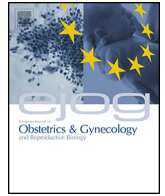




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Invited Editorial

Postoperative hormonal therapy after surgical excision of deep endometriosis

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ABSTRACT

The clinical management of women with deep peritoneal endometriosis remains controversial. The debate focuses mainly on the precise role of hormonal medical treatment and surgery and on the most suitable surgical technique to be used. In particular, considering the risks of second-line surgery, prevention of recurrences after first-line surgery is a priority in this context. Post-surgical medical therapy has been advocated to improve the effectiveness of surgery and prevent recurrences. However, adjuvant therapy, i.e. a short course of 3–6 months of hormonal therapy after surgery, has been proven to be of limited or no benefit for endometriosis in general and for deep peritoneal endometriosis in particular. On the other hand, two cohort studies suggest a beneficial effect of prolonged hormonal therapy after surgery for deep endometriosis. Even if this evidence is too weak to confidently advocate systematic administration of prolonged medical therapy after surgery, we argue in favour of this approach because of the strong association of deep endometriosis with other disease forms. In fact, women operated on for deep endometriosis may also face recurrences of endometriomas, superficial peritoneal lesions and pelvic pain in general. The demonstrated high effectiveness of prolonged postoperative therapy for the prevention of endometriomas' formation and dysmenorrhea recurrence should thus receive utmost consideration in the decision-making process.

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Introduction

Deep peritoneal endometriosis is an infiltrative disease form that may involve vital structures. Lesions are commonly located in the most declivous part of the pelvis, i.e. the pouch of Douglas, the anterior aspect of the sigma, the utero-sacral ligaments, the broad ligaments, the ureter and the bladder. Albeit less common, locations have been described also in other parts of the abdomen, in the external genitalia and in distant locations [1]. Deep invasive peritoneal endometriosis can cause significant chronic pelvic pain including dysmenorrhoea, dyspareunia, dyschezia, dysuria and inter-menstrual pelvic pain. It can also cause local bleeding and obstruction of vital organs [2,3]. The relation with infertility is conversely more debated [4]. From a clinical point of view, deep

peritoneal endometriosis represents the most challenging form of the disease. However, to date, its therapeutic management remains controversial [3,5].

Surgery and hormonal treatment: from antagonism to mutual aid

From a pathological point of view, deep lesions are typically infiltrate adjacent or ligaments and their presence is associated with dense and diffuse adhesions [6]. The capacity of these lesions to infiltrate vital organs can pose relevant technical difficulties to surgeons. The concomitant presence of adhesions and fibrosis further complicates surgery. As a matter of fact, surgical excision of deep lesions may be very demanding and inevitably exposes affected women to significant peri-operative risks and long-term sequelae [5,7–10]. They include fistula formation, ureteral lesions, haemorrhage, infections and bladder and bowel dysfunction owing to denervation [2,5].

There is an on-going debate on the most suitable surgical technique to be used [11–14]. The ultimate aim is sorting out

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which approach may better combine high effectiveness in terms of symptoms relief, rate of recurrence and risk of complications. However, these requirements tend to go after opposite directions with more aggressive interventions being more effective but also more risky while the opposite is valid for less aggressive approaches. Not surprisingly, there is also a growing attention to medical treatment in this field. Once typically considered a surgical condition, convincing evidence is now cumulating on the benefits of hormonal manipulation alone for the treatment of deep endometriosis [5,15,16]. Noteworthy, a recent study comparing surgery and medical treatment in women with rectovaginal lesions documented a more rapid improvement in women receiving surgery but the difference between the two approaches lessens with time and, at one year follow-up, pain symptoms were similar in the two study groups [17,18].

Albeit not definitely curative (symptoms typically recur at discontinuation of treatment), medical treatment may consent to achieve good pain relief with very modest side-effects and risks [15,19]. More in general, there is now growing consensus that, in the decision-making process, the focus should be on symptoms relief and quality of life rather than on lesions removal. In fact, a transition from a “lesion-oriented” to a “patient-oriented” approach is now advocated by most [20]. However, surgical removal is not and presumably will never be definitely abandoned. Medical treatment may fail, its long-term use may be unbearable or contra-indicated, women may aim at natural pregnancy seeking but cannot stand pain symptoms and, finally, lesions may determine a significant impairment of the affected organs (i.e. clinically significant stenosis of the intestine or the ureters).

