MANAGEMENT OF ENDOMETRIOSIS:

TOWARD VALUE-BASED, COST-EFFECTIVE, AFFORDABLE CARE

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ABSTRACT

Endometriosis management seems influenced by outcome-independent biomedical, pharmacological, and technological developments. The propensity towards doing more affects several aspects of care, sometimes translating into proposals not based on sound epidemiological principles and robust evidence. Different stakeholders share the interest for doing more testing and using novel and costly drugs or devices in patients with endometriosis. Although some women may benefit from such an approach, the majority would not, and some may be harmed. Moreover, an uncontrolled increase in expenditure for endometriosis management without demonstrated and proportional health benefits, would waste the finite resources of national health care services, and would risk cost-related non-adherence. Cost-effectiveness analyses should be systematically pre-planned in future trials on endometriosis, and the concept of "value" of medical interventions should guide investigators and health care policy makers. Reducing low-value care, *financial toxicity,* and the burden of treatment, appears respectful not only of endometriosis patients, but of the entire society. Whenever possible, long-term therapeutic strategies should be tailored on each woman' needs, and high-value tests and treatments should be chosen based on her priorities and preferences. Moreover, listening to patients, understanding their concerns, avoiding disease labelling, explaining plainly what is known and what is unknown, and giving constant reassurance and encouragement, may reveal exceedingly important for a successful management of endometriosis, and may change the patient's perception of her clinical condition. Physician empathy has no untoward effects, does not cause harms, and may determine whether a woman successfully copes or desperately struggles with her disease during reproductive life.

KEYWORDS: endometriosis; medical treatment; surgery, value of care, comparative cost-effectiveness research, burden of treatment.

INTRODUCTION. TOWARD AFFORDABLE ENDOMETRIOSIS CARE

Searching PubMed for "endometriosis AND review", identifies a total of 1219 such articles published in the last 5 years (accessed 29 May 2017). The available reviews cover all the aspects related to the condition, from epidemiology to pathogenesis and management. Most reviews are narrative, but many are systematic and several include meta-analyses.[1] Some reviews are methodologically adequate, very well written, updated, informative and balanced, and could be of great benefit for patients, physicians, and medical decision-makers when choosing among different therapeutic alternatives, writing guidelines, and defining health care policies.

Thus, we did not perform another comprehensive overview of the published data regarding diagnosis and treatment of endometriosis. Instead, here we have tried to offer a critical analysis of still open issues encountered in everyday practice, evaluating available data also from the perspective of health care systems and policy makers in addition to that of the individual patient-physician dyad. We believe that, especially in a period of global shrinkage of health care resources, also the endometriosis scientific community should begin to systematically consider the cost-effectiveness of tests and treatments, as the economic burden of any therapeutic choice may impact on the welfare of individual families and national health systems.[2]

The effectiveness of any strategy for long-term treatments of chronic disorders is based primarily on its affordability. Affordability of new medicines has been described also in terms of "value" of a product within the context of health care system budgets. The value of a medical intervention has been defined as the health outcomes achieved per dollar spent, or the balance between potential benefits, potential harms, and costs.[3] The implementation of the

concept of value of medical interventions has been suggested also in endometriosis management.[4]

Restrictions on the use of efficacious therapies can result from affordability concerns.[5] The cost of healthcare may act as a barrier for people with different chronic conditions who eventually forgo care because of out-of-pocket expenditure.[6,7] Approximately one-third of Canadians' prescription medical costs are paid directly out-of-pocket,[8] and about 1 in 10-12 Canadians who receive a prescription report cost-related non-adherence.[9] According to a recent cross-sectional study assessing the effects of costs on access to medicines in 11 developed countries offering different levels of prescription drug coverage for their populations, Canada had the second highest national prevalence of cost-related non-adherence.[10]

Thus, reducing low-value care and *financial toxicity* also in endometriosis, appears respectful not only of patients, but of the entire society. Providing the best possible care, at the same time limiting harms and costs, protects women and preserves precious resources for all patients and for the medical community at large.

Along this line, the advent and spread of intellectual pivotal movements such as the "*Choosing wisely*" initiative,[11-13] is shifting the attention from technical innovation to value of health care and sustainability. Similar campaigns have been undertaken also by general medical journals (e.g., "*Less is More"*, JAMA Internal Medicine; "*Too Much Medicine*", BMJ; "*Choosing Wisely Canada*", CMAJ), with the objective of limiting over-medicalization, with its inherent potential harms to patients in the absence of demonstrated improvements in outcomes. A series of international conferences are dedicated to this aspect of medicine.[14]

Health care systems are striving to evolve from an unsustainably expensive fee-for-service, high-volume care regulatory environment, that encourages wasteful use of high-cost

tests and procedures, to an evidence-based, high-value care model.[15] The endometriosis scientific community should not escape this common effort.[4]

The attitude toward careful selection of tests and treatments in women with endometriosis should not be viewed as a mere attempt at curtailing expenditures, but as a challenge aimed at investing resources in those medical interventions that have been demonstrated to be of sufficient benefit to patients to justify the associated risks and costs. Avoiding excessive emphasis on the purported absolute effects of some measures may also prevent harms. Gynecologists caring for women with endometriosis should assess treatments not only in terms of efficacy, that is whether an intervention works within the context of a formal trial conducted on selected participants, but also in terms of effectiveness, that is whether an intervention works in the entire population of women with endometriosis in everyday practice.[16,17]

Therefore, the objective of the present review is to approach endometriosis management highlighting measures that, based on the best available evidence, may be considered of low value, and suggesting alternative measures that could improve the quality of health care. A focus is provided on the extremes of reproductive life, adolescence and peri-menopause.

THE POTENTIAL INFLUENCE OF CONFLICTS OF INTEREST ON CLINICAL EDUCATIONAL ARTICLES, GUIDELINES, AND ENDOMETRIOSIS MANAGEMENT

The problem of conflicts of interest (COIs) is a heated debate in medicine, also because it may have an impact on prescribing patterns and health care expenditures.[18-20] The Journal of the American Medical Association dedicated the entire May 2, 2017 issue to a series of articles dealing solely with COIs.[21] The time has come to address this topic also when

appraising the available evidence on endometriosis management, as it has been done with general gynecology[22] and reproductive medicine.[23-25]

Several definitions of COIs have been suggested. According to Bekelman *et al*.,[26] "COI is a set of conditions in which a professional judgement concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)". Of relevance here, a COI is a condition, not necessarily a behavior. Financial COIs are common, and there is nothing wrong *a priori* with having COIs. Moreover, non-financial COIs also exist that may influence selection, synthesis, and interpretation of published data to at least the same extent than financial COIs. As an example, strong convictions regarding specific pathogenic theories or treatment modalities may well influence the information disseminated in narrative reviews and opinion papers.[24] As an example, if an investigator is persuaded that ovulation is crucial in the development of ovarian endometriomas, she/he is at risk of favoring the long-term use of oral contraceptives (OCs), consciously or unconsciously highlighting the evidence in support of the above hypothesis and dismissing the evidence contrary to it. The same is true for advocates of medical versus surgical treatment for pelvic pain, or of surgery versus IVF for infertility.

With regards to non-financial COIs, it has recently been suggested that speakers (and, by extension, also authors) should disclose whether they have a limited range of knowledge or only specific abilities in a particular field or topic, so that their expertise is restricted to a single treatment approach.[27] Pellicer and Zupi maintain that "*it can hardly be justified to hear about the lack of efficacy or suitability of surgical treatments from gynecologists who do not practice surgery on a regular basis*".[27] However, along this line, speakers and authors should also disclose whether they work in a public or private setting. Working part- or full-time in an environment based on a fee-for-service payment system may well be a condition influencing

individual investigators' positions regarding the need for costly diagnostic testing, or surgical procedures, or ART.

The aim of clinical educational articles, including literature reviews, is guiding patient care and conveying authors' own interpretation of selected data.[28] According to Schroter *et al.*,[28] "*author biases in educational articles tend to be less visible to readers compared to those in research papers*". Indeed, some medical journals are already accepting editorials, clinical reviews, and diagnostic and therapeutic series written exclusively by authors without financial ties to industry.[29] According to Chew *et al*.,[29] an author of a review article should not be an advisory board member for companies selling drugs for that condition, nor should she/he have received honoraria from industry for lectures on the topic.

The economic impact of industry seems pervasive also in the endometriosis field, and management is likely influenced by COIs of key opinion leaders. Industry supports conferences and CME activities, thus indirectly contributing to the financial welfare of committed professional associations.[25,30,31] It is unfortunate that annual financial statements of major international scientific societies focused on endometriosis are not available online and that quantitative information on industry sponsorship of periodic meetings is not printed in congress brochures nor indicated in official websites.

Guidelines and recommendations on endometriosis are mostly issued by scientific societies. In medicine, some clinical practice guidelines may be biased in favor of industry owing to the financial COIs of their authors and sponsors.[29,32-38] Several panel members of some recommendations on endometriosis have financial COIs, and disclosed having received money from industries marketing drugs for the management of the disease. When the ASRM Practice Committee opinion on treatment of pelvic pain associated with endometriosis was developed, "*all Committee members disclosed commercial and financial relationships with*

manufacturers or distributors of goods or services used to treat patients. Members of the Committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of this document".[39] This should serve as an example for the composition of panels of experts writing or revising guidelines on endometriosis. Indeed, also the impact of COIs of editorial board members of medical journals on the management of manuscripts reporting results of industry-sponsored trials has been matter of debate.[25,30,40-43]

Collaborating with industry has been, and always will be, crucial for improving health care of women suffering from endometriosis. Important results have been obtained in the past years and, hopefully, further achievements will soon be at hand thanks to strict collaboration between academic investigators and researchers working in the Research and Development divisions of pharmaceutical industries and device manufacturers. However, directors of Sales and Marketing divisions are accountable toward boards of trustees and shareholders, not patients and, admittedly, their mission is making profit, not defining the most cost-effective strategies to manage endometriosis.

The issue of COIs is rarely raised when discussing the evidence in support of different management modalities for endometriosis. In general, payments from industry are associated with greater prescribing costs.[44,45] In particular, endometriosis might represent a paradigmatic condition at risk of financial influence, as it is a frequent and chronic disorder negatively impacting on health-related quality of life, sexual functioning, fertility, and often necessitating prolonged pharmacological treatments and sometimes repetitive surgery. Thus, endometriosis may appear appealing for those stakeholders that profit from selling diagnostic tests, medications, and surgical instrumentation, as well as for those health care providers that profit directly or indirectly from the use of these products.

Again, COIs by no means imply misconduct. However, gynecologists caring for women with endometriosis should be conscious of their existence, and should systematically look for disclosures of authors before reading clinical educational articles and guidelines. This could help putting the presented information in the right perspective.

DIAGNOSIS AND OVERDIAGNOSIS OF ENDOMETRIOSIS

In clinical practice, linking diagnosis with treatment is of fundamental importance. In particular, pursuing a diagnosis to the point of performing an invasive procedure is justified exclusively if this can lead to demonstrable amelioration of health. It is a clinical tenet that only laparoscopy consents a definitive diagnosis of endometriosis. This might be true for superficial endometriotic lesions, but not for ovarian and deep ones. Therefore, if substantially better outcomes are not associated with a laparoscopic diagnosis of superficial peritoneal implants, only morbidity, costs, and anxiety are generated. Noteworthy, according to Holt and Weiss,[46] the mere presence of endometrial glands and stroma at ectopic sites without symptoms cannot be considered a disease: it is endometriosis, but not "endometriotic disease".

