TOWARDS COMPREHENSIVE MANAGEMENT OF SYMPTOMATIC ENDOMETRIOSIS: BEYOND THE DICHOTOMY OF MEDICAL VERSUS SURGICAL TREATMENT

Running title:

Medical versus surgical management of endometriosis

Velja Mijatovic, MD, PhD [a] ORCID 0000-0002-0435-9921 mijatovic@amsterdamumc.nl

Paolo Vercellini, MD, PhD [b] ORCID 0000-0003-4195-0996 paolo.vercellini@unimi.it

From [a]Academic Endometriosis Center, Department of Gynaecology & Reproductive Medicine, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands and [b]Department of Clinical Sciences and Community Health, Università degli Studi and Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

Correspondence: Velja Mijatovic, MD PhD
Academic Endometriosis Center, Department of Gynaecology & Reproductive Medicine, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.
Electronic address: mijatovic@amsterdamumc.nl

ABSTRACT

Except when surgery is the only option because of organ damage, the presence of suspicious lesions, or the desire to conceive, women with endometriosis-associated pain often face a choice between medical and surgical treatment. In theory, the description of the potential benefits and potential harms of the two alternatives should be standardised, unbiased, and based on strong evidence, enabling the patient to make an informed decision. However, doctor's opinion, intellectual competing interests, local availability of specific services and (mis)information obtained from social media and online support groups, can influence the type of advice given and affect patients' choices. This is compounded by the paucity of robust data from randomised, controlled trials, and the anxiety of distressed women who are eager to do anything to alleviate their disabling symptoms. Vulnerable patients are more likely to accept the suggestions of their healthcare provider, which can lead to unbalanced and physician-centred decisions, whether in favour of either medical or surgical treatment. In general treatments should be symptom-oriented rather than lesion-oriented. Both medical and surgical modalities appear to be similarly effective in reducing pain symptoms, with medications generally more successful for severe dysmenorrhoea, and surgery more successful for severe deep dyspareunia caused by fibrotic lesions infiltrating the posterior compartment. Estrogen-progestogen combinations and progestogen monotherapies are generally safe and well tolerated, provided there are no major contraindications. About three-quarters of patients with superficial peritoneal and ovarian endometriosis and two-thirds of those with infiltrating fibrotic lesions are ultimately satisfied with their medical treatment although the reminder may experience side effects which may result in non-compliance. Surgery for superficial and ovarian endometriosis is usually safe. When fibrotic infiltrating lesions are present, morbidity varies greatly depending on the skill of the individual surgeon, the need for advanced procedures such as bowel resection and ureteral reimplantation, and the availability of expert colorectal surgeons and urologists working together in a multidisciplinary approach. The generalisability of published results is adequate for medical treatment but very limited for surgery. Moreover, on the

one hand, hormonal drugs induce disease remission but do not cure endometriosis, and symptom relapse is expected when the drugs are discontinued; on the other hand, the same drugs should be used after lesion excision, which also does not cure endometriosis, to prevent an overall cumulative symptom and lesion recurrence rate of 10% per postoperative year. Therefore, the real choice may not be between medical treatment and surgery, but between medical treatment alone and surgery plus postoperative medical treatment. ~~As a rule, treatments should be symptoms-oriented rather than lesion-oriented~~ The experience of pain in women with endometriosis is a complex phenomenon that is not exclusively based on nociception, although the role of peripheral and central sensitization is not fully understood. In addition, trauma, and especially sexual trauma, and pelvic floor disorders can cause or contribute to symptoms in many individuals with chronic pelvic pain, and healthcare providers should never take for granted that diagnosed or suspected endometriosis is always the real or the sole origin of the referred complaints. Alternative treatment modalities are available that can help address most of the additional causes contributing to symptoms. Pain management in women with endometriosis may be more than a choice between medical and surgical treatment and may require comprehensive care by a multidisciplinary team including psychologists, sexologists, physiotherapists, dieticians, and pain therapists. An often missing factor in successful treatment is empathy on the part of healthcare providers. Being heard and understood, receiving simple and clear explanations and honest communication about uncertainties, being invited to share medical decisions after receiving detailed and impartial information, and being reassured that a team member will be available should a major problem arise, can greatly increase trust in doctors and transform a lonely and frustrating experience into a guided and supported journey, during which coping with this chronic disease is gradually learned and eventually accepted. Within this broader scenario, patient-centred medicine is the priority, and whether or when to resort to surgery or choose the medical option remains the prerogative of each individual woman. This paper is intended as a rebuttal to the debate article by Canis and Guo (2023).

KEYWORDS: endometriosis; pelvic pain; dysmenorrhoea; dyspareunia; medical treatment; surgery; central sensitisation; oral contraceptive; progestogens; GnRH agonists; GnRH antagonists; infertility; self-management.

MEDICAL OR SURGICAL TREATMENT FOR ENDOMETRIOSIS-ASSOCIATED PAIN: ON EMPIRICAL VERSUS DOGMATIC MEDICINE AND THE POLARISATION OF THE SCIENTIFIC COMMUNITY

In recent decades, there has been a surprising lack of high-quality comparative effectiveness research on treatments for symptomatic endometriosis. Unfortunately, this has mirrored the paucity of useful new knowledge about the pathogenesis of the disease. In general, the lack of robust translational and clinical research is conducive to the flourishing of strong personal opinions about the best management of chronic diseases. In the field of endometriosis, this has led to the elaboration of divergent and often opposing views by several experts on the safety, efficacy, and overall role of medical and surgical treatments for women with endometriosis in different clinical conditions (Pellicer and Zupi, 2016; Vercellini *et al*., 2018a). Thus, polarisation also appears to be flourishing in the endometriosis scientific community. An active role for medical journal editors to mitigate the potential effects of polarisation has been promoted (Plough and Holm 2015). In this regard, Earp (2015) suggested that whenever an editor perceives polarisation in a submitted manuscript, one of the possible options should be to solicit a commentary or response from researchers on the 'other side'.

Here, we present counterarguments to the debate article by Canis and Guo (2023), who, in an extreme and simplified synthesis, appear to favour physical removal of endometriotic lesions as the preferred upfront approach for symptomatic patients, with the role of medical treatment limited to post-operative maintenance of surgical results by preventing recurrence. The authors claim that, despite the proven benefits, many patients avoid surgery for fear of complications, and suggest that the risk of harm from surgery is exaggerated by gynaecologists who are not sufficiently surgically skilled to deal with the technically demanding conditions typical of severe, infiltrating fibrotic endometriosis (Canis *et al*., 2018). They also suggest that advice may sometimes be based on data from series of centres with suboptimal surgical performance. However, hormonal treatments may

also be refused or discontinued precisely because of fears of side effects and health concerns (Both *et al*., 2019), and it cannot be excluded that advocates of surgery may exaggerate the potential harms of pharmacological therapies for endometriosis and thus unduly influence doctors' and patients' choices. Overall, there is limited information available in order to understand why patients ultimately choose medical or surgical treatment (Leonardi *et al.,* 2020a), and the impact of clinician counselling, although likely, cannot currently be quantified. However, when complete, unbiased information is adequately provided and the alternative between medical therapy and surgery is presented equally, the potential harms of procedures for bowel infiltrating endometriosis have been found to be a determinant of patient preference (Metzemaekers *et al*., 2022).

