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Editorial

Toward minimally disruptive management of symptomatic endometriosis: reducing low-value care and the burden of treatment

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Endometriosis is a chronic gynecological disorder afflicting reproductive-age women. Different pathogenic hypotheses have been formulated to explain the development of this disease. According to a vast body of evidence, viable endometrial cells reach the abdominal cavity during menstruation via trans-tubal retrograde blood reflux, and implant on the pelvic peritoneum. Their metabolic activity at ectopic sites causes inflammation, adhesion formation, and fibrosis of affected structures. This may cause pain symptoms and infertility, with repercussions on physical and emotional well-being, sexual function, and health-related quality of life. Endometriosis prevalence rate among 15-49 year women is around 3-5% [1].

In case of women seeking conception, clinicians should consider that a satisfactory balance between adequate control of pain symptoms and optimization of reproductive performance is sometime difficult to attain. When a shared decision is to be taken, also the costs of surgery and assisted reproductive techniques in different clinical conditions should be compared and taken into account. However, diverse treatment alternatives are available also for women not wishing pregnancy. Thus, we here evaluate those factors that may influence the value, burden, and cost of chronic management in women with endometriosis-associated pelvic pain and not wanting a pregnancy immediately or in the future.

1. **Factors impacting on the financial burden of endometriosis**

Direct and indirect costs of endometriosis management in western countries are variable, as several factors influence reported estimates, including national healthcare system type, and local economic and social context. Average total direct and indirect costs per patient per year range, respectively, from $1109 (Canada) to $12118 (USA), and from $3314 (Austria) to $15737 (USA) [2].

Diverse diagnostic and therapeutic strategies associated with very different management costs can be adopted in women with symptomatic endometriosis who do not
seek a pregnancy. The resulting annual national economic burden is thus highly variable. This is particularly important when considering that the disease may cause symptoms for decades. Several international gynecological societies have issued guidelines for the treatment of endometriosis-associated pain [3-6], but strong recommendations may be hampered by a dearth of comparative effectiveness research concerning several clinical issues [6].

This permits ample margins of therapeutic individualism, with a potential risk of overmedicalization. Indeed, several stakeholders may profit from overdiagnosis and overtreatment of endometriosis. Industry influence, hospital revenues, competing interests, self-referrals, and fee-for-service payment systems, in addition to insufficient knowledge of healthcare economic evaluation, may impact on the financial burden shouldered by families and health services [7,8].

To maximize the benefit from a fixed sum of money, or minimize the resources required for a defined benefit, low-value diagnostic and therapeutic interventions (i.e., with an unfavorable balance between potential benefits, potential harms, and cost) should be identified based on the available evidence, and de-implemented.

According to the Practice Committee of the American Society for Reproductive Medicine, in symptomatic women not seeking a conception, “endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures” [5]. This recommendation takes into account that even adequate excisional surgery is associated with a symptom and lesion recurrence rate of about 10% per year, and that the outcomes of reoperations are generally less favorable compared with those of first-line procedures [9,10].

On the other hand, medical treatments for endometriosis are symptomatic and not curative, and may be needed for years or until pregnancy is desired. Consequently, not only
the efficacy of medications, but also their cost, safety, and tolerability, must be carefully considered. Also women with endometriosis may choose to forgo care when faced with unaffordable options [8,11].

Recently, the UK's National Institute for Health and Care Excellence (NICE) has issued a guideline on diagnosis and management of endometriosis that, for the first time, includes explicit consideration of cost effectiveness [12]. This guidance may help assess the overall financial burden of tests and treatments in combination with their clinical benefits and harms, and may inform resource allocation, thus increasing the efficiency of healthcare utilization.

2. Reducing low-value diagnostic modalities

Laparoscopy with positive histology on biopsy specimens is still considered the diagnostic gold standard [4-6]. However, systematically performing a laparoscopy in patients with pain symptoms suggestive of endometriosis implies high costs and increases morbidity, and prevents women from choosing between medical and surgical therapy. Thus, implementation of reliable non-surgical diagnostic modalities would have important clinical and economic implications [7].

