"WE CAN WORK IT OUT"*

THE HUNDRED YEARS' WAR BETWEEN EXPERTS OF SURGICAL AND MEDICAL TREATMENT FOR SYMPTOMATIC DEEP ENDOMETRIOSIS

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*Lennon J, McCartney P. The Beatles. UK, Parlophone, 1965

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Critically appraising the available evidence on management of pelvic pain symptoms associated with severe endometriosis with the aim of formulating therapeutic indications in individual patients, may reveal difficult even for skilled professionals, given the discouraging dearth of comparative effectiveness research in this field. When deciding between surgical or medical treatment for deep lesions, doubts may arise also because no consensus exists amid those experts who favor either one or the other option.

1. What type of evidence to inform surgical decisions in women with severe endometriosis?

The quality of the data regarding the outcomes of surgery for endometriosis seems particularly poor. Authoritative experts maintain that even the few surgical randomized, controlled trials (RCTs) conducted on women with endometriosis have methodological shortcomings that limit the validity of the observed results (1). These authors also emphasize that the *efficacy* demonstrated in highly selected participants under strictly controlled conditions, may not systematically translate into equivalent *effectiveness* when the same interventions are applied to the general endometriosis patient population in everyday practice.

Owing to the difficulties that nowadays render the planning and conduction of surgical RCTs in endometriosis rather cumbersome, Koninckx *et al*. conclude that, when dealing with severe, deep forms, a practical solution already at hand would be relying on "*the pool of a consensus-opinion of the world wide community of (expert) surgeons*" that "*should be given a much more important ranking than 'ideas and opinions' in the pyramid of evidence of EBM* [evidence-based medicine], *and this should be reflected in our guidelines*" (1).

However, it might be argued that precisely because no robust evidence defining the outcomes of surgery for deep endometriosis is available, physicians and patients should not rely on an opinion, even when it stems from a consensus of experts. Moreover, the issue here is not only "how" to perform surgery for these difficult disease forms, but also, and no less importantly, "when" to undertake surgery. Lowering or raising the bar for indicating surgery should contemplate

not only a precise estimate of its potential benefits and harms in different clinical conditions, but also an adequate knowledge of treatment alternatives.

Is a reliable demonstration available on the validity of the consensus-opinion of expert surgeons in terms of in-depth knowledge of the potential role of medical therapy in women with deep endometriosis? In this regard, it has been considered that "*excellent speakers have promoted the efficacy of hormone treatments without knowing the benefits of surgical approaches; talented surgeons are explaining the benefits of a radical removal of lesions without any experience with the medical treatment options*" (2).

2. Intellectual and financial conflicts of interest underpinning therapeutic contrapositions

The question here is whether relying solely on the opinion of expert surgeons, however widespread and shared, may ensure therapeutic equipoise. The same problem would arise in case only experts in medical therapy would express their consensus-opinion on the management of deep endometriosis. Would the common view of same-faction experts, just because is the results of exchange of information and comparison of experience, lead *per se* to a balanced and truly patient-centered treatment approach, or would heard mentality among the endometriosis community lead us astray?

When debating the role of medical and surgical treatment for endometriosis, Pellicer and Zupi warn against both intellectual and financial conflicts of interest (COIs), which may influence the audience of a conference or readers of clinical educational articles. They consider that biased speakers and authors are prone to attempting to convince colleagues to follow their suggestions (2). Personal and public gratification of surgeons performing technically demanding procedures may constitute a driver of the tendency toward approaching lesions only mechanically instead of pharmacologically. Also working in a fee-for-service healthcare system may well skew therapeutic indications towards surgery (3). In addition, administrators may boost complex or high-tech procedures, such as colorectal resection or robotic surgery, with the objective of increasing hospital revenues.

Transfer of money from industries to key opinion leaders may similarly influence the position of experts fostering new and costly medical therapies for endometriosis. Moreover, manufacturers of surgical devices and instrumentation as well as pharmaceutical companies, offer financial support to individual investigators, scientific societies, and congress organizers on a regular basis (4-6). In such an environment, straight implementation of consensus-opinions of experts into guidelines independently of the quality of the evidence on which such consensus-opinions are based (1), appears problematic and should be considered with great caution.

3. Epidemiological and clinical analogies between severe endometriosis and severe gastroesophageal reflux disease (GERD)

Reasoning on how the medical community at large behaves when dealing with other clinical conditions showing similarities with deep endometriosis, may help understand what can be reasonably expected by medical and surgical treatment, and may facilitate the achievement of a consensus on management of deep endometriosis. One such condition is severe erosive GERD.

