

MINERVA

GINECOLOGICA

VOLUME 65 · N. 2 · APRILE 2013



EDIZIONI · MINERVA · MEDICA

## Predictive factors and treatment of recurrence of endometriosis

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**Endometriosis remains an enigmatic disease process. The key is early recognition of symptoms and treatment. Treatment may begin with hormonal suppression. If medical suppression fails or if fertility is desired, surgical intervention should be used. During primary surgical intervention, the goal is for optimal treatment to decrease disease burden. However, despite adequate treatment, reoperation is needed in a good proportion of woman. Factors contributing to recurrence are multifactorial and some can be predicted and some pain recurrence occurs despite obvious evidence. Recurrent surgery should also aim to decrease disease burden and conservative versus definitive treatment is based on patient's childbearing status. In addition, use of medical treatment can temper recurrence rates. There is still tremendous work that must still be completed in the field of pain recurrence and disease recurrence with endometriosis.**

**KEY WORDS:** Endometriosis - Laparoscopy - Pelvic pain - Hormone replacement therapy.

**E**ndometriosis is an estrogen-dependent chronic inflammatory condition affecting 6% to 10% of reproductive aged women.<sup>1, 2</sup> It is the leading cause of pain and infertility in women.<sup>3</sup> Endometriosis is characterized by the presence of endometrial-like tissue outside the uterine cavity.

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Three clinically distinct forms exist: pelvic endometriosis, endometriomas and extra-genital endometriotic lesions.<sup>2, 4</sup> Although endometriosis was described as early as 1690 by Shroen, a German physician, and a year later, Ruysch, a Dutch anatomist, proposed an early version of retrograde menstruation, its pathogenesis remains elusive.<sup>5</sup>

The progress of this clinical enigma can be moderated by the use of hormonal therapy. Medical management, used to suppress symptoms, includes non-steroidal anti-inflammatory drugs, oral contraceptives, antigestogens and GnRH agonists. However, this intervention is not desired in those seeking fertility, and the rate of recurrence is high after discontinuation.<sup>6-10</sup> Video – assisted laparoscopic surgery (VALS) is the gold standard for definitive diagnosis and surgical treatment of symptomatic endometriosis.<sup>11</sup> Numerous studies support the use of laparoscopy in order to ameliorate pain and enhance fertility, especially when conservative management fails.<sup>12-16</sup> VALS offers many advantages over conventional laparotomy; namely a magnified view of the pelvis and greater exposure that allows for close examination and visualization of

endometriotic implants. Larger implants or deep endometriotic nodules are best treated with resection. Surgical treatment of all endometriosis has been proven to be the most effective method for symptom relief and prevention of recurrence.<sup>13, 17, 18</sup>

However, despite the growing acceptance of VALS, due to the relapsing nature of endometriosis, recurrence is commonly encountered even with optimal treatment.<sup>19, 20</sup> The recurrence ranges from 12% to 56% within five years of initial surgical intervention.<sup>21-24</sup> This leads to a dilemma with regards to balancing the benefit of reoperation and patient expectations.

### Predictive risk factors

Several studies have addressed various factors that account for recurrence of endometriosis. However, the endpoint of recurrence has been defined broadly and thus available evidence is somewhat scattered. Younger age at onset of symptoms and younger age at time of first surgery appears to be a determinant of recurrence of disease. Recurrence rates in a younger cohort of women ranges from 20-56% depending on the study population and upper limits of ages included in the analysis.<sup>21, 23, 24</sup> Possible theories include longer exposure time to estrogen states and more aggressive disease pattern in a younger age group. High preoperative pain levels are associated with a higher risk of recurrence.<sup>22, 25</sup> Additionally, those who initially were on hormonal suppressive therapy were noted to have increased rates of recurrence.<sup>21, 26</sup> This may be attributed to decrease in disease burden at the time of surgery after medical treatment, thus potentially leading to inadequate treatment and thus recurrence. Also plausible is that failed medical intervention is an indication of more severe disease. However, this finding is not consistent throughout the literature.<sup>27</sup> Multiple studies have shown that the use of continuous oral contraceptives postoperatively does significantly decrease recurrence rates.<sup>28-30</sup> Postoperative pregnancy

has protective effects on recurrence.<sup>26</sup> It is noted that early pregnancy after surgery may aid in regression of disease.<sup>31, 32</sup> Finally, and perhaps most consistently seen to effect recurrence, is ASRM staging.<sup>21, 26, 27</sup> Though the staging system is somewhat flawed with disease burden not relating to pain scales, larger lesions, which are not adequately treated are noted to impact recurrence rates.

### Primary surgical intervention

Surgical intervention of endometriosis has evolved from indiscriminate use of hysterectomy and bilateral salpingo-oophorectomy to more precise and directed excision of all endometriotic implants and restoration of normal anatomy, with the hope of alleviating pain and improving fertility (if the patient desires fertility). It is of utmost importance that in the prevention of and decrease in recurrence of endometriosis that the initial surgical intervention is systematically and thoroughly performed and optimal debulking attempted.