It should be emphasised that medical treatment is not an option in several circumstances, including but not limited to the following: i) presence of obstructive uropathy; ii) bowel endometriosis associated with subocclusive symptoms; iii) ovarian cysts with dubious ultrasound (US) appearance; iv) presence of large endometriomas (> 5 cm), especially in women over 40 years of age; v) women seeking pregnancy ; vi) women refusing hormonal therapies.

As a premise, it must be remembered that endometriosis is not the unique cause of chronic pelvic pain (Lamvu *et al*., 2021; Yosef *et al*., 2016), and that other determinants, such as trauma and especially sexual trauma (Hillcoat *et al*., 2023; Panisch and Tam, 2020), and pelvic floor disorders (Gyang et al., 2013) may act either independent of endometriosis (Bourdon *et al*., 2023; Lamvu *et al*., 2018) or in combination with endometriosis (Harris *et al*., 2018; Liebermann *et al*., 2018; Aredo *et al*., 2017) in the generation of symptoms. Avoiding tunnel vision is of paramount importance to prevent both, using ineffective hormonal treatments (Cetera *et al*., 2023; Till *et al*., 2023), and undertaking needless and potentially risky surgical procedures (Mowers *et al*., 2016), if endometriosis, even when present, is not the real or exclusive source of pain symptoms.

THE EFFECTIVENESS OF SURGERY AND HORMONAL TREATMENTS ON PAIN

Canis and Guo 92023) support the idea that surgically removing instead of pharmacologically suppressing endometriotic lesions is in the best patient interest. Unfortunately, data from randomised controlled trials (RCTs) comparing hormone therapy and surgery for different pain symptoms are not available. In any case, treatments should be symptom-oriented rather than lesion-oriented. This is important because different treatments may provide different levels of relief depending on main pain complaint. For example, the most effective treatment for severe dysmenorrhoea appears to be menstrual suppression through continuous use of combined oral contraceptives (COCs) or progestogens. On the other hand, when severe dyspareunia limiting sexual function is associated with the presence of infiltrating and fibrotic lesions of the pouch of Douglas, the uterosacral ligaments and the posterior vaginal fornix, radical surgical excision is a reasonable option.

Some concepts should be clarified to optimize the counseling process. As Canis and Guo themselves point out (2023), hormonal therapies control but do not eliminate ectopic endometrial foci, regardless of the magnitude of the effect. Therefore, at least from the time of non-surgical diagnosis to the time of trying to conceive, a pharmacological choice may imply several years of treatment. For a young woman, this can easily mean a decade of ovarian suppression. It makes no clinical sense to plan a few months of treatment in the expectation that symptom relief will continue despite discontinuation. Endometriosis is a chronic inflammatory disease and as such, if drugs are chosen over surgery, they should be continued indefinitely, no different from what is usually expected and done with any other chronic inflammatory disease. The reappearance of pain on discontinuation of medications is predictable and is not evidence of failure of medical treatment, simply because medications do not eliminate endometriosis, which immediately resumes its metabolic activity once ovarian function and oestradiol synthesis have resumed. The effect of hormone therapy is to induce disease remission, and relapse of symptoms is the rule when medications are stopped for any reason.

Jensen *et al.* (2018), based on the results of a systematic review of the effects of COCs in women with symptomatic endometriosis, concluded. "*combined and progestin-only hormonal contraception present affordable and effective treatment options for women with endometriosis. Our review supports that these methods reduce menstrual and nonmenstrual pain and improve quality of life. Continuous use may result in amenorrhea and further improve outcomes compared with cyclic use. Overall, the available literature is limited, but a consistency of effect is observed supporting these recommendations*".

Grandi *et al*. (2019) confirmed that COCs and progestogens are effective in relieving endometriosis-associated menstrual and pelvic pain and dyspareunia, thereby improving quality of life (QoL). As expected, Muzii *et al*. (2016) found that COCs used continuously were more effective in reducing postoperative dysmenorrhoea recurrence rates than COCs used cyclically (RR, 0.24; 95% CI, 0.06-0.91). The between-group differences observed for dyspareunia and nonmenstrual pain recurrence rates were not statistically significant.

According to the results of the systematic review by Mitchell *et al*. (2022), progestogens significantly improved endometriosis-associated pain symptoms during 6 to 12-months of treatment without substantial differences between progestogen types. The median discontinuation rate due to side effects was 0.3% (range, 0% to 37%), with only mild events reported. These findings are consistent with the position of Canis and Guo (2023), who affirm that progestogens are poorly tolerated also because of an increased risk of depression and significant weight gain. Canis and Guo (2023) maintain that "*there is a tendency to one-size-fits-all treating [medically] all patients with endometriosis as if they were made from the same mould irrespective of age or their pain individually*". However, different medical interventions have been suggested, distinguishing between different pain symptoms and different disease forms, and a three-tiered risk stratification system and a stepwise pharmacological approach have been proposed for individualised treatment (Vercellini *et al*, 2016).Indeed, three-quarters of women with superficial peritoneal and ovarian endometriosis and two-thirds of those with infiltrating, fibrotic lesions are satisfied with their

185 medical treatment (Vercellini *et al*., 2017 and 2018c), including patients with non-subocclusive
186 colorectal disease (Vercellini *et al*., 2018b and 2021).

187 When considering the use of hormonal treatments for endometriosis, the type and
188 completeness of information provided regarding probable side effects and how to deal with them is
189 crucial to ensure optimal acceptability, and thus effectiveness. In fact, in a cross-sectional study
190 among more than 3,000 endometriosis patients conducted via the most popular social media
191 channels, potential side effects affecting mental health was the most important reason for refusing
192 endocrine therapies. At the same time, a considerable proportion of subjects reported having limited
193 knowledge about these medications and reputed social media the most useful source of information
194 (Thurnherr *et al*., 2023). These findings further emphasise the importance of adequate counselling
195 to prevent misunderstanding and potentially increase adherence. Obviously, the same apply to
196 surgical treatment.

