

1 "WE CAN WORK IT OUT"*

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

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

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

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

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

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

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

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

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

62 **2. Intellectual and financial conflicts of interest underpinning therapeutic contrapositions**

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

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

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

87 **3. Epidemiological and clinical analogies between severe endometriosis and severe** 88 **gastroesophageal reflux disease (GERD)**

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

93 The prevalence of GERD and endometriosis is high, as both diseases affect approximately
94 10% of adult females (7). Both conditions have a chronic clinical course and greatly impact on
95 health-related quality of life. Symptoms are associated with organic lesions, such as erosive
96 esophagitis with large mucosal breaks extending between mucosal folds in the former case, and
97 nodules infiltrating the vagina, rectum, and parametria in the latter case. If left untreated, organic
98 lesions may progress, causing, respectively, esophageal strictures and Barrett esophagus, and
99 colorectal and ureteral stenosis. Patients with severe erosive GERD and those with severe
100 infiltrating endometriosis have only two treatment options, take medications indefinitely (proton
101 pump inhibitors (PPIs); hypoestrogenizing hormonal drugs) or undergo surgery (Nissen antireflux
102 fundoplication, diaphragmatic hiatoplasty and fundopexy; resection of rectovaginal plaques and
103 uterosacral ligaments, segmental colorectal resection). Medical therapy is effective in about two
104 thirds of patients with both severe disease forms (8-10), although it is definitively curative in neither
105 of them. In fact, disease-specific symptoms return quickly and severely in most cases if drugs are

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

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

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

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

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

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

152 But the difference that strikes most between expert of GERD and expert of endometriosis,
153 regards the consideration of the patient's role. According to Spechler, "*whether the greater than*
154 *80% possibility of long-term freedom from PPIs and their associated risks warrants the 4% risk of*
155 *acute surgical complications and the 17.7% risk of GERD recurrence is a decision that individual*
156 *patients should make after a detailed discussion of these risks and benefits with their physicians.*

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

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

162 **5. Patient centeredness is the way to overcome contrapositions**

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

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

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

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

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

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

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

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

201 **6. War is over (if you want it)†**

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

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

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

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

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

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