A non-surgical diagnosis of the "endometriotic disease" is feasible. Transvaginal ultrasonography (US) allows reliable identification of most relevant endometriotic lesions without the need for a laparoscopy (Figure 1).[4,47,48] The diagnosis of endometriomas is actually highly accurate[49] and the diagnosis of deep pelvic peritoneal lesions has greatly improved in recent years.[50,51] According to a recent Cochrane meta-analysis,[52] sensitivity and specificity of US for the diagnosis of endometrioma are 0.93 (95%CI: 0.87-0.99) and 0.96 (95%CI: 0.92-0.99), respectively. For deep invasive endometriosis, they are 0.79 (95%CI: 0.69-0.89) and 0.94 (95%CI: 0.88-1.00), respectively. Noteworthy, the authors concluded that transvaginal US actually approaches the criteria for *replacement*, i.e. a test that can replace

the gold-standard (laparoscopy) because it provides greater or similar accuracy, along with other advantages (no risks). Moreover, for deep invasive endometriosis, transvaginal US satisfies the criteria for *triage*, i.e. a test that should be used as an initial step in a diagnostic pathway. As a matter of fact, transvaginal US is sufficient in the vast majority of cases of deep peritoneal endometriosis. Rectosigmoidoscopy, barium enema, MRI and urinary apparatus imaging may be indicated to disentangle diagnostic uncertainties on deep peritoneal lesions only in selected cases.[53] Finally, the time-honored gynecologic bimanual examination still plays a crucial role in the diagnostic work-up, and can improve the potential of transvaginal US guiding it in the detection of deep lesions.[53,54]

Superficial lesions and adhesions are difficult to identify with all imaging techniques. Ultrasonography can provide some information on adhesions because it is a dynamic examination that consents to determine whether the uterus and ovaries glide freely over the posterior and anterior organs and tissues (*sliding sign technique*) but accuracy remains modest.[49,51] Even if laparoscopy thus remains the gold-standard for the detection of adhesions and superficial implants, it is however a surgical intervention, and the pros and cons must be carefully balanced on a case-by-case basis. The advantage of detecting these disease forms in terms of symptoms' improvement should overcome the morbidity and costs of the procedure. In other words, if symptoms can be properly managed without surgery (i.e. with hormonal therapies or assisted reproductive techniques), the lack of a visual diagnosis is of scanty clinical impact.

Indeed, the tenet that the "diagnostic delay" in women with endometriosis is the result of not performing a timely laparoscopy must be challenged. The diagnostic delay is the result of insufficient disease awareness among general practitioners and gynecologists, not of the "delay" in indicating surgery. If ovarian endometriomas and deep infiltrating lesions can be reliably diagnosed without a laparoscopy, only superficial peritoneal lesions may not be

identified, but this does not mean that they cannot be clinically suspected in women with pain symptoms and/or infertility. Thus, a laparoscopy performed with the objective of diagnosing minimal/mild endometriosis is meaningful only when surgical treatment is chosen instead of alternative options, such as medical therapy in women with pain and ART in those seeking conception.

The identification of a biomarker to detect endometriosis is deemed a priority for research.[55] However, based on the above facts, biomarkers are substantially aimed at detecting minimal-mild superficial peritoneal forms, not endometriosis in general. Up to now, blood and urinary biomarkers, both singly and in combination, are of limited diagnostic value.[56-58]

Biomarkers for the detection of early endometriosis forms would be important if lesion progression to more advanced stages would be the rule. However, the available evidence on the natural history of early disease, derived from patients allocated to the placebo arm of RCTs and who underwent follow-up laparoscopies, depicts a different story. In fact, progression of limited superficial peritoneal implants was demonstrated in less than one third of women and was unpredictable.[59] Moreover, superficial lesions are a common finding (3-44%) in asymptomatic, fertile women undergoing tubal sterilization.[4] If early peritoneal endometriosis is a transient para-physiologic condition in many women,[53,59,60] the availability of a biomarker with high sensitivity would all too often detect superficial implants that in most cases would subside spontaneously or would not progress to more advanced stages.

Moreover, an additional risk here is the possibility that when a reliable blood biomarker intended to be used in selected symptomatic women will become available, it could instead be used by asymptomatic women willing to know whether they harbor early peritoneal implants in their pelvis. This potential shift from *diagnosis* to *screening* would be

associated with several and potentially detrimental consequences, including diagnostic labelling, women's anxiety over test results, performance of further testing, and request for a laparoscopy in order to confirm the existence of endometriosis and prevent its purported spread into the pelvis.

The cascade of additional downstream interventions that would follow a positive test result would be left to pay by the health care system or individual families, and would have beneficial effects in a few patients, but potentially detrimental effects in many women. Manufacturers would likely try to offer medical testing for endometriosis directly to consumers, as it has been done with several other high-prevalence disorders including Parkinson, Alzheimer, and celiac disease.[15] Several stakeholders could profit by an increase in the identification of a condition of uncertain clinical importance, including pharmaceutical companies selling drugs for endometriosis. In extreme situations, this attitude might even degenerate into *disease mongering*, i.e. the "selling of sickness that widens the boundaries of illness in order to grow markets for those who sell and deliver treatments".[61]

More in general, a pragmatic diagnostic approach to minimal-mild endometriosis appears advisable. Noteworthy, given the debated role of the classification of endometriosis in the management of the disease, advocating surgery exclusively to obtain an accurate staging is unsupported.[62] The available guidelines issued by major international scientific gynecologic societies do not indicate mandatory surgical exploration before initiating inexpensive and safe medical treatments, such as OCs and progestins, in women with pelvic pain and suspected early endometriosis.[39,63-65] In these circumstances, the Society of Obstetricians and Gynaecologists of Canada (SOGC)[63] recommends history and physical examination plus transvaginal ultrasonography as a first-line diagnostic modality. Laparoscopy is not indicated for diagnostic purposes, but as a treatment, and empirical medical therapy is contemplated.[66]

In conclusion, a non-surgical diagnosis of the definite endometriotic disease is possible and reliable combining history and physical examination with easily available imaging modalities.[4,53,54] Superficial peritoneal lesions and adhesions can and should be suspected without delay in all women of reproductive age with pelvic pain symptoms and/or infertility. The availability of a bio-marker to identify minimal-mild endometriosis may not be expected to modify substantially medical decision-making, which includes medical treatments or surgery for pain and ART or surgery for infertility anyway.

MANAGEMENT OF WOMEN WITH PAIN: A STEPPED-CARE MODEL

Overcoming methodological preconceptions

In some reviews on endometriosis management, costly medications such as gonadotropin-releasing hormone (GnRH) agonists and dienogest are sometimes favored based on the consideration that only these drugs have been tested in randomized, controlled trials (RCT). In other words, only the conduction of RCTs would ensure the production of data that are sufficiently robust and meaningful to be translated in clinical practice. In general, this is indisputable, as only random allocation of treatments adequately limit selection bias and confounding. However, around 90% of RCT are supported by industry, as the planning and conduct of RCTs have become administratively and financially too bothersome for many independent investigators.[67-70] Of relevance here, industry-supported trials are significantly more prone to favor experimental compounds over standard medications compared with non-sponsored RCTs.[71,72]

Moreover, RCT is not necessarily synonymous of production of evidence that is of interest for patients with endometriosis. Most pharmacologic RCTs are conducted for registration purposes, and outcomes and comparators are often accurately chosen with the objective of favoring the experimental drug. In other words, the results are easily predictable.

In addition, selective reporting is another worrisome and apparently still unsolved issue in the endometriosis field.[73,74] Supposedly, patients might be more interested in knowing whether new drugs are better than OCs or safe and inexpensive progestins (e.g., nor-ethyndrone acetate, NETA), as they would not use placebos and GnRH agonists alone anyway. Regrettably, OCs and NETA do not seem to have ever been chosen as comparators in industry-sponsored RCTs.

Indeed, some observational study designs may constitute an acceptable alternative to RCTs. When adequately planned, and analyzed, observational studies may yield results similar to those derived from RCTs.[75,76] When the resources are insufficient for the conduction of a formal RCT, observational studies allow independent investigators to verify the effectiveness of new registered medications for endometriosis choosing the comparators that the majority of patients actually uses.[70]

Medical treatment

We have recently proposed a lesion-based three-tiered risk stratification system,[17] with low-dose, monophasic OCs suggested as a first-line therapy for women with peritoneal or ovarian endometriosis, and progestins for those with deep infiltrating lesions and those who do not respond to or do not tolerate OCs. GnRH agonists with add-back therapy should be restricted to selected patients at high risk of surgical complications or those refusing surgery. Indeed, the superiority of these costly and less safe compounds over OCs and progestins has not been consistently demonstrated.[77,78] The results of available studies comparing OCs and progestins with other drugs in women with symptomatic endometriosis are summarized in Table 1.

The future role of GnRH antagonists is difficult to define, as the results of only three phase 3 trials have been published. In two similar, double-blind, 6-month RCTs, elagolix at the dose of 400 mg/day was significantly superior to the same drug at the dose of 150 mg/day

and to placebo in relieving menstruation-related pain.[104] In another double-blind, 6-month RCT, elagolix 150 mg/day was compared with subcutaneous depo-medroxyprogesterone acetate (DMPA).[99] The main outcome measure was bone mineral density variation, and no significant between-group difference was observed. However, differently from NETA, a bone-sparing progestin approved for endometriosis management, DMPA has been repeatedly demonstrated to reduce bone mineral density.[105-107] Moreover, in this trial elagolix was used at the dose of 150 mg/day, whereas the dose that demonstrated the best effect on pain in the most recent RCTs was 400 mg/day. Predictably, the higher-dose elagolix determined a greater variation in bone mineral density compared with the lower dose.[104]

The potential advantages of GnRH antagonists over GnRH agonists are currently undefined. In fact, the so-called "flare-up phase" does not seem to be a major issue when starting GnRH agonists' use during the mid-luteal phase. Whether oral use is more acceptable than monthly or three-monthly intra-muscular or subcutaneous use is a matter of personal preferences, as depot preparations could reveal practically advantageous compared with repeated oral administrations every day for long periods of time. No information is publicly available on future costs of elagolix treatment. Indeed, in a before and after study comparing dienogest and NETA, cost was the main determinant of patient adherence and treatment effectiveness.[16]

Medical treatment has been proposed for unilocular ovarian endometriomas with a maximum diameter of 5 cm, without septa or vegetations, and no tendency to growth at repeat ultrasonography performed 3 to 6 months apart.[108,109] In fact, the malignant potential of endometriomas with these ultrasonographic characteristics is very low.[47,52,110,111] Adding cyst aspiration to medical treatment does not seem to confer further benefits.[112]

Oral contraceptives and progestins have been demonstrated to relieve pain and improve health-related quality of life also in about two thirds of women with rectovaginal endometriosis.[16,82,88,97,98,113-116] Thus, maintaining that surgery is the only effective treatment alternative in these patients appears deceptive. In particular, the effectiveness, safety, and tolerability of low-dose NETA (2.5 mg/day) have been recently reported in a cohort study with a 5-year follow-up.[115]

A crucial aspect of endometriosis management is prevention of post-operative lesions and symptoms recurrence, occurring at a rate of around 10% each year.[117,118] Oral contraceptives reduce the risk of endometrioma recurrence by over 90%[119] and should be systematically proposed after surgery to women not seeking immediate conception. Oral contraceptive or progestin use until pregnancy seeking improves quality of life and preserves the already impaired reproductive potential that would be further damaged by repeat gonadal surgery.[118-121]

The use of a levonorgestrel-releasing intrauterine device (LNG-IUD) after surgery for symptomatic endometriosis has been demonstrated effective in reducing dysmenorrhea recurrence.[122,123] The effect on deep dyspareunia is less definite and probably limited. In addition, the LNG-IUD does not inhibit ovulation, thus it does not seem effective in preventing postoperative endometrioma recurrence.[123]

Surgical treatment

Surgery is mandatory in cases of ureteral endometriosis causing hydroureteronephrosis, bowel lesions causing sub-occlusive symptoms, and adnexal masses of unclear nature at trans-vaginal US.[63] In all other circumstances surgery is a choice among alternatives. Surgery is indicated particularly in women with deep dyspareunia and dyschezia, that is, in women with organic-type pain associated with deep lesions in the postero-uterine pouch, and that do not

respond to medical treatments. Women should be informed that surgery may result in only partial or temporary pain relief and that about half of the patients that underwent surgery because of pain, experienced symptoms' recurrence at two-year follow-up.[124] Women should also be informed that, although rarely, pain may even worsen after surgery, and that the outcome, as well as the risk of complication, are operator-dependent. Complications must be described in detail and crude percentages must be indicated based on the available evidence and the surgeon's personal experience. This is particularly important when planning excision of deep infiltrating lesions such as recto-vaginal plaques and bowel nodules. Women must know that non-subocclusive bowel endometriosis is not necessarily progressive when adequately managed with hormonal therapies.[116] To facilitate counselling, the incidence and type of complications associated with colorectal surgery for endometriosis reported in studies published in the period 2010-2017 are summarized in Table 2.