197 Canis and Guo (2023) maintain that "the effectiveness of surgery in the treatment of pain
198 has been demonstrated in several double-blinded, randomised clinical trials", but cite two old small
199 studies only. Sutton et al. (1994) recruited 63 symptomatic patients with minimal to moderate
200 endometriosis and observed pain improvement or resolution at 6-month follow-up in less than two-
201 thirds of subjects allocated to laparoscopic laser ablation of lesions and uterosacral nerves, and in
202 almost one-fourth of those allocated to diagnostic laparoscopy. Abbott et al. (2004) randomised a
203 selected group of 39 patients with minimal to severe endometriosis to lesion excision or diagnostic-
204 only laparoscopy. Six months after the procedure, symptoms improved in four-fifths of the
205 participants in the surgical treatment group and in almost one-third of those in the no-treatment
206 group. Although we agree that conducting such type of trials is challenging, we also consider that
207 more high-quality data are needed to define the effect of surgery on endometriosis-associated pain
208 in different clinical conditions. Leonardi *et al*. (2020a) reviewed the published controlled trials on
209 the effectiveness of surgery for endometriosis-associated pain and found a significant overall
210 difference between operative and diagnostic laparoscopy (RR, 2.65; 95% CI, 1.61–4.34). However,

the specific effect on dysmenorrhoea, dyspareunia, and dyschesia was inconsistent among the considered studies, and there was limited data on the long-term effect of surgery *per se*. When surgery is combined with postoperative medical treatment, it is not possible to distinguish between the effects of the two interventions separately. There was not enough evidence to assess the impact on disease progression. This does not rule out a benefit from surgery.

Destruction of superficial peritoneal endometriosis in women with chronic pelvic pain has been criticised and its effect questioned (Horne *et al*. 2019), and multicentre RCTs (ESPriT1 and ESPriT2) are underway to assess the clinical and cost-effectiveness of this treatment modality (Whitaker *et al*., 2021; Mackenzie *et al*., 2023).

In women with ovarian and infiltrating fibrotic endometriosis, numerous uncontrolled, mostly retrospective studies report favourable outcomes of surgery for all types of pain, in all types of advanced anatomic conditions, and with all types of instrumentation, including laser-and robot assisted surgery. However, without the support of randomized data , it is impossible to assess whether drugs or surgery should be chosen for pain relief in different clinical conditions. Although the effectiveness of correctly performed surgery for pain relief in women with moderate to severe endometriosis is evident in everyday practice, it cannot be precisely quantified and compared with medical therapies because of major biases inherent in the available studies, including a very high likelihood of publication bias (who is willing to submit bad results that compare unfavourably with the available evidence?). Overall, almost a third of patients who undergo surgery for endometriosis-associated pain do not benefit from the procedure, and no predictors of response to treatment have been identified (Ball *et al*., 2021). It is also unclear what proportion of patients experience only partial or temporary pain relief.

It cannot be excluded that most of the available results, both medical and surgical, are influenced by patient self-selection and therefore may not be generalisable to women who have not chosen their preferred treatment modality. Currently, women who have already been diagnosed with endometriosis tend to seek information on the internet and from peers through patient

organisations. As a result, many patients self-select their favoured referral centre based on their priorities, preferences, or previous experience. Women who are dissatisfied with medical therapies because they are ineffective or intolerable or who are unwilling to take hormones for long periods of time, tend to choose centres of expertise known for their excellent surgical profile, whereas those who prefer to avoid surgery or who have already undergone unsuccessful procedures tend to choose centres known for their extensive experience with pharmacological therapies. From a methodological point of view, when assessing this type of evidence, it is important to remember that the reported findings apply only to those women who have deliberately chosen their preferred treatment modality. However, many women do not have the opportunity to self-select their referral center and are designated to consult community gynaecologists without specific expertise. Also- there are many centres that have established a good balance between medical and surgical therapy for endometriosis.

THE SAFETY OF SURGERY IN WOMEN WITH SUPERFICIAL PERITONEAL IMPLANTS, OVARIAN ENDOMETRIOMAS, AND INFILTRATING FIBROTIC ENDOMETRIOSIS

Superficial peritoneal endometriosis is a surgically low-risk condition that can be treated by most gynaecologists. Ovarian endometriomas could be considered moderate-risk lesions that can be safely managed outside centres of excellence, provided the surgeon is aware of the potential damage to ovarian reserve and applies microsurgical principles (Canis *et al*., 2003; Matsuzaki *et al*., 2009; Bourdel *et al*., 2020). Infiltrating fibrotic lesions may instead be classified as high-risk lesions if the bowel and ureters are involved and opening of the intestinal lumen is required to achieve radicality (Kondo *et al*., 2011).

According to Canis and Guo (2023), "*the risk of complications from surgery could be exaggerated out of proportion*", and "*the patient's fear of transient colostomy and the surgeon's fear of litigation are likely driving the no surgery decision*". However, Bendifallah *et al*. (2021) reported the results of a systematic review of surgical outcomes of colorectal surgery for endometriosis. The mean

263 complication rate after rectal shaving, disc excision, and segmental resection was 2.2%, 9.7%, and
264 9.9% respectively. Complications included bowel leakage, rectovaginal fistula formation, voiding
265 dysfunction, and anastomotic stenosis. According to the authors, "*colorectal surgery exposes*
266 *patients to a risk of severe complications*". Rectal shaving appears to be less risky but is not feasible
267 in all women with extensive bowel infiltration.

268 IN addition, the results of an exceptionally large series of 1102 women who underwent
269 surgery for infiltrating rectosigmoid endometriosis were published by Roman *et al*. (2020). A total
270 of 23 patients developed a rectovaginal fistula and 14 presented with bowel leakage. Almost half of
271 these women (n = 11) required more than one additional procedure to repair the rectovaginal fistula.
272 The authors concluded that laparoscopic treatment of rectosigmoid endometriosis is associated with
273 a relatively low risk of bowel fistula. Yet, except in the presence of clearly subocclusive lesions,
274 whether a 3.4% risk of bowel fistula is high or low should probably be determined by the woman
275 rather than the physician, especially when conservative alternatives are available (Vercellini *et al*.,
276 2018b and 2021). The same research group published the results of a series of 363 women who
277 underwent concomitant vaginal and rectal excision for rectovaginal endometriotic plaques (Roman
278 *et al*., 2022). A rectovaginal fistula developed in 31 patients (8.5%) regardless of performance of a
279 protective stoma. The risk was more than tripled if the rectal suture was placed within 8 cm of the
280 anal verge.

281 Of relevance, the above percentages were observed when the procedures were performed by
282 unusually talented surgeons with probably the largest experience in bowel surgery for endometriosis
283 in the world. Obviously, these results cannot be generalised, and it cannot be assumed that the
284 technique *per se* is associated with the reported complication rates. Although the complication rate
285 is lower when the digestive and urinary tracts are not involved (Vallee *et al*., 2018), the correct
286 information still is that the above results are to be expected only in the hands of a few super-
287 surgeons and that both efficacy and safety may be substantially different in less favourable
288 circumstances. Contrary to what Canis and Guo (2023) suggest, this is not meant to scare women; it

is honest advice. The patient, not the surgeon, bears the burden of complications. Different women can accept different levels of risk, and they, not the physician, should decide how high to set the bar (Bretthauer and Kalager, 2023).