There are two randomized clinical trials of laparoscopic surgical intervention for treatment of endometriosis. Sutton *et al.* studied laser ablation, and they noted that at 6 months postoperatively 62% of treated patients had decreased pain versus 23% in the control group.<sup>12</sup> Abbott *et al.* studied excision. At 6 months postoperatively, 80% of treated patients had decreased pain versus 32% in the control group.<sup>14</sup> Additionally, there are randomized studies evaluating excision versus ablation of peritoneal implants for relief of pain, which have not shown that either technique is superior.<sup>33, 34</sup> However, for ovarian pathology, namely for endometriomas, it has been well established that recurrence is less likely with complete excision versus drainage and ablation.<sup>35-37</sup> It is notable that excision can be difficult because endometriomas can be adherent to the ovarian cortex.

The gastrointestinal tract is involved in endometriosis in up to 37% of patients.<sup>38, 39</sup> Endometriotic implants can be found any-

where between the small intestines to the anal canal, and the clinical manifestations range from incidental finding to obstruction.<sup>40</sup> The most frequently involved site for endometriosis is the rectosigmoid, accounting for 70-88% of all cases. This is followed by the sigmoid colon, rectum, appendix and cecum.<sup>4, 41-43</sup> Surgical intervention of intestinal endometriosis remains debatable.<sup>44</sup> In the absence of bowel obstruction or other emergent presentation, the optimal timing of surgery and extent of intervention has not been determined. Various minimally invasive surgical techniques are currently available for treatment. Determining which approach to use is based on the extent, location and expertise of the surgical team. Less invasive approaches, as long as there is complete excision and adequate margins, are often the preferable option.<sup>17, 45-47</sup>

Pelvic endometriosis can also involve the urinary tract system in approximately 1% of cases.<sup>48</sup> The bladder is the most commonly involved and the urethra the least commonly involved. Treatment of bladder endometriosis is aimed at symptomatic relief, as it often does not involve the ureteral openings. The surgical intervention that appears to allow for complete removal of disease is a combination approach of cystoscopy and laparoscopy.<sup>49-52</sup>

Another primary intervention that can be used in a well-selected population of women with midline pain is a laparoscopic presacral neurectomy. This procedure has been shown to effectively decrease midline pain.<sup>53</sup>

### **Repeat conservative surgical interventions**

The decision to reoperate on a patient is based on various clinical scenarios such as, recurrence of pain, presence of mass or infertility.

Limited data exists with regards to long-term pain recurrence after conservative primary surgical treatment, as well as after reoperations. Candiani *et al.*<sup>54</sup> prospectively evaluated the long-term improvement in

pain in women with advanced stage disease after repeat conservative surgical treatment. They concluded that conservative treatment was an effective option in a majority of their cohort, however 14% did require a subsequent third operation. Busacca *et al.*<sup>55</sup> found similar findings in their cohort of 81 patients that repeat conservative surgery was an option for pain recurrence. Fedele *et al.*<sup>56</sup> further added to the body of evidence that repeat conservative surgery was beneficial in their study of 54 reoperations and found that the recurrence of pain was similar to the primary surgery after a repeat surgery.

The use of the denervation technique of presacral neurectomy has been used as an adjunct for treatment of pain. Studies have shown that the procedure effectively reduces pain in those undergoing primary surgical treatment. However, the results may be extrapolated to patients with recurrence of pain after initial surgical intervention. A small cohort was prospectively evaluated by Tjaden *et al.*<sup>57</sup> In this study of Stage III and IV endometriosis, a majority of women, who underwent presacral neurectomy, experienced pain relief versus those women who underwent conservative treatment. Candiani *et al.*<sup>58</sup> showed only slight improvement between the presacral neurectomy group versus the conservative therapy group. However, there the findings were not statistically significant. Zullo *et al.*<sup>59, 60</sup> further confirmed that the use of presacral neurectomy showed improved dysmenorrhea compared to conservative treatment. It is important to recognize that the application of presacral neurectomy must be to appropriately screened women with midline pain. Also, important to consider is the potential for bowel and bladder dysfunction postoperatively, which can further impact quality of life.<sup>20, 61</sup>

### **Repeat definitive surgical interventions**

Definitive therapy for endometriosis involves a total hysterectomy, bilateral salp-

ingo-oophorectomy and complete treatment of endometriosis. Overall, women who undergo definitive treatment will experience pain relief even with estrogen replacement. However, a small minority may still have pain persistence, and therefore women should be counseled appropriately as to expectations postoperatively.<sup>62</sup> Up to 18% of hysterectomies performed are done for the primary complaint of pelvic pain.<sup>63</sup> This indication is further compounded by the fact that when pelvic pain is the indication, the age group of the patients tends to be younger, though the overall satisfaction tends to remain high.<sup>64, 65</sup> MacDonald *et al.*<sup>66</sup> compared age groups who underwent hysterectomy. Both the <30 years of age and >40 years of age showed improvement in pain scores. However, the younger group had symptoms of dyspareunia and dysuria that persisted.

