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Women's Health

Recurrence of endometriosis: risk factors, mechanisms and biomarkers

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While the incidence of endometriosis is up to 40–60% in women with severe dysmenorrhea/chronic pelvic pain, patients with subfertility carries a risk up to 20–30%. In symptomatic patients, although medical therapy is preferred in women with endometriosis, surgery might be needed in nonresponders or patients with an endometrioma. Following the surgery, recurrence of the disease and/or symptoms might be still noticed which will progressively increase as times goes by. Nevertheless, some risk factors have been identified for the risk of recurrence that decreases the success of the procedure. Those risk factors might be classified as patient-disease related and surgery-associated variables. Herein, we will address about the management of endometriosis regarding the risk factors for relapse, mechanisms of recurrence and potential biomarkers to predict the event.

Keywords: biomarker • endometriosis • NF-κB • recurrence

Endometriosis is the presence of endometrial tissue with glands and stroma outside the uterus. The clinical spectrum might present dysmenorrhea, chronic pelvic pain, dyspareunia and infertility, even though most of the cases are asymptomatic. Interestingly, the presence or severity of the disease reveals no correlation with the symptoms or findings. Therefore, the management of asymptomatic patient is not clear.

According to the available literature, whereas the incidence of endometriosis is up to 40–60% in women with severe dysmenorrhea/chronic pelvic pain, patients with subfertility carries a risk up to 20–30% [1]. However, the prevalence might be quite lower in asymptomatic patients going under tubal ligation [1]. In symptomatic patients, although medical therapy is preferred in women with endometriosis, surgery might be needed in nonresponders or patients with an endometrioma. On the other side, recurrence of the disease and/or symptoms might be still noticed which will progressively increase as times goes by.

Herein, we will address about the recurrence rate of endometriosis after treatment, related risk factors, mechanistic explanations and potential biomarkers for prediction.

Recurrence rates

As the prevalence of endometriosis might differ according to the cohort of women, the recurrence rate also depends on the study group, the definition of recurrence, sample size, length of follow-up, the radicalism of the surgery, the experience of the surgeon and postoperative intervention. The definition of recurrence has been made as relapse of pain, absence of improvement in infertility or revisualization of lesions with ultrasonography or surgery in those studies. Furthermore, the feature of follow-up period is also crucial. In the literature, whereas some authors give overall recurrence rate, some report the rate during a certain time of window. Of note, we rarely have information beyond 5 years after surgery. Other than duration of follow-up, the recurrence rate also diminishes when the cohort of women increases that is given in the study. To sum up, the overall recurrence rates ranges between 6 and 67% according to the criteria that is taken into consideration

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and that clearly yields the heterogeneity of the available studies [2,3].

The primary location of the lesions might also influence the risk of relapse. Busacca *et al.* [4] evaluated 144 recurrences of endometriosis and found the 4-year recurrence rates as 24.6, 17.8, 30.6, 23.7% for ovarian, peritoneal, deep and peritoneal endometriosis, respectively. The rates of recurrence increases as time passed after the diagnostic surgery and 8 year recurrence rates are 42, 24.1, 43.4 and 30.9%, respectively [5]. Similarly, Parazzini *et al.* [6] reported that whereas the 2-year recurrence rates for stage I and II endometriosis were 5.7%, they were 14.3% for stage III and IV endometriosis.

Once meta-analysis or systematic reviews are taken into account, when 23 trials are analyzed, Vignali *et al.* [3] expressed that the respective rates of recurrence for 3 and 5 years are 20.5 and 43.5% for the relapse of pain. However, the clinical recurrence rates after those periods of time were 9 and 28% [3]. Exacoustos *et al.* [7] defined the term of recurrence as cysts with a diameter of more than 10 mm and found that pain is a realistic determinant factor on surgery and 76% of patients who have a recurrence had pain related symptoms. Those findings suggest that recurrence rates for pain and related symptoms are higher than the clinical recurrence rates detected by presence of imaging findings such as endometrioma.

