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## Surgical treatment of endometriosis: prognostic factors for better quality of life

Silvia Vannuccini<sup>a,b</sup>, Fernando M. Reis<sup>c</sup>, Larissa M. Coutinho<sup>c,d</sup>, Lucia Lazzeri<sup>b</sup>, Gabriele Centini<sup>b</sup> and Felice Petraglia<sup>e</sup>

<sup>a</sup>Department of Neuroscience, Psychology, Pharmacology and Child Health (NEUROFARBA), University of Florence, Careggi University Hospital, Florence, Italy; <sup>b</sup>Department of Molecular and Developmental Medicine, Obstetrics and Gynecology, University Hospital of Siena, Siena, Italy; <sup>c</sup>Department of Obstetrics and Gynecology, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; <sup>d</sup>Department of Maternal and Child Health, Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil; <sup>e</sup>Department of Experimental, Clinical and Biomedical Sciences, University of Florence, Careggi University Hospital, Florence, Italy

### ABSTRACT

The present study investigated the effect of surgical treatment of endometriosis on physical and mental health. We undertook a prospective survey including 153 premenopausal women with histological diagnosis of endometriosis. The Short Form 12 (SF-12) questionnaire comprising physical and mental component scales was used. Two groups of patients were distinguished: Group A ( $n=42$ ) with SF-12 scores above the median in both physical and mental scales; Group B ( $n=111$ ) with SF-12 scores below the median in either physical or mental scale. Group A was diagnosed and operated for endometriosis for the first time at an older age (30 vs. 26 years), had undergone more frequently a single surgical intervention (64% vs. 46%), was less affected by symptom or lesion recurrence and had reported less intense current pain symptoms than Group B. Having the first endometriosis surgery at a later age was an independent predictor of better health status (adjusted odds ratio 1.146 per year, 95% confidence interval 1.058–1.242) after accounting for the potential confounding effects of reoperation, pelvic pain and time elapsed since the first surgery. In conclusion, patients with endometriosis who had a single surgery at an older age have good symptom control and better quality of life (QoL).

### ARTICLE HISTORY

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Endometriosis; surgery; physical health; mental health; SF-12; quality of life; recurrence; pain

### Introduction

Endometriosis is a chronic benign disease that affects women in the reproductive age [1,2], with a negative impact on quality of life (QoL) due to painful symptoms, infertility and high levels of perceived stress [3–5]. Medical therapy and surgical interventions are available for the management of endometriosis [6–8]. Laparoscopy is prescribed in patients with painful symptoms and subfertility in order to remove endometriotic lesions and adhesions and restore the pelvic anatomy [9–11]. Surgery is required also for patients with contraindications or poor response to medical therapies, for acute pelvic pain events and to make differential diagnosis with malignant adnexal mass [12]. However, as a chronic and heterogeneous disease, endometriosis is seldom treated just once with a definitive therapeutic approach [13] and requires a life-long management plan [14].

Recurrence of symptoms or lesions is highly concerning in patients who have undergone surgery for endometriosis [15,16]. The surgical treatment is planned to remove the disease as completely as possible, but residual foci may be left behind due to incomplete diagnosis, technical difficulties and conservative surgical interventions often performed in young patients who wish to conceive [17]. In addition, new lesions may arise and reactivate the disease after a temporary therapeutic achievement [12,18]. The best indicator of a successful surgical treatment of endometriosis is a complete and durable symptom relief, with the achievement of good physical and mental health [19]. This outcome depends on the completeness of the surgical treatment,

but other prognostic factors may also be relevant in order to offer the best information to patients undergoing surgery.

The aim of the present study was to investigate whether there is any association between specific features of women with surgically treated endometriosis and impaired post-surgery QoL, measured by the SF-12 questionnaire.