An international committee with representatives from patient associations and gynaecological scientific societies should develop a list of potential complications, together with percentage probabilities derived from a systematic literature review, for all surgical procedures performed in women with different forms of endometriosis. Such a document should be endorsed by major professional organisations and then published in high-impact journals in the field. This document, which should be used as a reference for all endometriosis patients scheduled for surgery, would overcome incessant discussions, and could prevent medico-legal sequelae. Informing women quantitatively about the possible complications of surgery and their frequency is not optional, as generally it is a state law. Failure to do this violates the principle of patient empowerment.

THE SAFETY AND TOLERABILITY OF LONG-TERM COMBINED OESTROGEN-PROGESTOGEN THERAPY AND PROGESTOGEN MONOTHERAPY

Canis and Guo emphasise the potential harms of hormonal treatments for endometriosis, including the increase in risk of thromboembolism, myocardial infarction, stroke, meningiomas, and malignant transformation of endometriotic lesions (2023). However, combined oral contraceptives and progestogens are safe, provided that guidelines and recommendations on absolute and relative contraindications are followed (Altschuler *et al*., 2015; https://elearning.rcgp.org.uk/mod/page/view.php?id=6961; https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/summary.html; accessed on June 29, 2023). Extremely long-term, large, prospective cohort studies have clearly shown that former COC users are not at increased risk of death from any cause including cancer (Hannaford *et al*. 2010; Vessey *et al*., 2010). Long-term use of COC is associated with dramatic reductions in the risk of ovarian and endometrial cancers that persist for decades after hormone withdrawal. The risk of

colorectal cancer is also reduced (Vessey *et al*., 2013; Iversen *et al*., 2017 and 2018). Thus, ~~even taking into account the modest increase in breast cancer risk,~~ also considering that the risk of breast cancer attributable to COCs is extremely low and rapidly vanishing at discontinuation, their use is associated with a favourable overall oncological balance (Hunter, 2017). After 10 years of COC use, the risk of ovarian cancer in women with endometriosis is lower than that observed in the general female population of corresponding age (Modugno *et al*., 2004). This is particularly important given the increased risk of ovarian cancer associated with endometriosis.

The increased risk of meningioma observed in nomegestrol acetate (NOMAC) users appears to be of uncertain individual clinical significance in young women using a commercially available COC containing E2 valerate 1.5 mg and NOMAC 2.5 mg per tablet, as age is by far the most important risk factor (Vercellini *et al*., 2023a). Recently, the EMA's Pharmacovigilance Risk Assessment Committee reviewed the available data, including post-marketing safety data, and concluded "*that the benefits of medicines containing nomegestrol or chlormadinone outweigh the risks, provided new measures are taken to minimise the risk of meningioma*". On 28 October 2022, the European Commission (EMEA/H/A-31/1510) eventually informed that, "*No new safety concern regarding a risk of meningioma associated with the use of […] low dose (2.5 mg) nomegestrol acetate containing contraceptives could be identified*". (https://www.ema.europa.eu/en/medicines/human/referrals/nomegestrol-chlormadinone; accessed on November 27, 2022). Absolute estimates of attributable risk according to strata of age and duration of use of COCs containing NOMAC have been defined to be used for patient counselling (Vercellini *et al*., 2023a).

Thromboembolic risk should be contextualised considering the baseline risk of the population being studied. Young women with no known additional risk factors, including a positive family history of hereditary thrombophilia, have a very low absolute risk of thromboembolic events, so even a two- or threefold increase in risk may represent a marginal absolute individual risk. In addition, COCs containing natural oestradiol or oestetrol, which have been shown to have a lower

risk of thromboembolic events than those containing oethinyl-oestradiol could be chosen. (Chen *et al.*, 2022; Heikinheimo *et al.*, Klipping *et al*., 2021; 2022; Morimont *et al.*, 2022). To limit both thromboembolic events and stimulation of endometriotic lesions, oestrogen-progestogen combinations with the lowest possible oestrogen content should be preferred (Oedingen *et al*., 2018).

The norelgestromin and oethinyl-oestradiol transdermal contraceptive patch is associated with higher EE serum levels compared with a standard dose COC containing 30 μg EE (Di Meglio *et al*., 2018). Probably, this is the reasons for the frequently reported mastodynia and the increased venous thromboembolic risk in current users compared with other available oestrogen-progestogen contraceptive combinations (Lidegaard *et al*., 2012; Galzote *et al*., 2017; Tepper *et al*., 2017; Heikinheimo *et al*., 2022). Moreover, presumably because of the frequency of detachment, the discontinuation rate of contraceptive transdermal patches has been reported to be high particularly in young individuals, i.e., precisely those patients that may be prone to scarce treatment adherence (Powell, 2017; Lahoti *et al*., 2021).

An increase in venous thromboembolic risk compared with COC users has been observed for contraceptive vaginal ring users also (Lidegaard *et al*., 2012). Use of vaginal rings has been associated with increased vaginal discharge and frequency of vaginitis (Lopez *et al*., 2013). The hypothetical acceptability among non-ring users has been reported to be limited (Ridgeway *et al*., 2022). Moreover, frequent spotting and breakthrough bleeding have been experienced by patients using hormonal rings continuously with the intent of providing amenorrhoea (Vercellini *et al*., 2010). Thus, cost of therapy may increase when newly inserted rings have to be removed to allow a hormone-free interval in case of prolonged uterine bleeding (MacGregor and Guillebaud, 2018).

For the above reasons, transdermal patches and vaginal rings do not seem to qualify as the optimal first-line hormonal treatment modalities for patients with symptomatic endometriosis.

In women with endometriosis COCs are generally used not as a contraceptive, for which there are non-pharmacological alternatives, but rather as an effective therapy for an often disabling

condition, for which the alternative is to use less safe and more costly drugs or surgery. Moreover, patients with endometriosis do not appear to be at increased risk of thromboembolic events (Wiegers *et al*., 2022). Women with endometriosis who smoke should be advised to stop smoking due to their numerous negative health consequences, and this would also allow them to use COCs. In addition, oral progestogen monotherapies do not increase the risk of thromboembolism (Mantha *et al*., 2012).

A decision aid for women with endometriosis, developed by the National Institute for Health and Care Excellence (2017a), is available online (https://www.nice.org.uk/guidance/ng73/resources/patient-decision-aid-hormone-treatment-for-endometriosis-symptoms-what-are-my-options-pdf-4595573197) With this decision aid, patients can better understand the characteristics of different hormone treatments for endometriosis and visually quantify absolute increase in risk of thromboembolism and breast cancer associated with COCs according to duration of use.