The main endometriotic phenotypes are superficial peritoneal implants, ovarian cysts, and deep lesions infiltrating the vagina, the rectosigmoid, the bladder, and the parametria. Transvaginal ultrasonography (TVUS) has a demonstrated high overall accuracy as a test for the identification of ovarian and deep endometriotic lesions, approaches the criteria for replacement of laparoscopy, and satisfies the criteria for triage (i.e., a test that should be used as the initial step in a diagnostic pathway) [8,13,14].
Magnetic resonance imaging (MRI) may add useful information only in selected circumstances, as in case of doubtful TVUS findings or before high-risk surgery for excision of deep lesions. The NICE Guideline Committee discourages the use of MRI as a first-line test and recommends fewer MRIs than current practice [12].

Only superficial peritoneal implants cannot be diagnosed by imaging techniques. However, it has never been demonstrated that elimination of early lesions would benefit most patients in terms of disease progression, pain recurrence, and reproductive outcome [7]. Women should be informed that safe and inexpensive medications would likely relieve their complaints, that a laparoscopy should be indicated in non-responders, and that not removing early, limited implants would not necessarily translate into worse prognosis, provided adequate medical suppression is consistently used [7,8].

A diagnostic delay of 6-8 years has been repeatedly reported [2]. However, this is likely the result of inadequate awareness and knowledge of endometriosis, rather than of not timely performing a diagnostic laparoscopy in all women with pelvic pain. Even when physical examination and TVUS are negative, endometriosis can and should be suspected and treated medically without delay, independently of direct lesion visualization [7]. The burden of undiagnosed and untreated endometriosis is undefined [2], but prompt empirical hormonal therapy (i.e., based on symptoms rather than definitive diagnosis), in addition to providing rapid symptom relief in most women, could also substantially reduce indirect costs.

3. **Reducing low-value medical treatment**

According to international guidelines, pain relief obtained with various compounds is similar, whereas safety and costs differ [3-6,12]. In Italy, the cost of one year of treatment with the most widely used medications for endometriosis varies widely, ranging from €17-£16-$20 to €1840-£1693-$2190 (Table 1). The cost of the GnRH antagonist elagolix, a new
A hypoestrogenizing drug that soon will be launched on the market, is currently unknown. Of relevance here, good efficacy may translate into sub-optimal effectiveness when women have to pay for a novel, expensive therapy [11].

In order to improve the efficiency of medical treatment for endometriosis (i.e., the effect of hormonal therapies in relation to the resources they consume), costly drugs should be used solely when safe and inexpensive medications are ineffective, not tolerated, or contraindicated. Based on a recently proposed stepped-care approach for the management of symptomatic endometriosis [15], very-low-dose oral contraceptives and low-cost progestins should be used first, stepping up to dienogest, a high-cost progestin, and then to GnRH agonists selectively in non-responders. Laparoscopy should be considered when drugs fail or when informed women prefer surgery over hormonal treatments. Such an approach would greatly reduce the direct cost for long-term endometriosis management.

According to the NICE Guideline Committee, empirical diagnosis followed by cheaper hormonal treatments was extremely likely to be the most cost-effective therapeutic strategy [12]. The quality of the evidence was not sufficient to recommend COCs over progestins, although COCs generated slightly more quality-adjusted life-years on average. Moreover, the Committee suggested to give priority to women's preferences regarding the type of cheap hormonal treatment to use.

4. Reducing low-value surgical treatment

Costs and harms of endometriosis management may be here increased by: i) systematically pursuing surgery to relieve pain and performing bowel resection when not strictly clinically indicated [7]; ii) using costly instrumentation such as the surgical robot [18]; iii) not preventing postoperative recurrences medically [10].
i) According to Soliman et al. [2], surgery greatly impacts on direct costs of endometriosis. When pelvic pain is the issue, and no large adnexal masses or ureteral and bowel stenosis are present, surgery is always optional, never mandatory. Performing surgery selectively when medical treatment is not effective, not tolerated, contraindicated, or declined, greatly limits costs of management. Moreover, colorectal resection is the single pelvic procedure associated with the highest risk of severe complication (5-10%), including anastomotic dehiscence, rectovaginal fistula formation, ureteral damage, and bladder/bowel denervation [8]. If an endometriotic bowel nodule does not cause manifest sub-occlusion, rectosigmoid resection should be considered with caution, being associated with undefined benefits, definite harms, and increased direct and indirect costs.