### Materials and methods

#### Study design

A prospective survey was performed including 153 premenopausal women at mean age  $36 \pm 3$  years old, and normal BMI ( $22 \pm 2.0$  Kg/m<sup>2</sup>) with surgical and histological diagnosis of endometriosis. Data were collected after routine outpatient care at the Gynecologic Clinic of the University of Siena/Italy, by using our Endometriosis Archiving Software (ENEAS) database [20], and validated through review of medical records of all participants. The study was approved by the local Institutional Review Board and all participants provided written informed consent to be included in the series.

The database contained all information about: (a) demographic and clinical characteristics (age, BMI, age at menarche, age at diagnosis of endometriosis, current pelvic pain severity); (b) surgical treatments (age at each operation, localization of endometriotic lesions at first surgery, surgeon expertise and type of surgical technique at first operation, post-operative medical

therapy, total number of surgeries and time since first surgery); (c) recurrence of lesions (identified by imaging or surgical visualization and/or histology) or symptoms (dysmenorrhea, dyspareunia, non-cyclic pelvic pain). The current pelvic pain severity was assessed by Visual Analog Scale (VAS) and defined as no pain (VAS  $\leq 4$ ), mild pain (VAS 5–6), moderate pain (VAS 6–7), severe pain (VAS  $\geq 8$ ). The localization of endometriotic lesions was classified according to the three phenotypes: ovarian endometriosis (OMA), superficial endometriosis (SUP), deep infiltrating endometriosis (DIE) and mixed phenotypes [21].

### Study protocol

All participants answered to a validated tool for health-related QoL, the Short Form 12 (SF-12), comprising both mental and physical component scales [22]. This instrument contains 12 items selected from the SF-36, including at least one item from each of the SF-36 scales. SF-12 scores correlate strictly with those of SF-36, but SF-12 has the advantages of being shorter and having country-specific scoring systems adjusted for each population [22].

As in the Italian general population the median physical and mental scores of SF-12 are reported to be 51.2 and 47.8, respectively [22], we have used these cut-offs for identifying two groups among the participants. Group A was composed by patients who had SF-12 scores above the median in both physical and mental scales, and they were, therefore, considered the patients with a satisfactory QoL. Group B comprised the patients who presented at least one score (physical and/or mental) below the medians, and it consisted of the cluster with an impaired QoL. By identifying these two groups, we aimed to compare if the patients' characteristics (i.e. demographic and clinical features, information about the surgery/s and endometriosis recurrence) would differ according to the health-related QoL, as measured by the SF-12 questionnaire.

### Data evaluation and statistical analysis

Statistical analysis was performed using IBM SPSS Statistics software, version 22 (IBM Corporation, Armonk, NY, USA).

Statistically significant differences between groups were determined using Mann–Whitney  $U$  test and Chi-square test or Fisher's exact test. A value of  $p < .05$  was considered statistically significant.

We performed a stepwise backward logistic regression to assess potential clinical characteristics independently associated with SF-12 scores. Data are reported as adjusted odds ratios (OR) with 95% confidence intervals (95% CI).