Pelvic denervation procedures should be suggested rarely and in highly selected patients. Pre-sacral neurectomy may be effective for mid-line pain,[167] but necessitates an unusual knowledge of retroperitoneal anatomy and is associated with intraoperative bleeding complications and post-operative sequelae on urinary and bowel function.[168,169] Ablation of uterosacral ligaments was not demonstrated effective,[170-172] and should not be performed unless endometriotic nodules infiltrates the posterior parametria.

Robotic surgery is becoming increasingly popular as an alternative to standard laparoscopy to excise endometriotic lesions. However, systematic literature reviews demonstrated that robotic surgery does not confer benefits to patients, but that it does increase operative time and costs per procedure.[173,174] The lack of clear benefits of robotic surgery in benign gynecology has been highlighted in a position statement by the American Association of Gynecologic Laparoscopists.[175] The American College of Obstetricians and Gynecologists included an item on robotic surgery in benign gynecology in its "Choosing Wisely" list. The

College discourages the use of the daVinci robot, fostering a laparoscopic approach, due to lack of advantages of robotic surgery in terms of perioperative outcomes, intraoperative complications, length of hospital stay and rate of conversion to open surgery, and evidence of disadvantages in terms of operating time and costs.[176]

A recent systematic literature review conducted specifically on the use of the daVinci robot for the conservative surgical treatment of endometriosis confirmed the above positions.[177] The six comparative studies identified were all retrospective. A total of 749 women underwent robotic surgery and 705 conventional laparoscopies. Operative time was longer for robotic surgery in five studies. Major complications and laparotomy conversions for robotic surgery and standard laparoscopy were 1.5% vs 0.3% and 0.3 vs 0.5%, respectively. Surgical treatment of endometriosis by means of the daVinci robot did not confer benefits over standard laparoscopy, overall and among subgroups of women with severe endometriosis, peritoneal endometriosis and obesity. The available evidence was of low quality, and data regarding long-term pain relief and pregnancy rates were lacking.

According to the results of the only published RCT conducted on women with endometriosis, robotic surgery and conventional laparoscopy performed similarly in terms of operative time, perioperative complications, and postoperative quality of life outcomes.[178] However, comparative effectiveness research evaluating robotic surgery against standard laparoscopy should include also set-up times, and not just the operative time from skin incision to skin closure, as this might convey incomplete practical information. In fact, the final economic balance may result worse than at first sight, owing to a reduction in the overall number of procedures that can be scheduled per operating session.

Despite these facts, robotic surgery is presented as the ultimate technology and it has become a symbol of providing advanced care.[177] At the same time, the daVinci robot appears also as a paradigm of the impact of the financial pressure of industry on gynecology in

general, and on reproductive medicine in particular.[22] The risk here is that a self-propagating cycle takes place involving gynecologists, hospital administrators, healthcare policy makers, and patients themselves, leading to the development of an irreversible dependence from the daVinci robot, with detrimental consequences for the limited resources of national health systems.[179-181] Based on the available evidence, routine treatment of peritoneal and ovarian endometriosis with the daVinci robot should be definitely discouraged. Robotic surgery for deep, colorectal, and urinary tract endometriosis should be performed within the context of controlled studies.

The stepped-care approach

The general attitude of investigators and clinicians when dealing with endometriosis management is all too often trying to identify the "best" treatment in absolute terms, and then apply that treatment to all patients independently of the variable severity of different clinical conditions or cost considerations. In the research environment, head-to-head comparisons are essential to define the potential effects of new drugs and new methods of cure. Whereupon, long-term therapeutic strategies for endometriosis patients should be based not only on absolute efficacy, but also on safety and cost-effectiveness, and the most expensive measures should be used when first-line treatments are not effective, not tolerated, or contraindicated. This alternative approach should be based on sequential stages of endometriosis management, starting from the safest, most tolerable, and inexpensive drug. In this way, only a limited proportion of symptomatic women would use expensive medications or undergo surgery, as low-dose monophasic OCs used cyclically or continuously or progestins, would relieve pain in two thirds to three fourths of women.[17,77] The true issue in not whether GnRH agonists and antagonists are better than OCs and progestins, or whether surgery is better than medical treatment, but indeed who should use third-line treatments such as GnRH agonists and antagonists and who should undergo surgery, and when. According to this model, the

identification of non-responders triggers the decision to "step up". This would create a sort of "therapeutic pyramid", with a broad base of users of first-line medications, a progressively narrower body of users of second- and third-line drugs, and an apex of patients undergoing surgery. The broader the pyramid base, the less patients would be operated and the less women would use potentially less safe and more costly compounds.

MANAGEMENT OF INFERTILE WOMEN: CONCEPTION AND BEYOND

Infertility is a typical symptom of endometriosis, but is not pathognomonic of the disease, and a consistent proportion of affected women are fertile.[182] It has been reported that 24-43% of patients with advanced stages who did not seek conception before, became pregnant naturally in less than one year without undergoing surgery or ART.[183,184]

The most important therapeutic issues related to infertility-treatment are synthesized in Table 3, and have been exhaustively addressed in several recent reviews,[65,66,182,186,187,200] and will not be here further discussed. However, in our opinion, the current role of surgery as a fertility-enhancing measure, and the importance of not isolating fertility issues from other features of disease management, including obstetrical aspects, deserve more in-depth considerations.

Re-defining the role of surgery in the time of improving IVF performance

In vitro fertilization (IVF) has become the most suitable approach to endometriosis-related infertility,[193,201-203] as its effectiveness appears superior to surgery.[182] The available evidence rules out a major detrimental impact of IVF on disease progression.[198,199,204] Moreover, the risks associated with IVF seem inferior to those of surgery, particularly in advanced cases.[133,196,205] In this scenario, the possible role of surgery as a fertility-enhancing procedure should be carefully reconsidered.

The benefit of laparoscopic treatment of superficial peritoneal forms (minimal-mild disease) is statistically significant, but of questionable clinical importance. Around 25 laparoscopic procedures should be undertaken to obtain one more live birth compared to expectant management.[186,187,200,206] Women should be offered crude estimates, as the overall chances of delivering a baby are slightly over one in four after surgery and slightly under one in five without surgery.[186,200,206] Before making a choice, they must also be informed about the effectiveness of IVF. From the point of view of a national health system, the balance between potential benefits, harms, and costs of laparoscopy appears unfavorable in such clinical circumstances, and would likely lead to labelling this measure as "low-value care" when performed exclusively to increase the likelihood of pregnancy.[4] From an individual point of view, whether it is worthwhile to undergo a laparoscopy is a personal decision, and other determinant factors, such as co-existence of pain symptoms and preference for a natural conception or refusal of IVF, should be taken into account.

Randomized comparisons between surgery and expectant management for ovarian endometriomas in infertile women are not available, and data on the background pregnancy rate are almost lacking. Barri *et al*.[207] reported a 10% conception rate in a retrospective cohort study on infertile women undergoing expectant management. Leone Roberti Maggiore *et al*.[183] observed a 43% pregnancy rate in a large series of women with a unilateral ovarian endometrioma and unknown fertility status followed prospectively for 6 months. Comprehensive reviews including non-comparative series indicate an overall postoperative pregnancy rate of around 50%.[200,206] However, the fertility status of many study subjects was not reported and, considering the above-mentioned findings on natural pregnancy in unoperated women, ascribing this 50% post-surgery success entirely to the intervention seems misleading. In addition, several types of bias limit the robustness of the available data on surgery for endometriomas in infertile women.[206] Therefore, counselling is more difficult

506 compared with situation in which superficial peritoneal endometriosis is suspected. Cyst
507 diameter plays a role in everyday practice, but the dimension over which surgery is indicated
508 is currently undefined and decisions are usually taken arbitrarily and mostly based on
509 personal experience and opinions. As no relation has been demonstrated between cyst
510 diameter and natural conception rate,[183] when pain is not a major issue a surgical indication is
511 generally suggested also with the objective of excluding a malignancy. Removing ovarian
512 endometriotic cysts is advisable also when oocyte retrieval is rendered cumbersome in case
513 IVF is chosen.

514 On the other hand, with the exception of iatrogenic gonadal damage, the risk of
515 complications when excising ovarian endometriomas in women undergoing their first
516 procedure is limited. Moreover, given the reliability of transvaginal ultrasonography in
517 identifying endometriotic cysts,[52] there is no "risk" of not founding preoperatively diagnosed
518 lesions, as it happens in women undergoing laparoscopy for suspected superficial peritoneal
519 implants. Overall, defining the value of endometrioma removal as a fertility-enhancing
520 procedure is difficult. Surgery and IVF are not mutually exclusive. When endometriomas are
521 smaller than 5 cm[109] and do not impede oocyte retrieval, whether undergoing IVF first and
522 resort to surgery only in case of persisting infertility, or vice versa, again is a personal choice.
523 The presence of pain symptoms mandates surgery in those women refusing IVF.

524 Resection of deep infiltrating endometriotic lesions with the aim of increasing the
525 likelihood of pregnancy in infertile women is gaining momentum. Differently from conditions
526 where only superficial peritoneal and ovarian endometriomas are present, surgery for deep
527 infiltrating endometriosis is technically demanding and associated with high risks of major
528 intra- and postoperative complications, especially when colorectal resection is undertaken
529 (Table 2). Overall, around 1 out of 20 women undergoing radical surgery for colorectal and
530 rectovaginal endometriosis experience bladder denervation of variable duration, a

rectovaginal fistula formation, or large bowel anastomotic leakage.[133,190,208,209] The incidence of the latter two complications is influenced by concomitant performance of diverting colostomy or ileostomy.[209] Surgery for deep infiltrating endometriosis is effective for reducing severe pain symptoms, especially deep dyspareunia not responding to medical treatment. Therefore, when the objective is pain reduction to improve sexual functioning, and thus allow women to seek a natural conception for a prolonged period of time, suggesting surgery seems reasonable, provided that women are informed in detail regarding the risks and the alternative of IVF.[210]

Conversely, great caution is needed when suggesting radical surgery specifically as a mean for increasing the likelihood of conception, as no robust and precise estimate of the effect (if any) is currently available regarding this outcome. In a comprehensive literature review, the overall postoperative pregnancy rate after radical surgery for deep endometriosis in infertile women was around 25%.[206] In a comparative but not randomized study, we have observed a similar 2-year pregnancy rate between women who underwent rectovaginal endometriosis resection at laparotomy (34%) or expectant management (36%).[211] In a retrospective study conducted on 75 women with deep lesions combined with other endometriosis forms, Douay-Hauser *et al*.[212] observed similar pregnancy rates when undertaking radical endometriosis excision including deep lesions (20%) or when treating only intraperitoneal lesions (18%). Finally, Leone Roberti Maggiore *et al*.[183] observed a pregnancy rate of 42% in 76 women with deep endometriotic lesions and a unilateral endometrioma undergoing expectant management for 6 months. The fertility status of the study population was unknown, as the women had not attempted to get pregnant before. In a retrospective cohort study, the same group recently observed a pregnancy rate of 25% in women with rectovaginal endometriosis who sought conception without surgery.[184] The percentage decreased to 12% in case also ovarian endometriomas were present. Surgery

apparently was beneficial, as pregnancy rate rose to 43% when only rectovaginal lesions were resected, and to 30% when also ovarian endometriomas were excised. Again, the baseline fertility status was unknown.