The prevalence of GERD and endometriosis is high, as both diseases affect approximately 10% of adult females (7). Both conditions have a chronic clinical course and greatly impact on health-related quality of life. Symptoms are associated with organic lesions, such as erosive esophagitis with large mucosal breaks extending between mucosal folds in the former case, and nodules infiltrating the vagina, rectum, and parametria in the latter case. If left untreated, organic lesions may progress, causing, respectively, esophageal strictures and Barrett esophagus, and colorectal and ureteral stenosis. Patients with severe erosive GERD and those with severe infiltrating endometriosis have only two treatment options, take medications indefinitely (proton pump inhibitors (PPIs); hypoestrogenizing hormonal drugs) or undergo surgery (Nissen antireflux fundoplication, diaphragmatic hiatoplasty and fundopexy; resection of rectovaginal plaques and uterosacral ligaments, segmental colorectal resection). Medical therapy is effective in about two thirds of patients with both severe disease forms (8-10), although it is definitively curative in neither of them. In fact, disease-specific symptoms return quickly and severely in most cases if drugs are

discontinued (8-10). Adverse effects of PPIs are common but generally minor, as are those associated with progestins. The complications of long-term PPIs use are not completely defined, but potentially important, including increased risks for various types of infections, chronic kidney disease, and bone fractures. Long-term progestin use is associated with a slightly increased risk of breast cancer. The effects on serum lipid profile and bone mineral content vary depending on the type of progestin used. In both conditions surgical procedures can be performed at laparoscopy with reduction of morbidity and costs. The incidence of severe intra- and immediate post-operative complications is similar (fundoplication, 4-5%: infection, bleeding, esophageal perforation; deep endometriosis excision, 5%: neurogenic bladder atony, rectovaginal fistula formation, pelvic abscess, ureteral injury). Long-term surgical sequelae are relatively frequent after fundoplication (dysphagia, gas bloating) and rare after surgery for deep endometriosis (motor paralytic bladder, stenosis of bowel anastomosis). The 5-year postoperative symptom recurrence rate is between 20 and 30% after fundoplication (7,9), and between 40 and 50% after resection of infiltrating endometriotic lesions (11,12). The proportion of patients needing long-term medical therapy despite previous surgical treatment is high, being between 20 and 40% after fundoplication (7,9,10), and 20 and 50% after endometriosis resection (11-13). The proportion of patients undergoing second-line surgery is about 20% after both procedures, and the complication rate at secondary surgery is similarly increased compared with primary surgery after both fundoplication and endometriosis resection (7,9,11,12). The oncological risk is moderately increased if severe GERD is left untreated (esophageal adenocarcinoma), and slightly increased if severe endometriosis is left untreated (type I epithelial ovarian cancers).

4. Differences in management approaches to severe endometriosis and severe GERD

Despite the close similarities between severe GERD and severe endometriosis, recognized authorities in the respective fields tend to behave differently when considering treatments. Experts of GERD acknowledge that PPIs, without surgery, must be taken for decades. The symptomatic and not curative nature of PPIs is not considered equal to "inefficacy", and undertaking surgery is

deemed a choice in patients unwilling to take PPIs for life, or as a second-line therapeutic option when PPIs do not relieve symptoms *during treatment* (7,10). Some expert endometriosis surgeons do not contemplate that progestins, without surgery, should be taken for years or until pregnancy is desired, and dismiss these medications as ineffective or temporary because symptoms recur *after treatment* (14).

Large cohort studies and RCTs have been conducted on the effect of fundoplication for GERD, whereas mostly retrospective case series are available to assess the effect of excisional surgery for deep endometriosis. In the latter case, the risks of bias are not limited to recall bias, but include selection bias, reporting bias, and publication bias. It is an epidemiological tenet that non-comparative studies tend to systematically overemphasize the effect of medical interventions. Despite the limited strength of the evidence supporting surgery for infiltrating lesions, many expert endometriosis surgeons foster excisional treatment anyway, sometime maintaining at conferences that radical extirpation of lesions is curative. Unfortunately, as in the case of surgery for GERD, quite frequently it is not (11-13). Moreover, it is often difficult to discriminate how much of the effect is due to surgery and how much to postoperative medical therapy (11).

Despite the fact that surgery for GERD is supported by evidence of much higher quality with respect to surgery for deep endometriosis, surgeons experts of GERD do not seem to consider laparoscopy as the first or the only reasonable option. As an example, Maret-Ouda *et al*. maintain that "*laparoscopic antireflux surgery with fundoplication is a treatment alternative in patients with inadequate response to pharmacological treatment*" (7).