Canis and Guo state that the tolerability of COCs and progestogens used continuously is limited also by the risk of insurgence of depressive symptoms, decreased libido, and frequent , unscheduled uterine bleeding. In particular, repetitive bleeding episodes would boost tissue injury and repair processes, perpetuating lesion progression and worsening pain symptoms (2023).

We agree that irregular uterine bleeding is a common complaint of women using COCs or progestogens in continuous mode, but also believe that the frequency and severity of such episodes can be limited. The simplest way to manage these painful and disruptive events is to discontinue hormones for 4 to 7 days and then restart (Vercellini *et al*., 2018c). Informing women about the likelihood of unexpected bleeding and how to manage it is very important to reduce anxiety and ensure adherence. Prescribing a single injection of a depot GnRH agonist before starting progestogen therapy may reduce bleeding episodes, which occur mainly in the first few months of treatment (Kitawaki *et al*., 2011).

Although adverse effects on mood are often cited as a reason for discontinuation of COCs, a causal relationship has not been definitively established, and a large body of data published over the past 30 years supports the notion that most women report unchanged or improved mood (Schaffir et *al*. 2016). It cannot be excluded that a proportion of women experiencing depressive symptoms have underlying mood disorders that may be manifested or exacerbated by COC use (Schaffir *et al*. 2016; Buggio *et al*., 2022). Similar considerations also appear to apply to progestogen monotherapies (Worly *et al*., 2018).

In this regard, the effects of hormonal medications on mood in women with endometriosis seem difficult to interpret, as depressive symptoms are more common in these patients compared to the general female population (Gambadauro *et al*., 2019). In addition, the overall effect of COCs and progestogens on mood should be considered in balance, taking into account the proportion of women who may experience adverse effects, but also those who may experience relief from pre-treatment depression due to poor QoL as a result of the pain relief provided by hormones.

Despite the perception of an adverse influence of COCs and progestogens on sexual function, there is a paucity of robust data from adequately designed trials. A systematic review on this topic included a total of 8,422 women evaluated in 36 studies (Pastor *et al*., 2013). Almost two-thirds (5,358; 64%) reported no change in sexual desire, 1,826 (23%) reported an increase, and 1,238 (15%) reported a decrease. Thus, approximately one in seven women experienced a decrease in libido while using COCs, which may have an impact on health related QoL, especially considering the young age of most endometriosis patients and the negative effect the disease already has on a woman's self-image, self-esteem, and self-confidence. Data from a recent prospective cohort study suggest that progestogens also, when used at high doses to treat symptomatic endometriosis, may impair some aspects of sexual function (pleasure and satisfaction with frequency of intercourse) despite their beneficial effect on deep dyspareunia (Oppenheimer *et al*., 2021).

Finally, according to Canis and Guo (2023), "*extended use of COCs may result in endometrial thinning that is difficult to rectify by estrogen*". However,,hormonal contraception does not adversely affect fertility after discontinuation and does not delay conception (Girum and Wasie, 2018).

PREVENTION OF RECURRENCE OF SYMPTOMS AND LESIONS: THE SURGEON HAS NO CLOTHES

Guo (2009), the reported that the post-operative recurrence rate is estimated to be over 20% at 2-year follow up and between 40% and 50% at 5-year follow-up. This means that the probability of symptom recurrence is approximately 10% per year for the first five years after endometriosis surgery. Thus, Canis and Guo (2023) advocate a combined surgical-medical approach, because "*post-operative hormonal therapy reduces the risk of recurrence and is likely to maintain the systemic effect resulting from surgery*", but detailed quantitative information beyond general statements is needed here.

About 15 years ago, Seracchioli *et al*. (2009), based on an analysis of the available evidence on the preventive effect of postoperative medical treatment, suggested that long-term use of COCs reduces both symptom and lesion recurrence. Twelve years later, Zakhari *et al*. (2021) observed that the use of postoperative medical treatments reduced the risk of lesion and symptom recurrence at 18-month follow-up by almost 60% (RR, 0.41; 95% CI, 0.26 to 0.65). The relative risk point estimates were 0.36 for COCs, 0.21 for the levonorgestrel-releasing IUD (LNG-IUD), 0.17 for progestogens, and 0.62 for GnRH agonists. More recently, Chiu *et al*. (2022) conducted a systematic review and network meta-analysis to assess the effect of different hormonal therapies used for more than 1 year to reduce postoperative endometrioma recurrence. The use of several considered medical interventions, including dienogest, COCs, and GnRH agonists plus COCs, or LNG-IUD, was associated with a risk reduction of between 80% and 90%.

Two recent systematic reviews are available specifically on the effect of postoperative dienogest use. Zakhari *et al*. (2020) observed an incidence of postoperative endometrioma and pain recurrence of 2 per 100 women over a mean follow-up of 29 months in women treated with dienogest compared with 29 per 100 in women managed expectantly over a mean follow-up of 36 months. Muzii *et al*. (2023) confirmed the dramatic reduction in the risk of both lesion and pain recurrence after surgery in dienogest users compared with non-users (OR, 0.14; 95% CI, 0.07 to 0.26). The effect was similar to that of GnRH agonists (OR 0.81; 95% CI, 0.18–3.65), but with a different side-effect profile.

A favourable effect of postoperative LNG-IUD insertion was demonstrated by Song *et al*. (2018). According to their meta-analysis, the risk of endometriosis recurrence was reduced by 60% (RR = 0.40, 95% CI, 0.26-0.64) in users compared with nonusers of the medicated device. The effect was similar to that of post-operative COC use, but satisfaction with treatment was higher with the LNG-IUD.

Finally, the use of postoperative medical therapy in women who do not want to conceive immediately is recommended in the latest version of the ESHRE guideline on endometriosis (Becker *et al*., 2022). Therefore, long-term medical treatment after surgical removal of endometriotic lesions should now be considered an essential part of disease management in all patients who are willing and able to take and tolerate hormones, as failure to do so or to provide adequate information to women means exposing them to an increased risk of re-operation, further damage to the reproductive organs, and a reduced likelihood of achieving pregnancy (Vercellini *et al*., 2009a and 2009b). This has ethical and possibly medical-legal implications.

Therefore, while we agree with Canis and Guo (2023) that surgical treatment should always be followed by suppressive hormone therapy until conception is desired, at the same time we note that the elephant in the room here is that, it is unclear why the use of oestrogen-progestogen combinations or progestogen monotherapies is discouraged as an alternative to surgery, but the use of the same drugs after surgery is recommended . In fact, all the safety and tolerability issues raised

for prolonged medical treatment, including thromboembolic and oncological concerns, apply without difference regardless of the timing or sequence of use.