Beyond the well-known methodological issues, the reliability of the evidence on resection of deep endometriosis to enhance fertility is limited by several other factors.[210] Firstly, it seems impossible to discriminate between the specific effect of excision of deep lesions from that of other lesion types. Of relevance, Somigliana *et al*.[213] demonstrated that superficial and ovarian lesions co-exist in 94% of women with deep endometriotic lesions. Secondly, in the majority of available studies the co-existence of uterine adenomyosis was not investigated. A strong association between deep infiltrating endometriosis and adenomyosis has been repeatedly demonstrated[214-216] and, according to a systematic review, the postoperative likelihood of conception dropped from 43% to 11% when the two conditions co-existed.[217] Thirdly, the available data, in terms of both pregnancy and complication rates, are the results of procedures performed by the best surgeons in the world. Whether these results are replicable in more ordinary settings is far from demonstrated, and this greatly interest our patients and the information that should be conveyed during preoperative counselling. On the other hand, systematically referring all infertile women with deep endometriosis to a restricted group of experts, appears impractical and unfeasible from the point of view of public health care policy makers.

Undertaking colorectal resection to enhance fertility appears counterintuitive, and the extreme heterogeneity of the available data regarding the effect of this type of surgery must be taken into consideration when informing infertile women. The risk of complications can be quantified, whereas the benefit in terms of improvement in reproductive performance currently cannot. Thus, surgery for deep endometriosis in infertile women should be carried out in research settings or in women with pain symptoms who desire a natural conception.

Patient not refusing ART should also know that in their condition the chances of pregnancy with IVF are around 50%.[210]

Management of infertility within a comprehensive vision of endometriosis

Endometriosis-associated subfertility should not be addressed exclusively after failed attempts at conception, but should rather be part of a far-sighted comprehensive approach to patients with endometriosis. For instance, given the detrimental role of ovarian endometriomas and their surgical removal on ovarian reserve,[196,218] systematic prescription of OCs or progestins is recommended in women who are diagnosed with endometriosis and are not yet seeking pregnancy.[118,219] In fact, ovulation is crucial in the development of ovarian endometriomas,[220] and OCs have been proven effective in preventing progression and recurrence of this disease form.[119,221]

The timing of surgery also merits attention, especially in women refusing or not tolerating prolonged post-operative medical treatments. In these cases, the recurrence rate is around 20% at two-year follow-up, and 40-50% at five years.[117] Moreover, the probability of conception after repeat surgery for recurrent endometriosis is substantially reduced compared with that after primary surgery. According to a specific meta-analysis, the OR for pregnancy after second surgery was 0.44 (95%CI: 0.28-0.68).[191] When feasible, it appears wiser to treat patients with hormonal therapies and delay laparoscopy (if needed) at the time of pregnancy seeking, in order to combine the beneficial effect of surgery on pain symptoms and that on infertility.[222] This would also consent the use of the validated Endometriosis Fertility Index (EFI) model for the prediction of natural pregnancy.[62]

Physicians should also not separate fertility from obstetrical issues. In particular, severe endometriosis has been associated with spontaneous intra-peritoneal hemorrhage and placenta previa.[223,224]

Spontaneous hemoperitoneum in pregnancy is a rare but potentially fatal condition. In a recent systematic literature review, Brosens *et al*.[223] identified 45 articles reporting on 64 cases and two maternal deaths. In most instances, bleeding originated from the serosa of the posterior uterine aspect, the broad ligaments, or the utero-sacral ligaments, and it was more common in the second half of pregnancy. Advanced endometriosis stages, deep lesions, and IVF seem to constitute risk factors.[223] Spontaneous hemoperitoneum in pregnancy is usually associated with severe blood loss and warrants prompt transfusion and surgical exploration. Delivering the fetus is generally necessary to empty the uterus and allow the identification and treatment of the source of bleeding. Fetal demise and adverse perinatal outcome are common.[223] Women with severe endometriosis seeking pregnancy should be aware of this possible complication but, at the same time, they should also be reassured about the extreme rarity of the event. No data is available demonstrating a beneficial effect of surgery as a preventive measure before conception.

The association of endometriosis with placenta previa is epidemiologically and clinically more relevant.[224,225] The reported ORs of the association varied between 2.2 and 6.4.[226-228] The relation was stronger for severe endometriosis in general,[228,229] and for deep endometriosis in particular.[230-232] Women with rectovaginal lesions had an almost six-fold increase in risk of placenta previa when compared to those with superficial and/or ovarian lesions (OR 5.8; 95% CI 1.5–22.0).[230]

Placenta previa may reveal a demanding obstetrical complication that can cause profuse and uncontrollable bleeding and may require caesarean hysterectomy. In women with severe endometriosis, this condition could be particularly perilous because of adjunctive surgical difficulties.[225] In patients with extensive adhesions, and especially in those who underwent previous procedures, such as colorectal resection or ureteral-bladder re-implantation, even gaining access to the abdominal cavity may be cumbersome. Moreover,

when the caesarean section is urgent rather than elective, the need for prompt fetal extraction requires a quick access to the uterus, thus enhancing the risk of iatrogenic injuries to the bladder and bowel. Therefore, caesarean sections for placenta previa in women with severe endometriosis should be performed by experienced obstetricians in tertiary referral centers where urologists, abdominal surgeons, and interventional radiologists are available. In these women the above risks must be discussed before initiating pregnancy seeking, particularly when IVF is being scheduled. Single embryo transfer is mandatory because of the independent but potentially additional increase in risk of placenta previa associated not only with deep endometriosis, but also with IVF and with twin pregnancies.[225,233]

MANAGEMENT OF THE ADOLESCENT WOMAN: A PLEA FOR A CONSERVATIVE APPROACH

As endometriosis is a disorder of reproductive life, not surprisingly it can be identified also during adolescence or young adulthood.[234-237] Endometriosis should be considered in the diagnostic work-up of young girls with both acyclic pelvic pain and severe dysmenorrhea not responding to common non-steroidal anti-inflammatory drugs.[234,235] Peritoneal lesions may have different clinical characteristics when compared to adult forms (i.e., red/flame-like, clear/polypoid, or vesicular lesions).[236] It has also been suggested that ovarian endometriomas are less common and that deep lesions may be more frequent, but the evidence is conflicting and exposed to biases.[234] Most likely, women who are diagnosed with endometriosis in adolescence may represent a subgroup with a more severe form of the disease that actually presents earlier. The need for surgical diagnosis and the concerns about performing surgery in young girls are important confounders in the interpretation of the evidence. The effectiveness of OCs in lowering dysmenorrhea further complicate the scenario. In fact, the vast majority of gynecologists consider this option first and, when menstrual pain improves, they do not schedule further assessments. Interestingly, adult women with endometriosis were shown to

be more likely to have started assumption of oral contraceptives during adolescence because of dysmenorrhea rather than contraceptive needs.[238,239]

In recent years, the interest in adolescent endometriosis has grown also as a consequence of a novel theory regarding the possible neonatal origin of the disease.[240] According to this hypothesis, endometriosis, especially when arising during adolescence, may be a consequence of the *genital crisis*, i.e. the vaginal bleeding episode that is sometimes observed in female newborns a few days after birth. This event has been ascribed to the typical fall of peripheral sex steroids, which causes a sort of withdrawal bleeding. Because of the structure of the neonatal uterus (i.e., long cervix with stick mucus), it has been hypothesized that a "retrograde menstruation" could be markedly favored in case of genital crisis.[240] In this first uterine flow, the shed endometrial cells may be immature, and the proportion of stem cells may be high. These types of refluxed neonatal endometrial cells might implant in the peritoneal cavity, survive in a quiescent status, and then give rise to overt endometriosis after the start of full estrogen synthesis during adolescence.[240]

The neonatal origin of endometriosis theory is certainly intriguing, but the supporting evidence is scanty and weak. No study ascertained whether retrograde menstruation at the time of the genital crisis does indeed exist and, consequently, whether these purportedly refluxed endometrial cells are actually particularly prone to implant at ectopic sites and grow later in life.[241,242] Despite this, the suggested clinical implications are strong, and include prompt laparoscopic identification of endometriosis in adolescent women, based on the presumption that, if the disease originates from the genital crisis and develops after menarche, timely detection and removal of early lesions would prevent disease progression and achieve a definitive cure.[243]

Such a recommendation, if adopted, would imply systematically performing laparoscopies in all symptomatic adolescent women independently of response to non-steroidal anti-inflammatory drugs (NSAID) and OCs. The World Health Organization (WHO) defines an adolescent as any person between ages 10 and 19. Dysmenorrhea is very common in women below the age of 20.[236,237] The psychological consequences of undergoing surgery and disease labelling have not been evaluated in this population, but are potentially particularly distressing. Being diagnosed during this delicate stage of life with a disease that will likely interfere with fertility, sexual functioning, and general health, until menopause ensues or definitive pelvic surgery is undertaken, could reveal overwhelming, and the information retrieved from the web may aggravate the issue.

In order to equipoise this risk of psychological harm, the indication to systematically perform a laparoscopy without trying low-dose OCs first, limiting surgery to non-responders, *must* be based on robust evidence of substantially better long-term outcomes (in terms of lesion progression, reproductive performance, pelvic pain recurrence, and need for further surgical procedures) in adolescent women undergoing immediate surgery compared with those undergoing medical treatments. Such good-quality evidence does not exist. Thus, this aggressive approach may reveal of low-value, and those gynecologists fostering it may be taking a great responsibility, given the particular psychological vulnerability of these very young women.[4]

Also, those who oppose this approach are taking a great responsibility in case the clinical implications of the genital crisis theory will reveal correct, as timely and definitive disease cure will be denied to innumerable adolescent women, with all the associated detrimental consequences. However, the ethical principle "first do no harm" appears here of particular importance, and the experimental evidence demonstrating the benefit of invasive treatments should be derived from adequately designed trials conducted in qualified research

703 settings, and must be provided *before*, not *after* their implementation in standard medical
704 practice.

705 Based on published data, the adoption of a different therapeutic attitude with respect to
706 that usually embraced in adult women seems hardly justifiable.[235] Physicians must plan a far-
707 sighted and stepwise combination of the available measures, i.e., hormonal treatments and
708 surgery. In particular, low-dose OCs and progestins have been demonstrated effective in
709 relieving endometriosis-associated pelvic pain[236,244] and in preventing postoperative
710 endometrioma recurrence in adolescent women.[245]

711 The prolonged use of dienogest in young women who have not achieved their peak
712 bone density should be carefully evaluated, as this progestin is not "bone-saving" and was
713 associated with a -2.3% mean lumbar bone mineral density decrease in 60 adolescents who
714 used the drug continuously for 1 year.[246] As an alternative to dienogest, GnRH agonists plus
715 add-back hormone therapy have been suggested, but this treatment should be indicated in
716 highly selected girls not responding to first-line medications and refusing laparoscopy.[247]

717 Surgery should be generally considered as a second-line option, also in order to
718 prevent young girls from being exposed to repeated surgical procedures. Of interest, recent
719 evidence suggests that surgery might facilitate endometriosis progression in the mouse model.
720 Whether surgery can promote the development of endometriosis in humans warrants further
721 investigation.[248] Oocytes cryopreservation may be considered but, to date, it remains an
722 experimental approach.[249]

723 Finally, screening strategies must be based on specific epidemiological criteria.[250,251]
724 The active investigation of early endometriosis in asymptomatic adolescent women fails to
725 satisfy them and, based on current evidence, appears unfounded.[252]

MANAGEMENT OF THE PERIMENOPAUSAL WOMAN: LIGHT AT THE END OF THE TUNNEL?