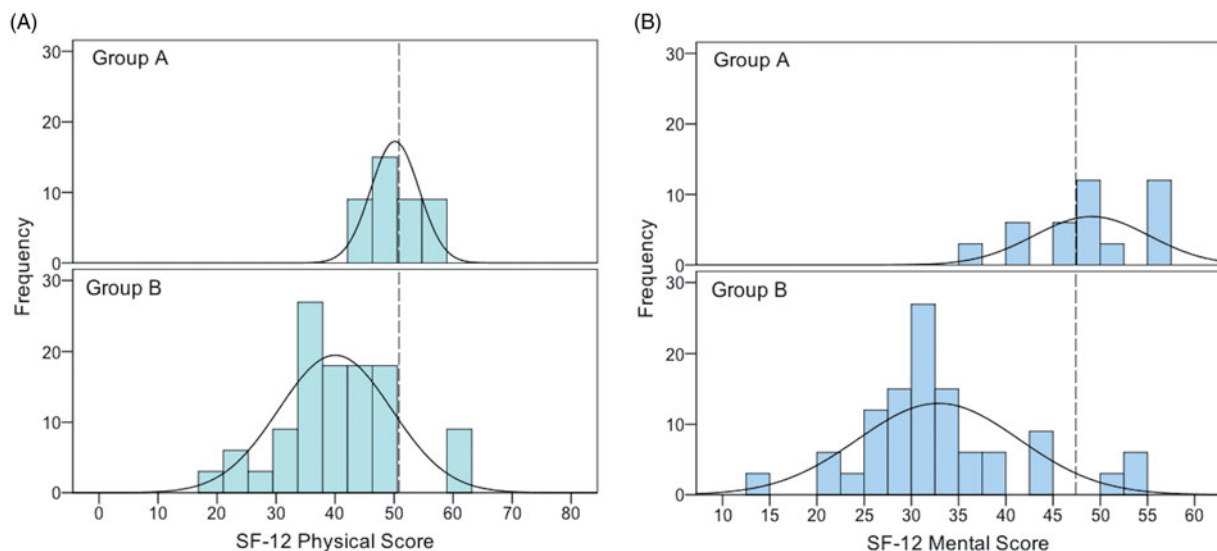
The sample size was estimated to detect differences of at least 0.5 standard deviations in quantitative variables or 20% in the frequency of categorical variables between groups with 80% statistical power and 95% confidence level.

### Results

In the study sample, the median physical and mental scores of SF-12 were 44 and 35, respectively, and they did significantly differ from the Italian population normal values ( $p = .0001$ ). The distribution of physical and mental SF-12 scores in the study participants is shown in Figure 1, which displays also the mean value of the representative sample of the general Italian population [22]. According to these cut-offs, Group A ( $n = 42$ ) and Group B ( $n = 111$ ) were compared.

The two groups did not differ in terms of actual age or BMI. However, Group A has been diagnosed and operated for endometriosis for the first time at an older age (30 vs. 26 years,  $p < .001$ ) and the surgery has been done more recently (82 vs. 115 months,  $p < .01$ ) than in Group B. More patients of Group A had undergone a single surgical intervention (64% vs. 46%,  $p < .05$ ) and Group A was less affected by symptom or lesion recurrence than Group B (Table 1). Current pelvic pain was less intense in Group A compared to that reported by Group B (Chi-square for linear trend = 10.9,  $p = .001$ , Figure 2).

As shown in Table 1, Groups A and B differed regarding the endometriosis lesions' localization. The association of the three phenotypes was more frequently observed in Group B ( $p = .0001$ ). Similarly, coexistent superficial and ovarian phenotypes were more commonly found in Group B, whereas the presence of DIE lesions alone was more often detected in Group A. There were no differences in terms of the surgeon who performed the operation (gynecologist, general surgeon or



**Figure 1.** Frequency distribution of SF-12 physical (A) and mental (B) scores of women with endometriosis in the present study. The dotted lines indicate the mean value of a representative sample of the general Italian population [21].

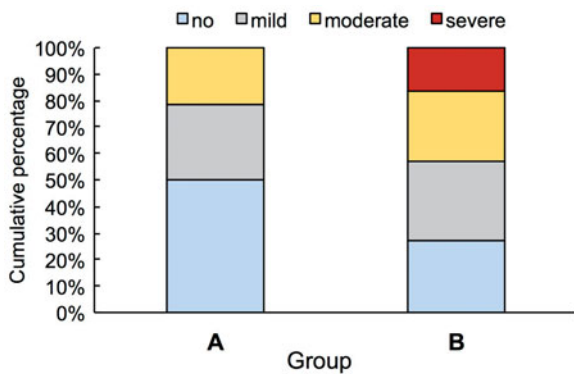
**Table 1.** Clinical characteristics of the study groups.