Risk factors for recurrence

There are a variety of factors that might be related with the risk of recurrence whether clinically or surgically [8]. However, there is paucity of data for a predictive tool that would be useful in all subgroup of patients. Li *et al.* reported that (n = 285; 36 months follow-up) bilateral pelvic involvement of endometriotic lesions, previous surgery, tenderness-nodularity at cul de sac, postoperative high revised American Fertility Society (rAFS) scores, younger age are all risk factors for the recurrence. One of the largest studies by Liu *et al.* [9] had followed up 710 patients after endometriosis surgery for an average of 22.4 months. The authors defined the term of recurrence either presence of an endometrioma during more than two consecutive menstrual cycles or relapse of pain. At last, they noticed that previous surgery, previous medication usage, younger age at surgery and total rAFS score are all risk factors for the recurrence of endometrioma. Of note, for both types of recurrence, although the hazard rate was constant in the first 28–30 months after surgery, they dramatically increased after that time.

All the available studies are not agree with the risk factors that had been mentioned above. Some authors reported that age at menarche, parity, previous medical treatment of endometriosis, age at surgery, BMI, size of largest cyst at surgery, co-existence of uterine myoma at surgery did not significantly affect recurrence risk.

Not only the severity of the disease but also the extensiveness of the surgery might affect over all recurrence risk. Fedele *et al.* [10] evaluated symptomatic patients with endometriosis in the bladder (n = 47) and stated that the wideness of the surgery is important for recurrence. Similarly, Vignali *et al.* [3] reported that the completeness of the first surgery is a prognostic factor for recurrence for those operated due to deep infiltrating endometriosis. Other related risk factors are given in Table 1. Meanwhile, efforts to distinguish a risk factor among adolescents have been failed, as reported by Tandoil *et al.* [11].

The available data about the type of surgery presents that laparotomy versus laparoscopy have comparable performance regarding the recurrence of dysmenorrhoea and pelvic pain but not dyspareunia. The pregnancy rate also did not show a significant difference between two groups at the end of 24 months. Of note, nerve-sparing approach in rectovaginal endometriosis does not negatively alter the risk of recurrence after bowel resection [12].

Pre- or post-operative medical therapy

Interestingly, while preoperative medical treatment seems to increase the risk of recurrence, postoperative treatment might present some benefits under certain circumstances. To cite an example, Koga *et al.* [13] followed up 224 patients for a minimum of 2 years after laparoscopic ovarian endometrioma excision. Sixty-five patients continued their medical treatment until the surgery with an average duration of 9.7 months and they noticed higher recurrence rates [13]. The absence of any benefit before surgery might be related with some issues. First medication might mask some lesions during surgery and subtle implants could not be resected. After the medication is ceased, probably they would be developed and symptoms recur. Second, medical treatment may alter some genomic process of lesions and suppress normal eukaryotic cells. Thus, it may lead to an increase in dyskaryotic cells in the implants by negative selection.

Mainly, the aim of postoperative medical treatment is suppressing ovarian activity and in turn, leading atrophy of the lesions. Actually, the success of treatment depends on the immediate application of medical treatment after desorption of all visible lesions and prescribing the treatment for a long enough period of time. Among medical treatment, NSAIDs may decrease the severity of pain but it is difficult to say that they have a role on recurrence rates than placebo [14]. In a review of Cochrane, NSAIDs stated to be used for pain in

endometriosis but the existing data were inadequate to say that they were effective for the treatment of pain caused by endometriosis and there was not a significant difference in pain relief between different types of NSAIDs [14].