In perimenopausal women who do not seek pregnancy and are affected by severe endometriosis-related pain not responding both to previous fertility-sparing surgical procedures and medical treatment, or in whom medical treatment is contraindicated or not tolerated, hysterectomy is an option to discuss together with the patient.

Hysterectomy with or without bilateral oophorectomy

The efficacy of hysterectomy with and without bilateral salpingo-oophorectomy for the treatment of patients with endometriosis-related pain has been evaluated in two studies.[253,254] In the first study, women undergoing hysterectomy with ovarian conservation, as compared to women undergoing complementary oophorectomy, had a 6 times greater risk of developing recurrent pain (62% vs 10%), and a 8 times greater risk of reoperation (31% vs 3.7%).[253] In the second study, patients in the hysterectomy with ovarian preservation group underwent reoperation in 19% of cases compared with 8% of those in the hysterectomy and bilateral oophorectomy group. As for the 2-, 5-, and 7-year reoperation-free rates, figures were 96%, 87%, and 77.0% in the former group versus 96%, 92%, and 92% in the latter one, respectively. Preservation of both ovaries increased the risk of reoperation by 2.4 times, regardless of the patients' age.[254] In another recent study, the estimated cumulative retreatment rates at 2, 5, and 8 years after hysterectomy were 3.3%, 4.7%, and 5.4%, respectively.[255] The hysterectomy-treated patients in this study included those with and without ovary preservation.

One study compared the outcome of hysterectomy for endometriosis-associated pain between women of < 30 years of age and women of > 40 years of age. A similar proportion of women reported alleviation of pain (80% and 87%, respectively). However, younger subjects were significantly more likely to report residual symptoms, such as dyspareunia and dysuria.

751 They also more often reported a sense of loss after hysterectomy and more overall disruption
752 in different aspects of life.[256]

753 Therefore, removal of the uterus should generally be limited to women in their forties,
754 unless the patients themselves insistently request definitive surgery. Moreover, when bilateral
755 removal of the ovaries is planned, surgeons must carefully excise all the gonadal parenchyma,
756 as leaving even a small part of the cortex may expose to the risk of developing the ovarian
757 remnant syndrome, characterized by severe abdomino-pelvic pain and sometimes even
758 ureteral stenosis.[257,258] In women with extensive and dense adhesions and with previous
759 adnexal surgeries, complete removal of ovarian tissue may reveal difficult and a
760 retroperitoneal approach may be required. High-risk surgical candidates must be informed
761 also of this potential complication in order to balance all the factors that may influence the
762 final decision on whether undergo surgery, and which type of procedure undertake.

763 When evaluating the effectiveness of hysterectomy in relieving endometriosis-related
764 pain, also the concomitant excision of deep endometriotic lesions should be discussed. A
765 recent review showed that, among women who underwent surgical menopause and
766 experienced a postmenopausal disease relapse, the vast majority of endometriotic lesions
767 involved the ureter, the bladder and the bowel, suggesting persistence rather than recurrence
768 of the disease.[259] Therefore, according to some authors, deep lesions should be removed to
769 achieve optimal symptomatic relief after hysterectomy, especially if hormonal replacement
770 therapy is foreseen.[260,261] However, publication bias seems probable here, and the need for
771 excision of deep lesions when bilateral oophorectomy is planned, should be carefully
772 discussed with the patient taking into consideration both the potential benefits and the definite
773 risks of major complication associated with deep lesion removal. When ureteral endometriosis
774 does not cause hydro-ureteronephrosis and when colorectal endometriosis does not cause sub-
775 occlusive symptoms, it is exceedingly rare that this will happen after castration. If residual

776 disease is left and the woman requests hormonal replacement therapy, compounds including a
777 progestin should be used.

778 The information available suggests that hysterectomy is effective in relieving
779 endometriosis-related pain. Nevertheless, in the medium-term, a 15% probability of
780 persistence of pain and a 3–5% risk of pain worsening or development of new symptoms
781 should be expected.[124] In premenopausal women, ovarian preservation carries a six-time
782 higher risk of further surgery because of recurrent symptomatic disease as compared to
783 ovarian removal.[262] At the same time, the detrimental consequences of premature ovarian
784 removal on cardiovascular risk and overall mortality should be carefully discussed with
785 patients before taking a shared decision.[263-265] Finally, in selected cases of severely distorted
786 anatomic conditions, and especially in women who already underwent repeated difficult
787 surgeries or bowel resection and ureter re-implantation, the alternative of long-term depot
788 GnRH agonist plus add-back therapy until physiologic menopause ensues, should always be
789 considered as an effective and potentially safer alternative.

790 **Bilateral oophorectomy for the prevention of endometriosis-associated ovarian cancer**

791 In recent years, both histologic and epidemiologic evidence has accumulated suggesting that
792 women with endometriosis may present a higher risk of developing a malignant ovarian
793 tumor compared to women without endometriosis.[266] In particular, a systematic review and
794 meta-analysis based on individual patient data demonstrated that endometriosis was
795 associated with a significantly increased risk of clear cell (OR = 3.05, 95% CI = 2.43–3.84)
796 and endometrioid (OR = 2.04, 95% CI = 1.67–2.48) invasive ovarian cancers.[267] A more
797 recent meta-analysis confirmed that endometriosis is a risk factor of epithelial ovarian cancer
798 (OR = 1.42, 95% CI = 1.28–1.57).[268]

799 According to the dualistic model of ovarian carcinogenesis,[269-271] most endometrioid,
800 clear-cell, and seromucinous carcinomas derives from endometriosis, whereas high-grade

801 serous ovarian cancers may develop through sloughing and implantation on the ovarian
802 surface of hyperplastic or malignant tubal epithelial cells.[269-271] Noteworthy, not all
803 endometriotic lesions, but only atypical ones, which have been reported in 2–3% of excised
804 ovarian endometriomas, should be regarded as precursor lesions for endometrioid and clear-
805 cell ovarian cancers.[270,272] Of relevance here is that, because of the relatively low incidence of
806 clear-cell and endometrioid ovarian cancers, the overall lifetime risk of all invasive epithelial
807 ovarian cancer forms in women with endometriosis is only slightly increased when compared
808 to the general female population, being 1.5% in the former and 1% in the latter group. This
809 limited increase does not seem to justify screening or systematic surgical exploration of
810 women with asymptomatic endometriosis, especially when considering the high prevalence of
811 the disease.[273,274] However, when planning surgical treatment of symptomatic endometriosis
812 in perimenopausal women, the prevention of future ovarian cancer may constitute an
813 argument in favor of oophorectomy in presence of endometriomas and independently of their
814 dimension. The oncological risk should always be described using crude percentages and
815 avoiding both under- and overestimation. Any measure should be based on each woman's
816 priority and preference and, in younger women, it should include also the risk-reducing long-
817 term use of OCs or progestins.[275]

818 Further studies are needed to assess the value of bilateral salpingo-oophorectomy as a
819 preventive oncological measure, as no data are currently available demonstrating a reduction
820 in mortality from any cause associated with removal of the adnexa in women with
821 endometriosis. In addition to the general detrimental effects of premature gonadal function
822 deprivation, confounding must be taken into account here, as removal of the tubes, in
823 concomitance with that of the ovaries, translates into a substantial reduction in the risk of
824 high-grade serous adenocarcinomas (type II tumours), which cause 90% of all deaths from
825 epithelial ovarian cancer.[271] This appears certainly beneficial, but has nothing to do with a

supposed decrease in disease-specific mortality resulting from oophorectomy performed purposely because of endometriosis.[53,274] Therefore, also the efforts for potential future screening modalities should be concentrated on high-grade serous adenocarcinomas, which are not associated with endometriosis.

Hormonal replacement therapy in women with endometriosis

In women who underwent bilateral salpingo-oophorectomy for the treatment of endometriosis, hormonal replacement therapy (HRT) should be administered with caution, because of the risk of recurrence of pain.[276] A continuous combined estrogen-progestin therapy rather than an estrogen-only treatment is commonly recommended for treating menopausal symptoms. In fact, although studies comparing the two treatments directly are lacking, combined estrogen-progestin regimens may be less likely to promote growth of endometriosis and disease recurrence than unopposed estrogens. In a randomized trial, among women treated by hysterectomy and bilateral salpingo-oophorectomy for endometriosis, the incidence of recurrent disease in those who subsequently received cyclic estro-progestins was relatively low (3.5%) compared with untreated controls in whom no recurrence was observed.[277] Tibolone, a synthetic steroid drug with estrogenic, progestogen, and weak androgenic actions constitutes an alternative to estro-progestin regimens for hormonal replacement therapy in menopausal women affected by endometriosis.[278,279]

Unfortunately, however, due to the lack of high-quality studies evaluating the management of menopausal symptoms in women with a history of endometriosis, the impact of HRT on the risk of disease recurrence and malignant transformation cannot be adequately quantified.[259]

THE WAY FORWARD: COMPARATIVE EFFECTIVENESS RESEARCH AND COLLABORATIVE CARE

Convincing physicians and patients to do less testing and treatments in endometriosis management seems hard. Cultural and practical forces push toward doing more rather than less. Gupta and Moriates[280] maintain that the current prevailing medical culture resists the transition toward value-based healthcare and contributes to over-testing, overtreatment, and resource waste. Physicians have been educated that doing something more or different is in the interest of patients and, in addition, patients themselves may nurture such expectations. This attitude frequently is not supported by sufficient evidence of definite benefits and, at the same time, often ignores the potential harms and cost raising associated with medical overuse.

Primary prevention, screening, systematic laparoscopic diagnosis of early forms, prophylactic surgery, radical procedures despite response to medical therapy, use of fashionable techniques such as robotic surgery, use of expensive drugs when cheaper and safer alternatives are equally effective, are just a few examples of questionable potential use of health services' resources in endometriosis management. Scientific societies and industry may share the interest for doing more testing and using novel and costly drugs or devices. Although some women may benefit from such an approach, the majority would not, and some may be harmed. Doing more whenever there is the possibility of doing good, independently of how probable is this occurrence, or despite a major increase in costs of management, does not seem to be in the best interest of patients, society, and science.

A candid, and sometimes naive, enthusiasm for what could expectantly reveal beneficial for women with endometriosis, combined with robust financial investments from pharmaceutical industries and medical devices' manufacturers, plumps this self-feeding system. The tendency toward doing more tests, more treatments, and more visits, may also

874 constitute a risk factor for physician self-referral, "*a term describing the practice of a*
875 *physician ordering tests on a patient that are performed by either the referring physician*
876 *himself or a fellow faculty member from whom he receives financial compensation in return*
877 *for the referral. Examples of self-referral include […] a surgeon suggesting an operation that*
878 *he himself would perform, and a physician ordering imaging tests that would be done at a*
879 *facility he owns or leases*".[281]

880 According to LeFevre, "*of course the existing payment system rewards doing more,*
881 *irrespective of whether doing more results in more good than harm, and certainly irrespective*
882 *of whether we are getting good value in terms of improvements in health for the resources*
883 *invested. Every dollar spent on health care is someone's income stream. In any move to do*
884 *less, there will be efforts from those who lose income to push back; […] we should be able to*
885 *buy more health for the money we spend*.[282]

886 Women with endometriosis have the right to receive a timely diagnosis combined with
887 planning of life-long therapeutic strategies with the objective of limiting morbidity and risks,
888 preventing lesion progression and recurrence, preserving or enhancing fertility, and
889 ameliorating health-related quality of life. However, at times clinical research on
890 endometriosis appears as a sort of "navigation by sight", with some measures based on
891 hypotheses rather than robust evidence of efficacy, some trials conducted on drugs used for a
892 few months when patients need therapies for years, radical surgical procedures based on
893 lesion-oriented rather than problem-oriented approaches, and proposals for screening and
894 prevention formulated without taking into adequate consideration basic epidemiologic
895 principles and realistic effects on long-term outcomes.[4,252] This is sometimes combined with
896 tenets that have escaped formal verification and survive untested since decades in the
897 endometriosis scientific community. One such example is the purported 10% endometriosis

prevalence in the general female population of reproductive age, when estimates in the range of 1-3% have been repeatedly reported.[283-285]