	Group A (n = 42)	Group B (n = 111)	p-value
Age (years)	36.6 ± 4.4	36.1 ± 7.0	.230
BMI (Kg/m <sup>2</sup> )	21.9 ± 2.6	22.1 ± 3.4	.868
Age at menarche (years)	12.1 ± 0.8	12.5 ± 1.4	.052
Age at first surgery (years)	30.4 ± 5.5	26.5 ± 5.0	.000
Lesions at first surgery			
SUP only	6 (14%)	6 (5%)	.000
OMA only	15 (36%)	51 (46%)	
DIE only	6 (14%)	0 (0%)	
SUP + OMA	3 (7%)	18 (16%)	
SUP + DIE	3 (7%)	3 (3%)	
OMA + DIE	6 (14%)	12 (11%)	
SUP + OMA + DIE	3 (7%)	21 (19%)	
Surgeon			
Gynecologist	33 (79%)	90 (81%)	.481
General surgeon	3 (7%)	3 (3%)	
Multidisciplinary team	6 (14%)	18 (16%)	
Technique			
Laparoscopy	33 (79%)	93 (84%)	.477
Laparotomy	6 (14%)	15 (13%)	
Both	3 (7%)	3 (3%)	
Post-operative medical therapy			
None	9 (21%)	24 (22%)	.001
GnRH agonist	15 (36%)	21 (19%)	
Progestin	15 (36%)	30 (27%)	
Combined hormonal contraceptive	3 (7%)	12 (11%)	
Multiple hormonal therapy	0 (0%)	24 (22%)	
Time since first surgery (months)	82 ± 51	115 ± 69	.003
No. of surgeries	1.6 ± 0.9	2.0 ± 1.2	.047
Two or more surgeries (n, %)	15 (36%)	60 (54%)	.042
Recurrence of pain (n, %)			
Dysmenorrhea	21 (50%)	75 (68%)	.047
Dyspareunia	9 (21%)	27 (24%)	.704
Non-cyclic pelvic pain	12 (29%)	57 (51%)	.010
Recurrence of lesion (n, %)	21 (50%)	75 (68%)	.047

Group A: women with SF-12 scores above the median in both physical and mental scales.

Group B: women with SF-12 scores below the median in either physical or mental scale.

SUP: superficial peritoneal endometriosis; OMA: ovarian endometrioma; DIE: deep infiltrating endometriosis.



**Figure 2.** Proportion of women currently experiencing several degrees of pelvic pain in the two study groups.

multidisciplinary team) and the technique used (laparoscopy, laparotomy or both).

Regarding the post-operative hormonal therapy, Group A underwent more frequently to GnRH agonist or progestins treatment, whereas in Group B multiple hormonal therapies were administered ( $p = .001$ ).

Multivariable logistic regression indicated that having the first endometriosis surgery at a later age was an independent predictor of better health status (adjusted odds ratio 1.146 per year,

**Table 2.** Multivariable logistic regression for variables possibly associated with good health status, defined as SF-12 above the median (Group A).

Variable	Adjusted OR	95% CI	p-value
Age at first surgery (per year)	1.146	1.058–1.242	.001
Non-cyclic pelvic pain	0.435	0.271–0.698	.001
Two or more surgeries	0.843	0.313–2.271	.735

95% confidence interval 1.058–1.242,  $p = .001$ ) after accounting for the potential confounding effects of reoperation and non-cyclic pelvic pain (Table 2).

**Discussion**

The present study showed that patients with endometriosis and impaired QoL had first surgery at a younger age, more symptoms recurrence and more reoperations. Therefore, having the first endometriosis surgery at a later age was an independent predictor of better health condition.

A timely first surgery plays a pivotal role in a life-long treatment of patients affected by endometriosis and a not well-performed intervention often makes the subsequent one harder. Cheong *et al* showed that age is the main factor that influences the likelihood of repeated surgery, which could be linked to increased aggressiveness of the disease when it occurs in young women or to a surgeon’s tendency to be less radical in the approach of younger patients [23]. The first surgery for endometriosis should be based on pain and desire for pregnancy not responsive to medical treatment or ART [12]. Asymptomatic young patients who do not wish a pregnancy in the near future should be informed about the possibility of post-operative recurrence and the risks and difficulties related to additional surgeries. In fact, an increased risk of disease recurrence and repeated operations was found in women having their index surgery before 30 years old [24]. In case of endometrioma, young patients must be also informed about the possible reduction of ovarian function and ovarian loss, as a result of the surgery [12,25–29].