Regardless of the vision of the disease and the precise role of surgery, a main priority in the field is prevention of recurrences after the intervention. Complications and risks of second surgery are inevitably markedly higher and there is thus the strong need to prevent this clinical situation. Endometriosis is indeed a chronic disease and recurrences are unfortunately common. Based on a systematic review of the literature Guo estimated that the rate of recurrences at two and five years is 20% and 40–50%, respectively [21]. The figure may be slightly different for deep lesions. In a systematic review dedicated to this specific aspect, Meuleman et al. reported a rate of recurrence in affected women varying between 5% and 25%, with most studies with a follow-up >2 years reporting a rate of about 10% [22]. Overall, even if this rate may markedly differ according to the severity of the disease and the quality of surgery, physicians facing affected women have to deal with this possibility and should consider available preventive options.

In this scenario, it is not surprising that hormonal manipulation that was shown to be effective in the primary treatment of deep peritoneal lesions can be claimed to have a role also after surgery. The goal of post-operative hormonal treatment is to improve the effectiveness of the intervention in terms of symptom relief and, most importantly, to prevent recurrence.

The intricate relation between pathogenesis and therapy

The debate on the most suitable therapeutic approach for deep lesions also reflects the debate on the origin and pathogenesis of endometriosis. Based on the most commonly accepted theory, i.e. the retrograde menstruation hypothesis, one could obviously not advocate surgery as a definite solution. Surgery may remove the endometriotic lesions but does not act on the pathogenesis of the disease. Once the woman re-starts having ovulatory cycles, she re-starts being exposed to the pathogenetic insult. If it will be definitely demonstrated that endometriosis arise from a chronic, repetitive and long-standing insult (like retrograde menstruation), the role of surgery would inevitably be circumstantial and limited

to particular situations. On the other hand, the recently emerging theory that endometriosis would mainly arise from retrograde menstruations occurring in the neonatal age contrasts with that view and would conversely strongly support surgery [23]. If endometriosis develops as a consequence of a single episode of retrograde menstruation occurring at birth, complete surgical removal of lesions can indeed be expected to definitely solve the problem.

This scenario is complicated by the existence of microscopic endometriosis [24]. Noteworthy, the debate on microscopic endometriosis is not academic and may have important clinical impact. The presence of these lesions could explain recurrence in the absence of new pathogenetic insults. Recurrences would be secondary to the development of lesions that were missed at first surgery and that subsequently progressed. In fact, discerning whether recurrence of endometriosis after surgery is due to a real recurrence (i.e. the development of *de novo* lesions) or, conversely, whether it is a persistence of residual endometriosis (i.e. microscopic lesions that develop after surgery) is challenging, if not impossible [11].

The failure of adjuvant therapy

The existence of microscopic lesions that can successively cause recurrences has inevitably fuelled the idea that treatment of the disease could be improved with the use of “adjuvant” medical treatment. This resemblance with cancer leads to the hypothesis that a 3–6 months course of medical therapy immediately after surgery could reduce recurrences. However, available clinical evidence clearly denies the effectiveness of this approach. According to the latest Cochrane meta-analysis, the benefits of different type of hormonal treatments (progestins, estroprogestins, GnRH analogues, danazol) for 3–6 months after surgery has been investigated in 12 randomized controlled trials (RCTs) [25]. The relative risk (RR) of pregnancy in treated women was 0.84 (95%CI: 0.59–1.18). Recurrences were unfortunately reported in an extremely heterogeneous manner, thus impeding meaningful meta-analyses. However, a clinically relevant beneficial effect can be confidently excluded [25,26]. A recent RCT including 450 women (not included in the Cochrane meta-analysis) and testing the benefits of a 3 months course of medical therapy after surgery confirmed these findings [27]. Noteworthy, we identified only one RCT specifically focusing on the benefits of adjuvant therapy in women operated on for deep peritoneal endometriosis [28]. These authors recruited 159 women and randomized them at 3 months post-surgical GnRH analogues or expectant management and showed that, at one year follow-up, pain score did not differ.

This failure is disappointing but actually not surprising. The oncological model of adjuvant therapy is inappropriate here. Chemotherapy for malignancies has a totally different logic. Chemotherapeutic agents interfere with cell cycle proliferation and are thus able to destroy micro-metastasis that can be present at the time of surgery. Hormonal therapy does not damage endometriotic cells. It just causes a transient state of quiescence that vanishes as soon as medical therapy is suspended [29].

Tertiary prevention

Endometriosis in general is now more and more viewed as a chronic disease requiring lifelong treatment [16]. Accordingly, the interest on prolonged long-term post-surgical therapy has grown and this approach has been in-depth reviewed in some recent revisions of the literature [29–31].

The most extensively studied issue here is the prevention of ovarian endometriomas' recurrences. The particular interest on this form of the disease is consequent to the growing awareness

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