Regrettably, there is an overall dearth of comparative effectiveness research to inform management of endometriosis in different clinical conditions .[4,65] Comparative effectiveness analyses based on trials with objectives that matter to patients are badly needed. Patient-reported outcomes and assessment of quality adjusted life year (QALY) are indispensable aspects to be addressed in future trials on endometriosis.[2]

A physician's duty of care extends to all patients and, in tax-funded national health services, demanding access to cost-ineffective drugs implies depriving other patients of cost-effective ones.[286] As an example, prescribing a drug costing $30,000 per QALY, deprives three patients of effective medicines costing $10,000 per QALY. According to Lexchin, also in Canada "*as new patented drugs come onto market, they are typically accompanied by aggressive promotion and marketing — more than half a billion dollars annually just for journal advertising and visits by sales representatives — and this alters doctors' prescribing choices. This shift means that the "mix" becomes more expensive, because new drugs are generally much more costly, although rarely more effective, than older ones*".[287]

Aronson fosters the model of collaborative care, defined as "*provision of care that is, as far as circumstances allow, respectful of and responsive to individual patient needs, values, priorities, and preferences, striving to maximise the patient's wellbeing without simultaneously compromising the needs, values, priorities, and preferences of others, achieved by collaboration among all of those involved*".[286]

Especially, but not exclusively, in those countries without universal health care coverage, novel payment mechanisms should be implemented whereby gynecologists caring for women with endometriosis are rewarded for cost-effective care, thus replacing the fee-for-

volume environment with fee-for-value alternatives.[288] Novel reimbursement systems are needed also for managing expenditures on pharmaceuticals in order to promote lower prices and the selection of lower-cost treatment options.[289]

Limiting the burden of treatment should become a priority. A life with less exams, less ultrasonographic scans, less gynecologic visits, less surgical procedures is possible. Safe, well-tolerated, and inexpensive medical treatments such as low-dose OCs and progestins allow this minimally disruptive management for most, albeit not all, patients with symptomatic endometriosis. One third of women with severe forms eventually needs surgery, and sometimes only hysterectomy with bilateral oophorectomy will bring relief after years of suffering. But patients with bowel and ureteral stenosis, or not responding to hormonal treatments, are a minority anyway, and most women with endometriosis can be managed conservatively. In this regard, the stepped-care model suggested above might limit the potential harms deriving from the use of less safe (and expensive) drugs, as well as the morbidity deriving from multiple surgical procedures in a reproductive life-cycle. Subfertility is still difficult to overcome, but ART performances are getting better over time, and oocyte donation programs may rapidly change the future scenario in case of failure of IVF with own eggs.

Endometriosis management is not "one-size-fits-all" and, whenever possible, long-term therapeutic strategies should be tailored on each woman' needs, and high-value tests and treatments should be chosen based on her priorities and preferences. Moreover, listening to patients, understanding their concerns, avoiding disease labelling, explaining plainly what is known and what is unknown, and giving constant reassurance and encouragement, may reveal exceedingly important for a successful management of endometriosis, and may change the patient's perception of her clinical condition. The importance of offering psychological and sexological support when needed must not be underestimated. Physician empathy has no

947 untoward effects, does not cause harms, and may determine whether a woman successfully
948 copes or desperately struggles with her disease during reproductive life.

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1749 289. Morgan SG, Leopold C, Wagner AK. Drivers of expenditure on primary care
1750 prescription drugs in 10 high-income countries with universal health coverage. CMAJ
1751 2017;180:E794-E799.

1752 Table 1. Effect of estrogen-progestins and progestins as assessed in comparative studies on the treatment of symptomatic endometriosis

1753 (literature data, 2002–2016).

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug**	**Comparator**	**Treatment period**	**Follow-up period**	**Outcome**
Vercellini *et al.*, 2002[79]	RCT	90	Continuous low-dose monophasic OC (EE 0.02 + DSG 0.15 mg)/day (*n* = 45)	Cyproterone acetate 12.5 mg/day per os (*n* = 45)	6 months	No follow-up	Similar pain relief and comparable improvements in QoL, psychological profile and sexual satisfaction. Slightly higher satisfaction with treatment in the cyproterone acetate group.
Cosson *et al.*, 2002[80]	RCT	142	Dienogest 2 mg/day per os (*n* = 74)	Triptorelin 3.75 mg depot i.m. injections/28 days (*n* = 68)	4 months	12 months (reproductive outcome only)	Similar postoperative pain relief during treatment; no pain evaluation at 12 months follow-up
Petta *et al.*, 2005[81]	RCT	82	LNG-IUD (*n* = 39)	Leuprolide 3.75 mg depot i.m. injections/28 days (*n* = 43)	6 months	No follow-up	Similar pain relief and psychological well-being. More bleeding with LNG-IUD.
Vercellini *et al.*, 2005[82]	RCT	90	Continuous low-dose monophasic OC (EE 0.01 + cyproterone acetate 3 mg)/day (*n* = 45)	NETA 2.5 mg/day per os (*n* = 45)	12 months	No follow-up	Similar pain relief and dropout rates. Higher satisfaction with treatment in NETA group.
Crosignani *et al*, 2006[83]	RCT	299	DMPA 104 mg s.c. injections/3 months (*n* = 153)	Leuprolide 3.75 or 11.25 mg depot s.c. or i.m. injections/28-90 days (*n* = 146)	6 months	12 months	Similar pain relief and improvement in QoL and productivity. Less BMD decline with DMPA.

Source	Study design	Patients enrolled (*n*)	Study drug	Comparator	Treatment period	Follow-up period	Outcome
Schlaff *et al.*, 2006[84]	RCT	274	DMPA 104 mg s.c. injections/3 months (*n* = 136)	Leuprolide 11.25 mg depot i.m. injections/90 days (*n* = 138)	6 months	12 months	Similar pain relief and improvement in QoL and productivity. More bleeding but less hypo-estrogenic side effects and BMD loss with DMPA.
Razzi *et al*, 2007[85]	RCT	40	DSG 75 μg/day per os (*n* = 20)	Continuous low-dose monophasic OC (EE 20 μg + DSG 150 μg)/day (*n* = 20)	6 months	No follow-up	Similar pain relief. Higher frequency of breakthrough bleeding in DSG group. Greater weight gain in OC group.
Kitawaki *et al.*, 2008[86]	Randomized comparative study	74	Danazol 300 mg/ day per os (dose was reduced to 200, 150 and 100 mg/day at interval of 2-3 months) (*n* = 21)	High-dose monophasic OC (EE 0.05 mg + norgestrel 0.5 mg or mestranol 0.05 mg + NETA 1 mg) (*n* = 34) or mid-dose monophasic OC (EE 0.035 mg + NETA 1 mg or EE 0.03 mg + DSG 0.15 mg) (*n* = 19)	12 months	No follow-up	Higher dysm score in OC groups. Similar effects on dysp and CPP. Comparable reduction of serum CA-125 levels. More frequent side effects with danazol.
Harada *et al*., 2009[87]	RCT	271	Dienogest 2 mg/day per os (*n* = 137)	Buserelin 900 mg/day i.n. (*n* = 134)	6 months	No follow-up	Similar pain relief and improvement in QoL. More bleeding, but less hypo-estrogenic side effects and BMD loss with dienogest.
Ferrero *et al*.,	PPT	82	Letrozole 2.5 mg +	NETA 2.5 mg/day	6 months	12 months	Greater pain relief with

Source	Study design	Patients enrolled (*n*)	Study drug	Comparator	Treatment period	Follow-up period	Outcome
2009[88]			NETA 2.5 mg/day per os (*n* = 41)	per os (*n* = 41)			letrozole + NETA, but fewer side effects and higher patient satisfaction rate with NETA only. Similar pain at follow-up.
Walch *et al.,* 2009[89]	RCT	41	Etonogestrel 68 mg implant (*n* = 21)	DMPA 150 mg i.m. injections/90 days (*n* = 20)	12 months	No follow-up	Similar pain relief. Comparable satisfaction with treatment and tolerability.
Vercellini et al., 2010[90]	PPT	207	Vaginal ring (EE 15 μg + etonogestrel 120 μg) (n =123)	Transdermal patch (EE 20 μg + norelgestromin 150 μg) (n = 84)	12 months	No follow-up	Pain symptoms reduced by both treatments, with ring more effective in patients with rectovaginal lesions. Higher satisfaction with treatments in ring group. Higher discontinuation rate in patch group.
Strowitzki *et al*., 2010[91]	RCT	252	Dienogest 2 mg/day per os (*n* = 124)	Leuprolide 3.75 mg depot i.m. injections/28 days (*n* = 128)	6 months	No follow-up	Similar pain relief. Higher improvement in QoL with dienogest. More bleeding but less hypo-estrogenic side effects and BMD loss with dienogest.
Ferreira *et al*., 2010[92]	RCT	44	LNG-IUD (*n* = 22)	Leuprolide 3.75 mg depot i.m. injections/28 days (*n* = 21)	6 months	No follow-up	Similar pain relief. Significant reduction in VCAM, CRP, total cholesterol, triglycerides, LDL-C and HDL-C levels in LNG-IUD group.

Source	Study design	Patients enrolled (*n*)	Study drug	Comparator	Treatment period	Follow-up period	Outcome
Wong *et al*., 2010[93]	RCT	30	LNG-IUD (*n* = 15)	DMPA 150 mg i.m. injections/3 months (*n* = 15)	36 months	No follow-up	Similar symptoms control and lesions recurrence rates. Irregular vaginal bleeding common in both group; frequency and severity of bleeding worse with DMPA. Improvement of BMD with LNG-IUD. Decline of BMD with DMPA. Better compliance in LNG-IUD.
Guzick *et al*., 2011[78]	RCT	47	Continuous mid-dose monophasic OC (EE 35 μg + norethindrone 1 mg)/day (n = 26)	Leuprolide 11.25 mg depot i.m. injections 3 months + NA 5 mg/day per os (n = 21)	48 weeks	No follow-up	Similar pain relief. OC treatment more cost-effective. No significant differences in BDI and ISS scores.
Cheewadhanaraks *et al*., 2012[94]	RCT	84	DMPA 150 mg i.m. injections/3 months (n = 42)	Continuous mid-dose monophasic OC (EE 0.03 mg + gestodene 0.075 mg)/day (n = 42)	24 weeks	No follow-up	Higher dysm scores in the OC group. Similar satisfaction and dropout rates.
Bayoglu Tekin *et al*., 2012[95]	RCT	40	LNG-IUD (*n* = 20)	Goserelin 3.6 mg depot s.c. injections/28 days (*n* = 20)	24 weeks	12 months	Similar pain relief at 1,3 and 6 months follow up; at 1 year follow-up patient treated with GnRHa had lower pain score compared with those treated with LNG-IUD. Higher patient satisfaction rate with GnRHa, More bleeding

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug**	**Comparator**	**Treatment period**	**Follow-up period**	**Outcome**
							with LNG-IUD.
Morelli *et al.,* 2013[96]	Retrospective	92	Continuous low-dose multiphasic OC (dienogest + E2V) /day (*n* = 48)	LNG-IUD (*n* =44)	24 months	No follow-up	Better pain relief in patients treated with OC. Disease recurrence rate was slightly lower in OC group. Higher satisfaction with treatment in LNG-IUD users.
Leone Roberti Maggiore *et al*., 2014[97]	PPT	143	DSG 75 μg/day per os (n = 60)	Vaginal ring (EE 15 μg + etonogestrel 120 μg) (n = 83)	12 months	No follow-up	Higher patient satisfaction with treatment in DSG group. Similar reduction in the volume of rectovaginal nodules. Comparable discontinuation rates.
Morotti *et al*., 2014[98]	PPT	144	DSG 75 μg/day per os (*n* = 62)	Cyclic low-dose monophasic OC (EE 20 μg + DSG 150 μg)/day (*n* = 82)	6 months	No follow-up	Higher satisfaction with treatment in DSG group. Similar pain relief (dysp and CPP). Lower rate of migraine attacks with DSG.
Carr *et al.,* 2014[99]	RCT	252	Elagolix 150 mg/day per os (*n* = 84); Elagolix 75 mg/twice a day (*n* = 84)	DMPA 104 mg s.c. injections/3 months (*n* = 84)	24 weeks	24 weeks	Minimal impact on BMD and similar pain relief in all study groups. Comparable improvements in QoL. More bleeding with DMPA. Rapid return to menses with Elagolix, delayed with DMPA after treatment discontinuation.