ALTERNATIVE FOR COLORECTAL SURGERY IN INFERTILITY: IVF AS COMPARATOR

Canis and Guo state that ART is not always an acceptable treatment for endometriosis-associated infertility as an increasing number of women are seeking a more physiological management, i.e., natural conception after fertility-enhancing surgery (2023). Although this may be reasonable, no evidence was provided to demonstrate this trend. Moreover, anatomical-clinical conditions vary widely in infertile endometriosis patients, and the final choice between surgery and ART is also based on trade-offs between potential benefits and potential harms of the two options. In this regard, colorectal endometriosis appears to constitute an exemplary situation.

In general, endometriosis patients with bowel symptoms associated with non-occlusive colorectal endometriosis and no wish to conceive can usually be treated with medical management (Egekvist *et al*, 2017). The indication for colorectal surgery should be based on symptomatology (obstructive bowel complaints, severe pain which is nonresponsive to medical treatment and diminished QoL), supported by findings on abdominal imaging such as nodules larger than 3 cm, multiple nodules, luminal stenosis of the bowel, and more than 50% invasion of the bowel circumference.

However, surgery for deep colorectal endometriosis is usually complex and carries relatively high risks with an overall postoperative complication rate of 18.5% and a mortality rate of 0.03%.(Balla *et al*, 2018).

Limited data are available on the outcomes of colorectal surgery regarding natural conception rates in infertile endometriosis patients, although it is suggested that surgery may increase pregnancy rates in the range from 24% to 50% (Vercellini *et al*, 2012, Cohen *et al*, 2014; Iversen *et al*, 2017). However, these results arise from observational studies lacking control groups and showing considerable clinical heterogeneity. In addition, it is known that results from observational studies, with limited strength of evidence, may overestimate the treatment effect

494 when compared to randomized trials. Moreover, outcomes of complex surgery are operator-
495 dependent and published data are usually more favourable in their outcome than what may be
496 expected in daily practice. Therefore, the reproductive outcomes from observational studies may
497 provide guidance, however, they should be interpreted with caution due to their methodological
498 shortcomings and they should not be generalized as long as we lack randomized studies on
499 colorectal surgery versus no surgery in infertile endometriosis patients (Vercellini *et al*, 2012).
500 As colorectal endometriosis is usually accompanied by advanced intra-abdominal disease
501 resulting in distortion of the pelvic anatomy and tubal dysfunction, it is not surprising that IVF may
502 be considered as first line treatment. Consequently, IVF can be seen as a realistic treatment
503 comparator to surgery as long as colorectal surgery has not proven to substantially improve natural
504 conception. However, randomized trials comparing IVF to surgery are non-existent as are trials that
505 focus on the effect of surgery on the reproductive outcomes of IVF as colorectal surgery is still
506 mainly performed for pain and reduced QoL rather than for treating infertility.
507 When counselling patients for IVF, it should be emphasized that IVF does not increase
508 disease progression and/or recurrence in women with deep endometriosis which is reassuring
509 (Vercellini *et al*, 2018)]. However, at the same time, it should also be pointed out that surgery is not
510 indicated to prevent progression of deep endometriosis or to lower the risk of complications
511 associated with IVF and/or pregnancy as evidence for the effectiveness of prophylactic surgery is
512 absent.
513
514 CENTRAL SENSITISATION: IS SURGERY THE ANSWER?
515 Endometriosis associated pain is considered a form of neuroinflammatory pain which is mediated
516 by inflammatory cytokines that bind to receptors on sensory neurons and cause a wave of signaling
517 kinases which induce the pain signal.
518 However, pain mechanisms in endometriosis should be considered as multifactorial (Coxon
519 *et al*, 2018. Alongside the peripheral pain contribution, it has been increasingly recognized that

central sensitization (CS) may contribute to the perception of endometriosis associated pain. This means that the central nervous system becomes hypersensitive to pain and gets involved in amplification and/or generation of endometriosis-associated pain. Beside this hyperexcitability of the central nervous system, CS may also be accompanied by comorbidities, such as cognitive impairment and mood disorders (As-Sanie *et al*, 2016). In women with endometriosis, CS can cause chronic pelvic pain which is disproportional to the severity of the disease and challenging to treat (Till *et al*., 2023).

In clinical practice the validated Central Sensitization Inventory (CSI) is increasingly used as a questionnaire to assess CS symptom severity and mental health showing a high degree of reliability and internal consistency (Scerbo *et al*, 2018).

According to Canis and Guo (2023), surgical removal of endometriotic lesions reduces not only local, but systemic inflammation also, and improves central sensitization. However, in a recent prospective study using the CSI in a cohort of 239 patients, it was shown that patients with high CSI scores at baseline were associated with persisting pain and persisting high CSI scores at follow-up after surgery. (Orr *et al*, 2023). This means that in patients with high preoperative CSI scores surgery may contribute to the decrease of peripheral pain caused by endometriosis but that the centrally generated pain is likely to persist when compared to those with low CSI scores prior to surgery This is in line with the findings of three recent studies, who showed that the risk of persistent chronic pelvic pain is higher if there is a high degree of CS preoperatively when compared to those with low degrees of CS (Bennet *et al*, 2017; Roh *et al*, 2018; As-Sanie *et al*, 2021).

So, which alternatives to surgery are available in endometriosis patients with CS ? Nerve stimulation techniques appear to be a very promising new modality in treating CS although in endometriosis patients the data are very limited, and more research is needed to establish its clinical relevance (Simpson *et al*, 2022). In endometriosis patients, hormone treatments are recommended

as an option to reduce endometriosis associated pain (Becker *et al*, 2022). In clinical research minor differences are seen between all hormone treatments in their ability to decrease pain.

However, the available evidence in endometriosis patients with CS (defined as CSI > 40) shows in 18% self-reported pain nonresponsive to hormonal therapy in comparison to 6% in women with CSI < 40, which was statistically significant Orr *et al*, 2022). This outcome should be taken with caution as the evidence is limited to one cross sectional study. Nevertheless, this does not disqualify hormone therapy in endometriosis patients with CS as it may still be required for suppression of cyclical worsening of endometriosis pain although its efficacy in women with high CSI should be addressed in future high-quality studies.

An innovative way to treat endometriosis associated pain may be offered by Virtual Reality. In the treatment of acute pain, and in particular procedural pain, Virtual Reality has now proven itself as an effective method of distracting pain. In chronic pain, the applications of Virtual Reality are growing rapidly, and it appears that its effect is mainly based on improving the coping of pain and modifying the emotional response to pain. Recently, a randomized controlled trial showed that the use of a single use 20-minute virtual reality treatment may offer short term pain relief in endometriosis patients experiencing moderate-to-severe pelvic pain when compared to 2D digital control (Merlot *et al*, 2022). If CS can be treated in this way has not been investigated yet.

For now, a multidisciplinary approach is advocated for treatment of CS in which pain education and cognitive behaviour therapy provides learning ways to change maladaptive illness perceptions and to develop better coping skills, even if the actual level of pain stays the same. To treat chronic pain, cognitive behaviour therapy is most often used together with other methods of pain management including pelvic floor physiotherapy, pharmaceutical or interventional treatments. It is important to note that there is no one-size-fits-all approach in treating CS in endometriosis. Treatment will depend on personal preferences and underlying mechanism causing pain in that individual.

