background figures (e.g. the additional probability of pregnancy expected after surgery or *in vitro* fertilization compared with that expected with natural attempts). Risk of complications or severe side effects must be presented and accurately quantified and not downplayed or dismissed, so patients can truly make informed decisions.

The patient's perspective is essential in the determination of the overall value of any intervention for endometriosis. Especially when there is no clear disproportion in the potential benefits and harms ratio, a shared decision should be achieved based on the woman's appreciation of the interaction between the available evidence and her personal priorities (Korenstein, 2015). This process may be a challenge (LeFevre, 2013; Colla, 2014), also because patients' overestimation of benefits and underestimation of harms is difficult to prevent in medicine more broadly (Korenstein, 2015). For this reason, physicians should develop the ability to effectively communicate quantitative information based on international guidelines and systematic literature reviews (Colla, 2014), and, preferably, not based on single studies or solely personal experience. In this context, increasing awareness about endometriosis and its alternative treatments among women and healthcare providers is important in delivering truly value-based medicine.

Women deserve to be informed about the many uncertainties regarding several aspects of endometriosis management, so they can make a fully informed decision. The panel members who developed the ESHRE guideline concluded 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). This further emphasizes the importance of a common culture change to promote high-value interventions tailored to the specific needs of the individual with full engagement of patients in the decision-making process.

There is an obvious need for more high-quality evidence in almost all aspects of endometriosis, including pathogenesis, non-surgical diagnosis (Johnson *et al.*, 2013) and 'minimally disruptive' chronic disease management (May *et al.*, 2009). Only the conjoint research efforts of our scientific and affected communities can shed light on unresolved issues and address the still many unanswered aetiological and clinical questions. An adequate methodological approach could also possibly prevent or limit the harms of overtreatment, which must be clearly distinguished from good clinical and experimental practices.

Authors' roles

P.V. conceived the idea for this article and wrote the first draft, and all authors worked collaboratively to contribute to the content of the paper and to revise it critically. All authors approved the final manuscript.

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Conflict of interest

P.V. and J.L.H.E. are past presidents of the World Endometriosis Society. L.G. received research grants from the National Institutes of Health to conduct research on endometriosis diagnosis and pathophysiology; is president of the World Endometriosis Society and board member of the World Endometriosis Research Foundation; holds stock in Merck and Pfizer; has a patent issued, and a patent pending, on the diagnosis of endometriosis by endometrial biopsy. M.S.A. was the president of the 12th World Congress on Endometriosis and is a member of the advisory board of AbbVie and Bayer.

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