ii) The impact of robotic surgery on direct healthcare costs are impressive, although it does not improve outcomes of endometriosis patients [16]. The American College of Obstetricians and Gynecologists included an item on robotic surgery in benign gynecology in its “Choosing Wisely” list. The College discourages the use of the daVinci robot, suggesting a standard laparoscopic approach, due to lack of advantages of robotic surgery in terms of perioperative outcomes, intraoperative complications, length of hospital stay and rate of conversion to open surgery, and evidence of disadvantages in terms of operating time and costs [17]. This view is shared by the American Association of Gynecologic Laparoscopists [18].

iii) Endometriosis has a marked relapsing tendency [9,10]. Surgery eliminates lesions, but does not eliminate the pathogenic factors that predispose to implantation of endometrium at ectopic sites. When COCs or progestins are used postoperatively, the risk of symptom and lesion recurrence is reduced by 80-90% [9,10]. This safe and inexpensive preventive measure may safeguard the already damaged reproductive potential, reduce morbidity, and contain costs. According to the NICE Guideline Committee, the addition of
hormonal treatment to delay the recurrence of endometriosis is an important health economic issue, as "for example, doubling average recurrence time would halve the number of operations required to treat a woman over the course of her lifetime, with clear cost implications" [12]. Based on the economic analysis model adopted, cheaper hormonal treatments like COCs were likely to be more cost-effective, and should be used in women not trying to conceive or in those who were planning pregnancy in the future.

5. Minimally disruptive endometriosis management: reducing the burden of treatment

The International Minimally Disruptive Medicine Workgroup consider that 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) [19,20]. Hidden costs, full or part payment of treatments, and the potential psychosocial burden of being medicalized and turned into a patient also should be considered [19].

"Minimally disruptive medicine" is an approach to providing high-value care that emphasizes individual priorities, at the same time minimizing the workload for patient and caregiver [19]. Modifying treatments taking into account the burden of treatment has the potential to improve outcomes [20]. According to Spencer-Bonilla et al. [20], "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. Limiting laparoscopy for diagnostic purposes, suggesting long-term treatments with cheap and well-tolerated COCs and progestins without delay, avoiding unnecessary surgical procedures, preventing symptom
and lesion recurrence via prolonged ovarian suppression, divesting from unjustifiably costly medical practices, and systematically adopting a stepped-care approach, has the potential to decrease the burden of treatment (e.g., the number of gynecological visits, imaging examinations, laboratory exams, frequency of re-operations), and improve outcomes for patients, at the same time limiting the progressive rise in costs for endometriosis management [7,8,15].

Finally, value-based assessment of health technologies appears crucial in order not to violate equity. According to Paulden, new technologies should no longer recommended "unless the value of the expected health gains exceeds the value of the expected health losses" [21]. In fact, given the fixed budget of national health services, costly technologies displace resources in other similar patients, with a net reduction in population health. Thus, the adoption of costly diagnostic and treatment modalities that do not consistently and substantially improve health outcomes of endometriosis patients, are implicitly inequitable towards other patients and society at large.

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**Declaration of Interest**
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

REFERENCES


Table 1. Cost of one year of continuous medical treatment for endometriosis. Italy, 2017

<table>
<thead>
<tr>
<th>Medication</th>
<th>€</th>
<th>£</th>
<th>$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depot GnRH agonists</td>
<td>1840</td>
<td>1693</td>
<td>2190</td>
</tr>
<tr>
<td>Dienogest 2 mg os/day</td>
<td>730</td>
<td>672</td>
<td>861</td>
</tr>
<tr>
<td>Estrogen-progestin vaginal ring</td>
<td>338</td>
<td>311</td>
<td>402</td>
</tr>
<tr>
<td>Estrogen-progestin transdermal patch</td>
<td>278</td>
<td>256</td>
<td>331</td>
</tr>
<tr>
<td>Danazol 200 mg per vaginam/day</td>
<td>275</td>
<td>253</td>
<td>327</td>
</tr>
<tr>
<td>Very-low-dose monophasic COCs*</td>
<td>159-167</td>
<td>146-158</td>
<td>188-197</td>
</tr>
<tr>
<td>Levonorgestrel-releasing IUD†</td>
<td>48</td>
<td>44</td>
<td>57</td>
</tr>
<tr>
<td>Nor-ethisterone acetate 2.5 os/day</td>
<td>17</td>
<td>16</td>
<td>20</td>
</tr>
</tbody>
</table>

*COC = combined oral contraceptive.

†IUD = intrauterine device.