Source	Study design	Patients enrolled (*n*)	Study drug	Comparator	Treatment period	Follow-up period	Outcome
Granese *et al*., 2015[100]	RCT	78	Continuous low-dose multiphasic OC (dienogest + E2V)/die (*n* = 48)	Leuprolide 3.75 mg depot i.m. injections/30 days for 6 months (*n* = 39)	6-9 months	9 months	Similar pain relief. Comparable recurrence rates. Equal satisfaction with treatment.
Oh *et al*., 2015[101]	Retrospective	218	Dienogest 2 mg/day per os (n = 98)	MPA 30-60 mg/day per os (n = 120)	6 months	No follow-up	Higher pain relief with DNG. More bleeding, alopecia, and headache with DNG. More weight gain, depression and breast tenderness with MPA.
Takaesu *et al*., 2016[102]	RCT	111	Dienogest 2 mg/day per os (*n* = 56)	Goserelin 1.8 mg depot s.c. injections/28 days (*n* = 55)	24 weeks	24 months	No difference in post-operative endometriosis recurrence rate. Similar pain relief, but fewer side effects with dienogest.
Vercellini *et al*., 2016[16]	Before-after study	90	Dienogest 2 mg/day per os (*n* = 90)	NETA 2.5 mg/day per os (*n* = 90)	6 months	No follow-up	Similar satisfaction with treatment, frequency of irregular bleeding and pain relief. Comparable improvements in QoL and sexual functioning. Better tolerability with dienogest. Higher discontinuation rate with dienogest (owing to drug cost)

Source	Study design	Patients enrolled (*n*)	Study drug	Comparator	Treatment period	Follow-up period	Outcome
Lee *et al*. 2016[103]	RCT	64	Dienogest 2 mg/day per os (*n* = 36)	Leuprorelin acetate 3.75 mg s.c. injections/28 days + NETA 0.5 mg/day or estradiol 1 mg/day per os (*n* = 28)	6 months	No follow-up	Similar pain relief. Comparable QoL improvements. Similar lumbar spine BMD loss in both groups (-2.5% for GnRHa plus add-back therapy and -2.3% with DNG)

BDI, Beck Depression Inventory; BMD, bone mineral density; CPP, noncyclic chronic pelvic pain; CRP, C-reactive protein; DMPA, depot medroxyprogesterone acetate; DSG, desogestrel; Dysm, dysmenorrhea; Dysp, dyspareunia; EE, ethinyl-estradiol; E2V, estradiol valerate; HDL, high-density lipoprotein cholesterol; i.n., intranasally; ISS, Index of Sexual Satisfaction; LDL, low-density lipoprotein cholesterol; LNG-IUD, levonorgestrel-releasing intrauterine device; MPA, medroxyprogesterone acetate; NA, norethindrone acetate; NETA, norethisterone acetate; OC, oral contraceptive; PPT, patient preference trial; QoL, quality of life; RCT, randomized controlled trial; VCAM, vascular cell adhesion molecule

1761 Table 2. Studies evaluating surgical complications after colorectal surgery for deep infiltrating endometriosis (literature data, 2010-2017).

Source, year	**No. of patients enrolled**	**Surgical approach**	**Conversion to LPT**	**Recurrence rates for follow-up periods of 2-5 years**	**Total No. complications**	**Gastrointestinal complications**	**Genitourinary complications**	**Late bladder and rectal nerve dysfunctions**
Fanfani *et al.*, 2010[125]	136 (discoid rectosigmoid resection *n* = 48; segmental resection *n* = 88)	LPS	0	13 (9.5%) (discoid rectosigmoid resection *n* = 5; segmental resection *n* = 8)	61 (44.9%) (discoid rectosigmoid resection *n* = 15; segmental resection *n* = 46)	6 (4.4%) (rectovaginal fistula *n* = 4; bowel perforation *n* = 1; suture leakage *n* = 1)	2 (1.5%) (vesicovaginal fistula *n* = 1; ureteral fistula *n* = 1)	18 (13.2%) (urinary retention after 30 days *n* = 13; constipation after 30 days *n* = 5)
Kossi *et al.*, 2010[126]	31 (segmental resection)	LPS	0	NR	7 (22.6%)	2 (6.5%) (rectovaginal fistula *n* = 1; suture leakage *n* = 1)	0	NR
Ruffo *et al.*, 2010[127]	436 segmental resection)	LPS	14 (3.2%)	NR	107 (24.5%)	23 (5.3%) (rectovaginal fistula *n* = 14; anastomotic fistula *n* = 5; rectal fistula *n* = 2; bowel perforation *n* = 2)	6 (1.4%) (urethral fistula *n* = 4; vesical fistula *n* = 1; vesicovaginal fistula *n* = 1)	49 (11.2%) (urinary retention after 30 days *n* = 34; constipation after 30 days *n* = 15)
Maytham *et al.*, 2010[128]	54 (segmental resection *n* = 27; rectal	LPS	2 (3.7%)	NR	9 (16.6%)	5 (9.2%) (anastomotic dehiscence *n* = 3;	2 (3.7%) (ureteral lesion *n* = 2)	NR

Source, year	No. of patients enrolled	Surgical approach	Conversion to LPT	Recurrence rates for follow-up periods of 2-5 years	Total No. complications	Gastrointestinal complications	Genitourinary complications	Late bladder and rectal nerve dysfunctions
	shave *n* = 20; disc excision *n* = 7)					small bowel section *n* = 1; postoperative ileus)		
Stepniewska *et al*., 2010[129]	60 (segmental resection)	LPS	NR	NR	26 (43.3%)	3 (5%) (anastomotic fistula *n* = 2; bowel occlusion *n* = 1)	2 (3.3%) (bladder lesion *n* = 1; ureteral lesion *n* = 1)	4 (6.6%) (urinary retention after 30 days *n* = 3; constipation after 30 days *n* = 1)
Dousset *et al.,* 2010[130]	100 (segmental resection)	LPT	--	2 (2%)	16 (16%)	6 (6%) (rectovaginal fistula *n* = 4; anastomotic leakage *n* = 2)	2 (2%) (ureteral lesion *n* = 2%)	11 (11%) (partial urinary retention after 30 days *n* = 11)
Donnez *et al*., 2010[131]	500 (shaving technique)	LPS	0	39 (7.8%)	16 (3.2%)	7 (1.4%) (rectal perforation)	4 (0.8%) (ureteral lesion)	4 (0.8%) (urinary retention)
Kavallaris *et al*., 2011[132]	55 (segmental resection)	LPS + vaginal	Not specified	3 (10%)	18 (32.7%)	3 (5.5%) (anastomotic leakage *n* = 2; bowel lesion *n* = 1)	--	1 (1.8%) (urinary retention after 3 months)
Kondo *et al*., 2011[133]	568 (rectal surgery in	LPS (*n* = 560),	13 (2.3%)	NR	90 (15.8%) [rectal surgery 54	12 (2.1%) (rectovaginal	9 (1.6%) (ureteral fistula *n* = 6;	3 (0.5%) (urinary retention)

Source, year	No. of patients enrolled	Surgical approach	Conversion to LPT	Recurrence rates for follow-up periods of 2-5 years	Total No. complications	Gastrointestinal complications	Genitourinary complications	Late bladder and rectal nerve dysfunctions
	225[a])	LPT (*n* = 8)			(22.6%)]	fistula *n* = 9; small bowel lesion *n* = 2; stenosis of the protective ileostomy n = 1)	ureteral stenosis *n* = 2; vesicovaginal fistula n = 1)	
Lim *et al*., 2011[134]	18	RALARH (*n* = 8), ELLARH (*n* = 10)	1	NR	4 (22.2%)	2 (11.1%) rectovaginal fistula in ELLARH group	0	0
Wolthuis *et al*, 2011[135]	42 (conventional sigmoid resection *n* = 21; laparoscopic sigmoid resection with transrectal specimen extraction *n* = 21)	LPS	0	NR	6 (14.3%) (UTI *n* = 4; pelvic hematoma *n* = 1; urinary retention that resolved in < 30 days *n* = 1)	0	0	0

Source, year	No. of patients enrolled	Surgical approach	Conversion to LPT	Recurrence rates for follow-up periods of 2-5 years	Total No. complications	Gastrointestinal complications	Genitourinary complications	Late bladder and rectal nerve dysfunctions
Meuleman *et al.*, 2011[136]	45 (CO_2 laser and segmental resection)	LPS		5[b] (11%)	2 (4.4%)	0	0	1 (2.2%) (urinary retention)
Moawad *et al*., 2011[137]	22 (LAR *n* = 14; ADR *n* = 8)	LPS	0	NR	4[c] (18.1%)	3 (13.6%) (anastomotic stricture)	0	NA
Bridoux *et al*., 2012[138]	6	LPS + transanal	0		2 (33%) (persistent dysuria *n* = 2)	0	0	1 (1.6%) (constipation after 30 days)
Ruffo *et al*., 2012[139]	750 (mid/low rectum resection)	LPS	12 (1.6%)	NR	67 (8.9%)	48 (6.4%) (anastomotic leakage *n* = 21; rectovaginal fistula *n* = 16; bowel obstruction *n* = 7; rectal bleeding *n* = 4)	5 (0.7%) (ureteral fistula *n* = 3; vesicovaginal fistula *n* = 2)	NA
Jelenc *et al*., 2012[140]	56 (segmental resection *n* = 52; disc	LPS	3 (5.4%)	NR	6[d] (10.7%)	5 (8.9%) (anastomotic leakage *n* = 3; rectovaginal	0	0

Source, year	No. of patients enrolled	Surgical approach	Conversion to LPT	Recurrence rates for follow-up periods of 2-5 years	Total No. complications	Gastrointestinal complications	Genitourinary complications	Late bladder and rectal nerve dysfunctions
	excision *n* = 4)					fistula *n* = 2)		
Ercoli et al., 2012[141]	22 (segmental resection *n* = 12; shaving technique *n* = 10)	RAL	0	NR	1 (4.5%)	1 (4.5%) (small bowel occlusion)	0	0
Ceccaroni *et al.*, 2012[142]	134[e] (classical segmental resection *n* = 65; nerve-sparing technique *n* = 61)	LPS	8 (6%)	NR	24 (17.9%)	7 (5.5%) (bowel fistula *n* = 7)	6 (4.8%) (ureteral fistula *n* = 3; bladder fistula *n* = 3)	11 (8.7%) urinary retention and/or incontinence for more than 2 years (classical segmental resection *n* = 10; nerve-sparing technique *n* = 1)
Roman *et al.*, 2013[143]	75 (shaving and disc excision *n* = 51; radical approach *n* = 24)	LPS (*n* = 67), LPT (*n* = 8)	6 (8.9%)	2 (2.7%)	20 (26.6%)	2 (2.7%) (rectal fistula)	1 (1.3%) (ureteral fistula)	7 (9.3%) (urinary retention after 30 days *n* = 4; somatic motor nerve injuries *n* = 3)