But the difference that strikes most between expert of GERD and expert of endometriosis, regards the consideration of the patient's role. According to Spechler,"*whether the greater than 80% possibility of long-term freedom from PPIs and their associated risks warrants the 4% risk of acute surgical complications and the 17.7% risk of GERD recurrence is a decision that individual patients should make after a detailed discussion of these risks and benefits with their physicians.*

There are wide variations among individuals in how they perceive and deal with different risks, and those factors should play a major role in guiding management choices" (10).

In other words, the main issue here is not how the physician should choose between the two treatment options, but how the physician should advise patients in order to allow them to take informed decisions. There is matter for reflection.

5. Patient centeredness is the way to overcome contrapositions

Paternalistic medicine (that is, the doctor knows what is best for the patient) seems to underpin the contraposition between the experts of surgery and those of medical treatment in the endometriosis field. If this is true, patient engagement does not appear to be a priority when deciding how to treat a woman with a symptomatic deep form. Both experts should begin to put aside their preferences, move toward a cultural change, and truly embrace patient-centered medicine (that is, informed women know what is best for them based on their priorities and preferences).

Patients should receive a complete, detailed, and balanced counseling on advantages and disadvantages of medical and surgical options for the treatment of pain associated with deep endometriosis. Data should be provided in a plain and easily comprehensible manner, using crude percentages and decision aids. The woman, and no one else in her place, should take the final decision, being aware that the main therapeutic objective is improving health-related quality of life, and that this may or may not necessitate radical removal of lesions.

According to Victor Montori, the answers to what is best for the patients and their families are complicated for at least three reasons (http://www.mayo.edu/research/labs/knowledge-evaluation-research-unit/overview. Accessed on September 23, 2017).

Firstly, the evidence regarding different treatment options may be incomplete, biased, imprecise, irrelevant, or inconsistent. This seems to be the case in the endometriosis area, and adequately designed, comparative effectiveness research is badly needed (3). In the meantime, the recent guideline issued by the National Institute for Health and Care Excellence could be used, as it

appears comprehensive, detailed, and based on a systematic and critical literature review. Moreover, aspects of cost-effectiveness are considered analytically for the first time (15).

Secondly, what is best is not an absolute notion, but depends on individual values and, given the options, what issues are more salient to personal goals for health and health care. The shared decision-making approach should here guide the patient-physician dyad.

Thirdly, what is best depends also on the inter-personal situation, in relation to family, job, community, and life at large. According to the International Minimally Disruptive Medicine Workgroup, patients affected by chronic diseases must face not only the burden of illness (e.g., symptoms and fatigue), but also the burden of treatment (e.g., visits to the physician, various types of tests, drug intake, self-monitoring, lifestyle changes, administrative tasks to access and coordinate care) (16). Hidden costs, full or part payment of treatments, and the potential psychosocial burden of being excessively medicalized also should be considered (16).

The "value" of any given intervention for endometriosis is the balance between potential benefits, potential harms, and costs, combined with personal patient preferences (3). According to Spencer-Bonilla *et al*. (16), "*ultimately, the value of care for patients should reflect the health outcomes achieved and the degree of burden that patients and their caregivers must bear to achieve those outcomes*". Organizing high-quality, high-value, patient-centered endometriosis care requires awareness of both, the burden of illness and the burden treatment, and this should become the common objective of all endometriosis experts, independently of their specific expertise.

6. War is over (if you want it)†

†Lennon J and Ono Y. From: Sometimes in New York City, UK, Apple Records, 1972.

The divergence of position of experts of surgery and experts of medical therapy does not benefit patients with severe endometriosis and does not improve outcomes, as women may be deprived of the potential benefits of the alternative option.

Ideally, physicians should be in the condition to offer both treatments. A written summary including the number and type of surgical procedures performed for severe endometriosis on an

annual basis, together with the number of main complications observed, would add important information and would allow women to decide whether undertake surgery in that center or ask for further consultations elsewhere. In case the woman decides for surgical treatment and adequate expertise is not available locally, the physician has the ethical duty to refer that patient to colleagues with sufficient technical capabilities, with the objective of maximizing the benefits and minimize the harms of the procedure. Likewise, surgeons with limited experience in hormonal therapy should refer those patients opting for long-term medical management to centers with specific expertise, in order to plan the best individual therapeutic scheme in terms of efficacy, tolerability, risks, and costs.

Experts on both sides should understand that collaboration, instead of confrontation, could pave the way toward improved patient care, acknowledging that some conditions might be amenable to hormonal manipulation and other to excision. Surgical and medical treatments may also be combined, thus potentially achieving an additive effect. This approach has the potential to improve outcomes, the only meaningful objective of gynecologists caring for women with endometriosis.

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