Other than NSAIDs, since endometriosis is an estrogen-dependent hormonal preparations advocated to be the first line treatment. However, Vercellini *et al.* failed to present a benefit in a multicentre randomized controlled trial (RCT) including 210 women when GnRH agonist is preferred or not [15]. After 24 months, medication arm was reported to have longer duration of time without any symptom, but the overall recurrence rate for the pain was similar. Concordantly, particularly in patients with severe endometriosis, usage of GnRH agonists for 3 months was also represented as ineffectual [15]. Of note, Jee *et al.* [16] reported that although postoperative GnRH agonist treatment did not reduce objective disease recurrence in stage III/IV disease, usage of GnRH agonists delay the time until recurrence, as quoted by Vercellini *et al.* [15]. In a recent prospective controlled trial [17], patients (n = 62) undergoing laparoscopic bilateral endometrial cystectomies with GnRH agonist treatment group had superior cumulative spontaneous pregnancy rate (57.1 vs 36.8%; $p < 0.05$) and lower recurrence rate (12.7 vs 27.4%; $p < 0.05$).

For the androgenic agents, whereas Morgante *et al.* [2] reported that low-dose danazol (100 mg/day for 6 months) and GnRH agonists treatment reduce pelvic pain, Bianchi *et al.* [18] stated that there is not a significant role of danazol on postoperative recurrence rates when used 600 mg/day for 3 months. The difference between the two studies might be related with the dose and duration of treatment.

Among medical options, oral contraceptive pill (OCP) has the best patient compliance with its usage and side effects. In addition, they have an important role on both recurrence rates and pain relief by the theory of ovarian inactivation, decreasing retrograde menstruation process and inhibition on proliferation of lesions. Muzii *et al.* [19] compared 70 patients who were taking low dose cyclic OCP for 6 months and nonusers after laparoscopic ovarian endometrioma excision in an RCT. The authors concluded that although recurrence rates were lower at the end of first year, they became similar at the end of 24 months and 36 months. In a similar design, Seracchioli *et al.* [20], stratified patients as nonusers, cyclic and continuous OCP users in an RCT including 239 women who were prescribed for 24 months in the postoperative period. The respective figures for the relapse of endometrioma were 29, 14.7 and 8.2%. The nonusers had significantly the highest rate of recurrence than the others and the mean diameter of the cyst was smaller in the continuous users. Cyclic or continuous users had comparable performance of relapse. However, one may assume that intermittent menstrual flow during cyclic usage might enforce the lesions. Therefore, the continuous OCP usage might be initiated, particularly if cyclic treatment fails in pain relief.

Levonorgestrel including intrauterine device (LNG-IUD) might be an alternative to oral medication. The progestin makes atrophy in the endometrial glands; downregulates proliferation of endometrial cells, increases apoptosis and reveals an anti-inflammatory and immunomodulatory effect. That causes amenorrhea in most of the patients, also leads to a relief in pain related to menstrual period [21]. In 2003, Vercellini *et al.* [21] assessed the effect of it in a pilot study consisting 40 patients randomized either insertion of LNG-IUD or not. Moderate or severe dysmenorrhea recurred in 2/20 subjects in the intervention arm and

Table 1. The risk factors for the recurrence of endometriosis according to the available data.

Study (year)	Risk factors
Fedele (2004), Vignali (2005), Vercellini (2006), Liu (2007), Moini A (2014)	Younger age
Ghezzi (2001), Jones and Sutton (2002)	Laterality of lesions
Waller and Shaw (1993), Busacca (1999), Parazzini (2005), Abbott (2003), Li (2005), Kikuchi (2006), Liu (2007), Moini A (2014)	rAFS stage rAFS >70 rAFS score
Saleh and Tulandi (1999), Koga (2006), Moini A (2014)	Size of cyst
Renner (2010)	High preoperative pain
Bulletti (2001), Fedele (2004), Li (2005)	Absence of pregnancy
Koga (2006), Liu (2007)	Previous medical treatment
Vignali (2005), Fedele (2000)	Completeness of the first surgery Extend of surgical excision
Li (2005)	Painful nodule

rAFS: Revised American Fertility Society.

it was 9/20 in the control group after 1 year. Bayoglu *et al.* [22] compared LNG-IUD and GnRH agonists in an RCT and found that it is as effective as GnRH after short and medium duration of follow-up.