Source, year	No. of patients enrolled	Surgical approach	Conversion to LPT	Recurrence rates for follow-up periods of 2-5 years	Total No. complications	Gastrointestinal complications	Genitourinary complications	Late bladder and rectal nerve dysfunctions
Neme *et al.*, 2013[144]	10 (segmental resection)	RAL	0	NR	0	0	0	0
Meuleman *et al.*, 2014[145]	203 (CO_2 laser without bowel resection *n* = 127; CO_2 laser with bowel resection *n* = 76)	LPS (*n* = 192), LPS + LPT (*n* = 7), LPT (*n* = 4)	2 (1.0%)	10 (5%) (CO_2 laser without bowel resection group *n* = 8; CO_2 laser with bowel resection group *n* = 2)	13 (6.4%)	2 (2.6%) (anastomotic leakage *n* = 1; rectovaginal fistula *n* = 1)	4 (2%) (bladder atomy *n* =2; bladder leakage *n* = 2)	0
Cassini *et al.*, 2014[146]	19 (segmental resection)	RAL	0	NR	2 (10.5%)	2 (10.5%) (rectovaginal fistula)	0	0
Siesto *et al.*, 2014[147]	43	RAL	0	NR	2 (4.6%)	1 (2.3%) (anastomotic leakage)	0	0
Oliveira et al., 2014[148]	11	DCS	0	NR	2 (18.1%)	0	1 (0.9%) (temporary urinary retention)	0

Source, year	No. of patients enrolled	Surgical approach	Conversion to LPT	Recurrence rates for follow-up periods of 2-5 years	Total No. complications	Gastrointestinal complications	Genitourinary complications	Late bladder and rectal nerve dysfunctions
Angioli *et al*., 2014[149]	34 (nodule excision)	LPS + vaginal	0	0	8 (23.5%)	1 (2.9%) (bowel obstruction)	1 (2.9%) (ureteral stenosis)	0
Collinet *et al*., 2014[150]	88[f]	RAL	1 (1.1%)	NR	4 (4.5%)	2 (2.3%) (bowel injury)	0	0
Bachmann *et al*., 2014[151]	35 (segmental resection, disc excision)	LPS (*n* = 33), LPT (*n* = 2)	3 (9.1%)	NR	2 (5.7%)	2 (5.7%) (rectovaginal fistula *n* = 1; anastomotic leakage *n* = 1)	0	0
Akladios *et al*., 2014[152]	41 (standard segmental resection *n* = 32; NOSE technique *n* = 9)	LPS	0	NR	8 (19.5)	4 (9.8%) (rectovaginal fistula n =1; vaginal dehiscence n =1; anastomotic leakage n =1; ileostomy intolerance n = 1)	1 (2.4%) (ureterovaginal fistula n = 1)	0

Source, year	No. of patients enrolled	Surgical approach	Conversion to LPT	Recurrence rates for follow-up periods of 2-5 years	Total No. complications	Gastrointestinal complications	Genitourinary complications	Late bladder and rectal nerve dysfunctions
English *et al.*, 2014[153]	74 (LSARR)	LPS, LPT	NR	NR	11 (14.9%)	8 (6.7%) (anastomotic leakage *n* = 4; fistula *n* = 4)	3 (4.1%) (ureteral injury)	0
Tarjanne *et al.*, 2015[154]	164 (segmental resection)	LPS (*n* = 112); LPT (*n* = 52)	24 (21.4%)	11 (6.7%)	19[g] (11.6%) (LPS *n* = 13; LPT *n* = 6)	8 (4.9%) (anastomotic leakage *n* = 4; rectovaginal fistula *n* = 3; rectal perforation *n* =1)	8 (4.9%) (ureteral fistula *n* = 3; ureteral injury *n* = 4; vesicovaginal fistula *n* = 1)	1 (0.6%) (urinary retention after 30 days)
Pellegrino *et al.*, 2015[155]	25 (shaving technique)	RAL	0	3 (12%)	0	0	0	0
Roman *et al.*, 2015[156]	50 (disc excision)	LPS[h] + transanal	4 (8%)	NR	21 (42%)	3 (6%) (rectovaginal fistula *n* = 2; rectorrhage *n* = 1)	1 (2%) (bladder fistula)	8 (16%) (urinary retention after 30 days)
Cao *et al.*, 2015[157]	55[i]	LPS (*n* = 47); LPT (*n* = 3); transvaginal (*n* = 1)	4 (8.5%)	NR	5 (9%)	1 (1.8%) (anastomotic leakage)	1 (1.8%) (ureter leakage)	0

Source, year	No. of patients enrolled	Surgical approach	Conversion to LPT	Recurrence rates for follow-up periods of 2-5 years	Total No. complications	Gastrointestinal complications	Genitourinary complications	Late bladder and rectal nerve dysfunctions
Malzoni *et al.*, 2016[158]	248 (segmental resection)	LPS	0	NR	20 (8.1%)	18 (7.2%) (rectorrhage *n* = 8; rectovaginal fistula *n* = 6; anastomosis leakage *n* = 4;	0	0
Morelli *et al.*, 2016[159]	10 (segmental resection)	RAL	0	NR	0	0	0	0
De La Hera-Lazaro *et al.*, 2016[160]	46	LPS (*n* = 38), LPT (*n* = 8)	NR	NR	14 (30.4%)	8 (17.4%) (rectovaginal fistula *n* = 4; intestinal anastomotic stenosis *n* = 4)	0	0
Abo *et al.*, 2016[161]	35 (32 with rectal involvement)[l]	RAL	0	NR	3 (8.6%)	0	1 (2.9%) (ureteral necrosis and fistula)	0
Roman *et al.*, 2016[162]	71 (shaving technique *n* = 46; segmental resection *n* = 25)	LPS (*n* = 53); LPT (*n* = 9); LPS + LPT (*n* = 9)	NR	4 (5.6%) (all in the shaving group)	45 (63.3%)	6 (8.4%) (rectal fistula *n* = 1; anastomosis stenosis *n* = 2; rectorrhage *n* =3)	3 (4.2%) (ureteral leakage *n* = 1; bladder leakage *n* = 1; ureter stenosis *n* = 1)	3 (4.2%) (urinary retention after 30 days *n* = 1; somatic motor nerve injury *n* = 2)
Vlek *et al.*,	11	LPS-LAR (*n* = 5),	0	NR	2 (18.1%)[c]	1 (9.1%) (anastomotic	0	0

Source, year	No. of patients enrolled	Surgical approach	Conversion to LPT	Recurrence rates for follow-up periods of 2-5 years	Total No. complications	Gastrointestinal complications	Genitourinary complications	Late bladder and rectal nerve dysfunctions
2016[163]		LPT-LAR (*n* = 1), TAMIS (*n* = 5)				leakage)		
Roman *et al*., 2017[164]	111 (disc excision)	LPS-transanal (*n* = 87), vaginal-LPS-transanal (*n* =20); RAL-transanal (n = 2), LPS+LPT-transanal (*n* = 2)	10 (9%)	2 (1.8%)	31 (28%)	12 (10.8%) (rectovaginal fistula *n* = 8; rectorrhage *n* = 3; bowel occlusion *n* = 1; colorectal anastomosis stenosis *n* = 1)	0	10 (9%) (urinary retention after 3 weeks)
Ercoli *et al*., 2017[165]	31 (rectal nodulectomy *n* = 30; segmental resection *n* = 1)	LAR	0	3 (9.6%)	3 (9.6%) (hemoperitoneum *n* = 1; periumbilical hematoma *n* = 1; paralytic ileus *n* = 1)	0	0	0

Source, year	No. of patients enrolled	Surgical approach	Conversion to LPT	Recurrence rates for follow-up periods of 2-5 years	Total No. complications	Gastrointestinal complications	Genitourinary complications	Late bladder and rectal nerve dysfunctions
FRIENDS group, 2017[166]	1135 (shaving *n* = 546; segmental resection n = 532; disc excision *n* = 83)	LPS (*n* = 933), RAL (*n* = 110); LPT (*n* = 92)	NR	NR	223 (19.6%)	40 (3.5%) (rectovaginal fistula *n* = 31; anastomosis leakage *n* = 9)	8 (0.7%) (ureter fistula)	98 (8.6%) (bladder atony after 7 days)

[a] shaving technique *n* = 183; segmental resection *n* = 25; excision and suture *n* = 17
[b] histologically proven recurrent endometriosis was observed in two patients (4.4%)
[c] all in LAR group
[d] only early post-operative complications were included
[e] only patients who underwent LPS were considered for analysis (*n* = 126)
[f] only patients with rectal involvement were considered
[g] major complications
[h] RAL in one patient
[i] only complete resection were included
[l] shaving technique *n* = 25; segmental resection *n* = 4; disc excision *n* = 3

ADR = anterior discoid resection; DCS = double-circular stapler; ELLARH = exploratory laparotomy low anterior resection with primary sigmoid rectal anastomosis/ureterolysis/hysterectomy with bilateral salpingo-oophorectomy; LAR = low anterior resection; LPS = laparoscopy; LPT = laparotomy; LSARR = limited segmental anterior rectal resection; NOSE = natural orifice specimen extraction; NR = not reported; RAL = robotic assisted laparoscopy; RALARH = robot-assisted low anterior resection with primary sigmoid rectal anastomosis/ureterolysis/hysterectomy with bilateral salpingo-oophorectomy; TAMIS = transanal minimally invasive surgery; UTI = urinary tract infections

Table 3. Foremost fertility-related statements to be considered in the management of women with endometriosis.

Statement	Level of evidence	Main references
Hormonal therapy does not improve natural fertility in women with endometriosis	+ + +	Hughes *et al*., 2007[185]; Duffy *et al*., 2014[186]
Laparoscopic removal of endometriosis stage I-II increases the chance of natural pregnancy but the magnitude of the benefit is modest. Systematic laparoscopy in the fertility work-up of women with unexplained infertility is thus not recommended.	+ + +	Practice Committee of the ASRM, 2012[187]; Dunselman *et al*., 2014[65]; Duffy *et al*., 2014[186]
Laparoscopic excision of ovarian endometriomas (stripping) may enhance fecundity but damages ovarian reserve.	+ +	Seyhan *et al*., 2015[188]; Brink Laursen *et al*., 2017[189]
The specific impact of deep peritoneal lesions on fertility and the role of surgical removal as a fertility-enhancing procedure are controversial.	+ +	Leone Roberti Maggiore *et al*., 2015[183] and 2017[184]; Iversen *et al*., 2017[190]
Repeat surgery to enhance fertility in women with endometriosis is poorly effective	+ +	Vercellini *et al*. 2009[120]; Vercellini *et al.* 2009[191]
Endometriosis is not an indication to intrauterine insemination (IUI): the effectiveness is doubtfull and IUI may increase recurrences.	+	Somigliana *et al*., 2017[182]
Endometriosis is an indication to IVF: chances of success may be lower for advanced cases but remain overall satisfactory.	+ +	Harb *et al*., 2013[192]; CDC 2013[193]; Hamdan *et al*., 2015[194]
Conservative surgery for endometriosis to enhance the effectiveness of IVF is not supported (except when hydrosalpinxes are detected).	+	Johnson *et al*., 2004[195]; Somigliana *et al*., 2017[182]
IVF can be performed in the presence of small endometriomas; it increases some risks, but the magnitude of these effects is modest and the potential benefits of surgery are unproven.	+ +	Somigliana *et al*., 2015[196]
Long-term medical therapy before IVF was reported to increase pregnancy rate, but evidence is insufficient for routine use.	+ +	Sallam *et al*., 2006[197]; Duffy *et al*., 2014[186]
In contrast to IUI, IVF was not shown to increase recurrences or favor progression of endometriosis.	+ +	Benaglia *et al*., 2011[198]; Santulli *et al*., 2016[199]

Level of evidence was judged in a subjective manner based on discussion among the authors and is reported on a 3 points scale.

Whenever possible, most recent and comprehensive reviews were chosen as references.

1780 FIGURE LEGEND

1781 Figure 1: *Upper panel*: two contiguous ovarian endometriomas. The cyst content
1782 displays the typical ground glass aspect. *Lower panel*: a large non-vascularized ipoechogenic
1783 endometriotic nodule located in the Douglas pouch.