SELF-MANAGEMENT BY COMPLEMENTARY TREATMENTS

Medical and/or surgical treatments can be inadequate in the relief of symptoms or may be accompanied with side effects or surgical complications which may adversely impact wellbeing and quality of life of women with endometriosis .

Therefore, there is an increasing interest from both the patient community as well as medical professionals in seeking additional symptom relief or finding other treatment options alongside standard medical care and we agree with Canis and Guo (2023) when they state that alternative therapies so far have received scanty attention.These complementary treatments include a range of self-management strategies. The need for self-management is influenced by the chronicity of complaints lacking cure and the impact of the disease on quality of life (Leonardi *et al*, 2020b) .

This brings us to question what the added value of self-management is for patients with endometriosis. In a recent cross sectional Australian study, an online survey was conducted via social media, and 484 women with a laparoscopically confirmed diagnosis of endometriosis were questioned (Armour *et al*, 2019). This study showed that one or more forms of self-management was applied in 76% of the cases. In addition, it became clear that different self-management strategies have a favourable effect on endometriosis-associated pain, with dietary interventions ranking in the top 3 for pain reduction and being applied by 44% of the respondents.

Whether self-management improves quality of life was studied in another Australian study using an online survey among endometriosis peer support groups including 620 patients with laparoscopically confirmed endometriosis (O'Hara *et al*, 2021). It was found that patients who used self-management strategies had a better quality of life (measured by SF36) and were better able to manage chronic pain complaints than patients who did not. This favorable impact on quality of life was confirmed in a recent survey among 211 Dutch women with endometriosis who used a dietary intervention (endometriosis diet) and showed a significantly improved quality of life (Van Haaps *et al*, 2022).

On the other hand, another Dutch study reported no impact of various diets on quality of life of women with endometriosis although the majority of studied dietary interventions were able to reduce chronic endometriosis complaints (Krabbenborg *et al*, 2021).

All in all, the scientific evidence regarding self-management and complementary treatment in endometriosis is limited. On the other hand, as pointed out by Canis and Guo (2023), by applying self-management patients gain more control over the disease which improves self-sustainability. In this light, it is recommended in the current ESHRE guideline to address complementary strategies and their value to wellbeing and coping with endometriosis symptoms although one should emphasize that their efficacy and/or harm in treating endometriosis symptoms is unclear (Becker *et al*, 2022).

WHAT DOES THE WOMAN WITH ENDOMETRIOSIS NEED?

Canis and Guo believe that doctors may provide biased advice and inaccurate or partial information to dissuade patients from choosing surgery (2023). However, there appears to be a lack of data on such a systematic phenomenon, whereas evidence is accumulating on the lack of empathy, limited ability to listen to and support suffering patients, and inadequate or non-existent humanistic approach, irrespective of surgical or medical preference. Indeed, from previous research we know that around 50% of women with endometriosis are dissatisfied with the care they receive (Lukas *et al*, 2018). They often feel that they are not well informed, that they are not taken seriously and that they do not receive proper support to deal with their endometriosis-associated complaints. Therefore, it is important to focus on patient centeredness in endometriosis care aiming to understand the needs and preferences, of women with endometriosis in order to increase their coping with the disease as well as to improve compliance to treatment

Patient centred care is care that takes into account the preferences and aspirations of individual health care users as well as the cultures of their communities (World Health Organisation, 2006). The quality of endometriosis care center can be addressed by using the ENDOCARE questionnaire

(ECQ) which is reliable in measuring patient centeredness. The ECQ enables a participating endometriosis care center to identify targets of improvement, to benchmark itself with other clinics s (Dancet *et al*, 2021; Schreurs *et al*, 2020a). as well as to assist in tailoring endometriosis care to individual patients (Schreurs *et al*, 2020b).

A person-centred approach in endometriosis care is associated with a greater feeling of control over endometriosis and more positive experiences regarding the healthcare providers involved (O'Hara *et al*, 2019). This is in line with a recent adequately powered study identifying relationships between experiencing less patient centeredness and having a poorer quality of life in patients with endometriosis (Schreurs *et al*, 2023). Therefore, it is plausible that improving patient centeredness may result in better quality of life in women with endometriosis (Schreurs *et al*, 2021).

THE PERSPECTIVE OF PUBLIC HEALTH AUTHORITIES: THE CONCEPT OF "VALUE" AND INCREMENTAL BENEFIT OF MEDICAL INTERVENTIONS

Canis and Guo (2023) only briefly mentioned the issue of the financial burden of some hormonal drugs and the lack of cost-benefit analyses of surgical versus medical treatment of endometriosis. We believe that this aspect should be expanded, also considering the prevalence of the disease, in the interest of both patients with endometriosis and the community at large.

In 2017, the National Institute for Clinical and Health Care Excellence published the only guideline (NICE guideline NG73. Endometriosis: diagnosis and management; 2017b) that, based on a through appraisal of the available evidence with systematic reviews and network meta-analyses, not only addressed the aspect of clinical benefits and harms of several diagnostic and treatment modalities in different clinical conditions, but also considered the individual and community economic benefits and harms of interventions with the calculation of absolute savings and additional costs, and cost-effectiveness analyses (https://www.nice.org.uk/guidance/ng73/evidence/full-guideline-pdf-4550371315; accessed on 30 June, 2023). Thus, not only efficacy (therapeutic effect under ideal or controlled conditions) and

clinical effectiveness (therapeutic effect in unselected patients in everyday practice) were considered, but also efficiency, i.e., whether the input to output ratio is favourable or, in other words, whether a medical intervention is worth its cost to the individuals or society (Haynes, 1999; Burches and Burches, 2020).

Indeed, the most clinically effective treatment based on data may not be the most cost-effective option. No public health system, even in high-income countries, can afford to provide every type of health care to the entire population, regardless of cost. This introduces the concept of "value", which is the relationship between the potential benefits, potential harms, and costs of any medical intervention, including those used in the endometriosis field (Vercellini *et al*., 2015). According to Pandya (2018), "*to ignore health care costs implies society would pay any amount of money for services that improve the health of patients even if those services result in patients achieving only marginal improvement in health outcomes"*. For example, GnRH agonists and antagonists are probably the most effective hormones for relieving endometriosis-associated pain and can be safely used for long periods when combined with add-back therapy (Veth *et al*., 2023; Xin *et al*., 2023; Yan *et al*., 2022). However, their cost may limit adherence or even prevent their use if individual patients have to pay for the medication. According to a recent report from the National Center for Health Statistics, in 2021, 8% of US adults did not take their medications as prescribed because of cost. Women and black people were more likely to forgo therapies to reduce costs (Mykyta and Cohen 2023; https://www.cdc.gov/nchs/data/databriefs/db470.pdf; accessed on 30 June 2023). Harris (2023) emphasized that "*to save money, people reported skipping doses of their medication, taking less of their drugs than prescribed, or delaying prescription refills*".