Mechanisms of recurrence

There are several studies that aim to research the mechanism of recurrence in endometriosis. Theoretically, the recurrent lesions might originate from either residual lesions or *de novo* cells coming through retrograde bleeding. For the former assumption, several studies demonstrate that the recurrence risk increases if the lesions are not completely removed at the initial surgery and they tend to arise on the same location. The surgical approach also impresses the risk of recurrence. According to a Cochrane review including two RCTs, excision of an endometrioma exceeding 3 cm is superior than bipolar ablation of the cyst wall in terms of recurrence of either endometrioma or pain (OR: 0.10; 95% CI: 0.002–0.56) [23]. The only available RCT comparing excision versus ablation with laser concluded that [24] recurrence was less in the excision arm after 12 months, but similar at 24 months. In addition, time to recurrence was shorter in the ablative group (18.1 ± 10.1 vs 7.5 ± 4.3 months; $p < 0.001$). The combined approach (cystectomy and ablation of the hilum with laser) defined by Donnez *et al.* [25] has to be evaluated with RCT, since there were no controls in the described study.

The experience of the surgeon is also a factor that implies the risk of recurrence. According to a prospective cohort study, recurrence rate was found to be less in later 30 cases, when compared with earlier 30 cases (30 vs 10%, respectively) in spite of similar patient characteristics [26]. For the extensiveness of surgery, in a systematic review [27] including 49 trials evaluating the optimal approach in colorectal endometriosis, total recurrence rate was lower in the bowel resection group (5.8%), when compared with full thickness disc excision or superficially excised group (17.6%). Radical hysterectomy was also reported to be superior to the standard extrafascial hysterectomy with a respective pain recurrence rate of 0 and 30.8% at the end of 24 months [28]. And lastly, in a recent cohort study evaluating the recurrence among patients with bowel endometriosis (n = 95), Cox regression analysis revealed a hazard ratio of 6.5 (95% CI: 1.8–23.5; p = 0.005) in women having positive resection margins after surgery [29]. Those findings all support that residual lesions seems to be the primary reason for the recurrence of the disease.

After the initial treatment, regarding the way of recurrence, theory of *de novo* formation of lesions is also debatable. It is noteworthy that, the risk of recurrence is significant up to 2 years after the surgery, even though the peritoneal lesions had been totally eliminated. After endometrial ablation or hysterectomy with bilateral oophorectomy, symptoms might still return 10% of women [30]. Besides, lymphovascular invasion might be noticed frequently in deep infiltrating endometriosis and they are well correlated with the size of the primary foci.

The immunological factors might also play a role on the recurrence of endometriosis. The higher existence of CD15a-positive natural killer cells in both peritoneal fluid and peripheral blood in women with endometriosis were shown previously. Of interest, even after treatment with surgery or medical treatment, they do not prone to decrease which might maintain inflammatory environment for recurrence.

Biomarkers for recurrence

Identifying a useful marker will provide some potential advantages. Initially, establishing risk factors for recurrence may provide classifying subgroups that have the highest risk for disease control. Therefore, consulting the patient to a more experienced team or performing a more extensive surgery might be preferred on those cases. On the other hand, we might not do unnecessary interventions to 'low-profile' women and maybe tailor the treatment modality on the basis of patient's characteristics. Second, while making research about biomarkers, we will probably consider the pathophysiology of the disease in detail.

Since endometriosis is an estrogen dependent disease, first candidate of biomarker is related to the mechanism of sex-steroid synthesis. To recall the basic principles, there are two types of estrogen receptors (ER), namely ER-α and ER-β. They consist of an E-binding and a DNA-binding domain. After binding to ligands, these receptors act as transcriptional factors that upregulate or downregulate gene expression by interacting with regulatory regions of target genes [31]. Regarding with the receptors, Luisi *et al.* [31] investigated whether there is a possible correlation between *ER* gene polymorphisms and both clinical and prognostic indices of recurrent endometriosis. After a total of 61 women with recurrent endometriosis are evaluated, *ER-α Pvu II* polymorphisms showed a frequency of PP, Pp and pp genotypes of 54, 46 and 0%, respectively [31]. In concordance with that, women with PP ERalfa genotype had been reported to have higher bone mineral density and increased risk of undergoing premenopausal hysterectomy due to leiomyoma than other genotypes.