As with research with conservative treatment, research on definitive treatment is somewhat scattered. This is because some studies do not specifically address definitive treatment for only endometriosis, but include pain irrespective of etiology. Additionally, in younger patients, some opt to have ovarian conservation, which leads to the potential for recurrence.<sup>20,61</sup> Namnoum *et al.*<sup>67</sup> compared bilateral salpingo-oophorectomy with ovarian preservation. This study showed that women who underwent a hysterectomy with ovarian preservation were more likely to develop recurrent pain and likely to have to undergo another operative procedure. This was further supported by Shakiba *et al.*,<sup>68</sup> who showed that ovarian preservation increased risk of pain recurrence and need for reoperation.

Fedele *et al.*<sup>69</sup> examined the radicality of hysterectomy chosen treatment of all endometriosis. The study showed that there was higher recurrence of pain in the standard extrafascial hysterectomy group versus the radical hysterectomy group. Additionally, Nezhat *et al.* showed that a total hysterectomy decreased need for reoperation compared to subtotal hysterectomy.<sup>70,71</sup>

### Postoperative nonsurgical interventions

The rationality of using nonsurgical methods postoperatively to reduce recurrence is to treat microscopic disease and suboptimally treated disease. More importantly, it is to suppress ovarian function that is critical in the development of endometriosis. Literature supports that postoperative medical treatment in the postoperative period decreases recurrence at least in the medium follow-up period of 24 months.<sup>72-75</sup> Studies have mainly focused in GnRH agonist therapy and oral contraceptive pills. Jee *et al.* showed that use of GnRH agonist for a six month period compared with no postoperative suppression was beneficial in recurrence rates after conservative treatment.<sup>76</sup> Vercellini *et al.* showed that cyclic low-dose oral contraceptive pills also effectively decrease recurrence rates after conservative surgical treatment.<sup>28</sup> However, other studies have shown that oral contraceptive pills were only a temporizing measure and recurrence is merely delayed.<sup>74,77</sup> Depot medroxyprogesterone and danazol have been also used for prevention of postoperative recurrence.<sup>78,79</sup> Recently, the use of the levonorgestrel-releasing intrauterine system has been shown to be effective in symptom control and prevention of recurrence.<sup>79</sup>

### Conclusions

Endometriosis remains an enigmatic disease process. The key is early recognition of symptoms and treatment. Treatment may begin with hormonal suppression. If medical suppression fails or if fertility is desired, surgical intervention should be used. During primary surgical intervention, the goal is for optimal treatment to decrease disease burden. However, despite adequate treatment, reoperation is needed in a good proportion of woman. Factors contributing to recurrence are multifactorial and some can be predicted and some pain recurrence occurs despite obvious evidence. Recurrent

surgery should also aim to decrease disease burden and conservative versus definitive treatment is based on patient's childbearing status. In addition, use of medical treatment can temper recurrence rates. There is still tremendous work that must still be completed in the field of pain recurrence and disease recurrence with endometriosis. Further studies are warranted to look at disease mechanism and methods to decrease recurrence rates.

### Riassunto

#### *Fattori predittivi e trattamento della recidiva dell'endometriosi*

L'endometriosi resta un processo patologico enigmatico. La chiave della sua comprensione risiede nel riconoscimento precoce dei sintomi e nel trattamento, il quale può iniziare con la soppressione ormonale. In caso di insuccesso della soppressione ormonale, o se si desidera preservare la fertilità, si deve ricorrere all'intervento chirurgico. Obiettivo dell'intervento chirurgico primario è quello di raggiungere un trattamento ottimale, riducendo il peso della patologia. Tuttavia, nonostante un trattamento adeguato, in un'ampia percentuale di donne è necessario un secondo intervento chirurgico. Gli elementi favorevoli alla ricorrenza sono multifattoriali, alcuni dei quali possono essere previsti; inoltre, un certo grado di ricorrenza del dolore si verifica nonostante evidenze ovvie. La chirurgia della recidiva deve anche mirare a ridurre il carico patologico mentre il trattamento conservativo *versus* definitivo è basato sullo stato di fertilità della paziente. Inoltre, l'utilizzo del trattamento medico può mitigare i tassi di ricorrenza. Vi è ancora molto lavoro da compiere nell'ambito della ricorrenza del dolore e della patologia.

PAROLE CHIAVE: Endometriosi - Laparoscopia - Dolore pelvico - Terapia ormonale sostitutiva.

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