Even if public health systems reimburse GnRH agonists and antagonists for endometriosis, the opportunity cost should be carefully considered, as the resources consumed for expensive drugs will no longer be available for other patients with endometriosis, or for patients with other diseases, or for health services in general (Vercellini *et al*., 2018d and 2018e). This may exacerbate healthcare inequalities. Therefore, a stepwise approach should be promoted, prescribing GnRH

analogues only when COCs and progestogen monotherapies are ineffective, not tolerated, or contraindicated (Vercellini *et al*., 2015 and 2018f; ETIC 2019).

Pandya (2018) asserts that "*substantial changes in price could be all that is needed to convert a low-value health care service (cost ineffective) to a high-value health care service (cost-effective)*" This occurred with the reduction in the prize of dienogest to one-fifth to one-sixth of the original amount when the generic drug was marketed in Europe. A less impressive cost reduction (-25% to -30%) can still be achieved by using depot triptorelin formulations with extended-interval dosing regimens (Vercellini *et al*., 2023b).

Similar considerations apply to surgery for endometriosis, especially when performed with the help of robots (ETIC, 2019). In any case, surgery is costly and consumes large amounts of healthcare resources. When comparing the effects of surgical and medical treatment for endometriosis-associated pain, cost-effectiveness analyses should also be conducted to weigh the trade-offs between health outcomes and costs. Ignoring the cost of surgery for endometriosis-associated pain implies that the community would pay any amount for an incremental benefit, if any, over pharmacological interventions that are currently difficult, if not impossible, to quantify. Furthermore, in countries without public health support, the fee-for-service reimbursement model, which may encourage surgical overtreatment, should be replaced by value-based payment (ACOG Committee, 2018).

Health authorities and clinicians may have different perspectives, as medical decision-makers must ensure global equity and inclusivity, providing the greatest amount of health to the greatest number of citizens, consuming the least amount of resources, and regardless of specific diseases. High-quality surgical services may not be available everywhere, especially in low- and middle-income countries. According to Leonardi *et al*. (2020a), the setting in which care is provided is relevant to treatment decisions, as it includes the accessibility and cost of health care. In countries with inadequate health care resources, would it be better to offer surgery for endometriosis to a few patients or to relieve the pain of many with low-cost progestogens?

CONCLUSIONS: RETHINKING THE APPROACH TO WOMEN WITH ENDOMETRIOSIS-ASSOCIATED PAIN

In light of the above considerations, should we not shift from a lesion-oriented to a patient-centered approach? An approach in which a personalized treatment plan acknowledges a patient preferences and specific endometriosis symptoms with a vision for the long term and guided by a dedicated team with knowledge and skills of endometriosis, reproductive medicine and pain management.

Assuming disease progression in at least 30% of individuals, it is conceivable that early diagnosis of endometriosis may also be associated with less extensive disease spread and thus possibly better clinical outcomes and less requirement of surgical treatment and assisted reproduction. Therefore, it is conceivable that an early diagnosis, ideally followed by early, adequate treatment will reduce the risk of chronic pelvic pain complaints and infertility as well as provide patients an explanation for their symptoms. A lesion-oriented surgical treatment is effective in a multitude of situations and should be applied in patients with a high severity of symptoms and low quality of life where medical treatment has failed or is associated with a high burden of side effects. However, it has become clear that it should be embedded in a patient-centered approach,

Within the framework of this type of care, other causes of pain, in addition to the endometriotic lesions, should never be overlooked (Lamvu *et al*., 2021; Yosef *et al*., 2016), as the available evidence suggests that a large proportion of women with chronic pelvic pain have pelvic floor involvement, either primary or secondary (Aredo et al., 2017; Gyang *et al*., 2017; Lamvu *et al*., 2018; Kadah *et al*., 2023), and report a history of sexual abuse (Bourdon *et al*., 2023; Harris *et al*., 2018; Hillcoat *et al*., 2023; Latthe *et al*., 2006; Liebermann *et al*., 2018; Panisch and Tam, 2020). Thus, in some cases, endometriosis per se may be asymptomatic, being an incidental finding in patients with symptoms caused by something else. We appear to have gone from a time when endometriosis was inadequately considered to one where, for some, it seems to be almost the only

cause of chronic pelvic pain symptoms, an approach that does not serve patients and our healthcare systems well.

Canis and Guo (2023) argue that surgery for endometriosis-associated pain should be considered as an upfront option, rather than being indicated only when medical treatments fail. However,in patient-centred medicine based on genuine shared decision making, the focus may not be on whether medical or surgical treatment offers the best outcomes *a priori*, but when, under what conditions, and sometime in what order, one of the two treatment alternatives should be used. Guidelines provide "recommendations" that are not intended to be rigidly applied, but rather to serve as a basis for impartial information and counselling (Thornton, 2009; Bretthauer and Kalager, 2023; Howick and Doshi, 2023). iIf patients are uncertain, it should be assumed that the two options have different clinical implications, as those who try medical treatment and are not satisfied may then choose surgery without major consequences once hormones prove ineffective or intolerable, whereas the reverse means accepting morbidity and the risk of potential surgical harm anyway.

The success of therapy should be measured by patient-reported outcomes, such as satisfaction with treatment (Dworkin *et al*., 2005). Women who are uncertain about the choice between medications and surgery should be offered to try the reversible alternative first, with a plan to reassess their clinical condition in three to six months. Patients who are not satisfied with the overall effect of medical treatment can then decide whether they think surgery is worthwhile, knowing that the best results are generally achieved with post-operative medical therapies anyway. An individual patient may not be completely relieved of pain symptoms or completely free of side effects, but still prefer to continue taking medications because her health related quality of life has improved sufficiently. No drug is free of side effects; the issue is the acceptable trade-off between benefit and tolerability, as this influences compliance and, ultimately, effectiveness.

Finally, experts and key opinion leaders should ultimately aim to overcome polarisation in a responsible way, as it can be detrimental to women with endometriosis, who may feel confused when seeking a second or third opinion and find it difficult to make an informed decision about

which treatment alternative to choose. Polarisation can potentially hamper women's empowerment, interfere with shared medical decision-making, and favour doctor-centred rather than patient-centred medicine. It cannot be ruled out that women with endometriosis will eventually pay the price for our debates, which unfortunately rarely lead to a consensus that translates into major changes in individual gynaecologists' practice. The fact that this debate is taking place only a year after the publication of the new ESHRE guideline on the diagnosis and management of endometriosis (Becker *et al*., 2022) could be seen as indirect evidence that the polarisation in our scientific community is far from being resolved.

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