COX-2 is a rate-limiting enzyme on prostaglandin (PG) synthesis and plays a crucial role in inflammation and proliferation related with endometriosis [32].

Naturally, factors regulating PG synthesis becomes potential candidates for the prediction of recurrence after treatment. Nevertheless, overexpression of COX-2 is correlated with the intensity of dysmenorrhea, and nonmenstrual chronic pelvic pain in women with endometriosis. Yuan *et al.* [32] evaluated 109 patients for recurrence who had histologically confirmed endometriosis from previous surgery. COX-2 expression was investigated by immunohistochemistry in endometrioma tissue samples and 53 patients detected to have recurrence while the remaining 56 did not. They showed a significantly higher level of COX-2 staining scores in the recurrent group than the controls. The authors concluded that overexpression of COX-2 might be a key factor in patients having high risk of endometriosis. Therefore, NSAIDs might be a better option for the success of the treatment in patients with high levels of COX-2 staining scores.

NF-κB is a dimeric transcription factor that promotes the expression of more than 150 genes that involve in cellular process including immune response, inflammatory process, cell adhesion, proliferation and apoptosis [33]. NF-κB inactivation occurs through the progesterone receptors (PRs). In the endometrium, there is a dynamic challenge with NF-κB activation and PR-B expression. Oxidants and cytokines are inducers of NF-κB activation, which in turn causes proliferation of endometriosis. Therefore, NF-κB seems to have a pivotal role on the pathogenesis of endometriosis and a promising biomarker to identify the patients having a high risk of recurrence in endometriosis. In that concept, Shen *et al.* [34] evaluated 109 patients having historically confirmed endometriosis and divided them according to the presence (n = 53) or absence (n = 56) of recurrence after 30 months from the surgery. When tissue blocks were stained of progesterone receptor isoform B (PR-B) and NF-κB p65 subunit, whereas immunoreactivity of NF-κB p65 was significantly higher in the recurrent group, PR-B immunoreactivity was significantly higher in the nonrecurrent group. In addition, statistically, they eclipsed the prediction power of COX-2 after regression model [34]. Again, those findings evoke the way of individualized treatment. To cite an example, progestin-only treatment modalities will not be appropriate for women having low PR-B immunoreactivity. On the other side, inhibitors of NF-κB will be more useful if there is significant reactivity after histochemical staining.

Conclusion

In conclusion, it is obvious that in spite of great efforts in the field of exploring the risk factors, the chance of eliminating the odds of recurrence is not optimistic. Nevertheless, there is urgent need for establishment of patient dependent factors and biomarkers that can be used for prediction. By that strategy, novel targeted and individualized treatments might be explored and used according to patient characteristics.

Future perspective

The current data fails to demonstrate a unique biomarker that can be preferred in the prediction of endometriosis. That is already related with the highly complicated nature in the pathogenesis of the disease. Once we understand the mechanisms underlying the occurrence and recurrence of the disease more clearly, we might be compatible to generate multivariate models with high success.

Financial & competing interests disclosure

The author has 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.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- In clinical practice, it is troublesome to eliminate the risk of recurrence totally, after the treatment of endometriosis.
- A variety of risk factors have been identified in the literature and they can be classified as patient/disease dependent and surgery dependent points.
- While more extensive surgery by a more experienced surgeon team minimizes the risk, patient/disease related factors still stay there.
- According recent data, the use of oral contraceptive pill clearly diminishes the risk of endometriosis after the surgery.
- The efforts to find an ideal biomarker for recurrence will not only give birth to individualized treatment, but also will make us understand the pathophysiology of endometriosis and abandon the risk factors related with the disease.
- Currently, COX-2 and NF-κB are two important candidates as a biomarker of recurrence. However, available data are scanty and specialized studies focusing on the recurrence of endometriosis are urgently warranted.

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