Our results showed a higher prevalence of coexistent phenotypes (SUP + OMA; SUP + OMA + DIE) in women with impaired QoL. Furthermore, those who had a worse QoL have been submitted to multiple surgical interventions. As shown by Sibiude *et al.*, patients with previous surgeries for endometriosis are more likely to have DIE and a higher disease stage at the time of the surgery [13]. Indeed, the number of operations increases the patient’s perceived stress, suggesting an adverse effect of multiple surgeries on mental and psychological state [5].

Despite the improvement of surgical techniques and the advances in preoperative evaluation of the extension of the disease [30–32], the recurrence of endometriosis and the need of repeated surgery remain frequent outcomes [18,25]. The reappearance of symptoms and endometriotic lesions increases over the time and varies according to the subtype of the disease and surgery-related variables [15]. The recurrence rates described reach 22% at 2 years of post-intervention and 40–50% at 5 years, and the probability of a further surgical procedure is about 15–20% [18,33–35]. The present study showed that patients with symptoms and lesion recurrence have the worse SF-12 scores, reinforcing the negative relationship of endometriosis recurrence and physical and mental wellbeing [36]. Pain is a crucial symptom in determining the health status, in fact women with chronic pelvic pain had poorer QoL and mental health [37]. Furthermore, those with severe pain showed a higher incidence of multiple psychiatric disorders [38].

A pivotal role after surgical treatment is played by medical treatment [39–42], in order to prevent recurrence [43,44] and to manage symptoms [45]. The use of a post-operative medical therapy has been widely addressed in literature for patients who are not seeking conception [40]. Our results showed, from one hand, that the patients with satisfactory QoL underwent more often to post-operative progestins or GnRH analogs treatment, whereas the use of multiple hormonal drugs was more common in those with low QoL scores. Long term treatment with progestins have been shown to reduce pain, improve health perception and prevent recurrence [46–50]. Similarly, GnRH agonists treatment after surgery for six months significantly decreases the recurrence rate of endometriosis [51,52]. The use of multiple therapies in Group B may reflect a more aggressive behavior of endometriosis, pharmacologic resistance and a worse clinical presentation of the disease in those who presented with low QoL.

One methodological strength of this study is the standardized documentation of clinical data on a dedicated database. In addition, the follow-up interviews were performed face-to-face, reducing the risk of recall bias. However, there are some limitations to acknowledge: patients who had undergone either single or multiple surgeries were included; all preoperative and surgical data were obtained from medical files and reports, despite the patients being interviewed prospectively. Furthermore, additional variables have not been assessed in the present study such as socioeconomic status, previous mental health, sexuality, coexisting painful conditions and lifestyle habits, that, among others, could also have influence over the health status of the patients [53,54]. It should be also observed that the association of a worse QoL and a younger age at the first surgery could reflect an initial less aggressive approach because of less severe forms of the disease. In fact, Groups A and B significantly differ in terms of lesions' localization. Unfortunately, no information about the surgical ASRM classification [55] were available, so we used the lesions' localization as a proxy for endometriosis extension [21], although this may not always provide a reliable picture of the severity of the disease. The endometriosis recurrence, on the other hand, could be also related to the experience and technical capabilities of the surgical team [56]. Our results, nevertheless, did not show any differences in terms of QoL depending on the surgeon who performed the operation. However, the small number of patients operated by a general surgeon or a multidisciplinary team does not allow to draw final conclusions.

In summary, our results suggest that patients with endometriosis undergoing first surgery at young age reported an increased frequency of multiple surgeries and disease recurrence, showing a poor physical and mental health status. Preoperative counseling is a key step of endometriosis management and the prognostic variables identified here may help the surgeon to better inform the patient about her odds of gaining a satisfactory health condition after pursuing this complex treatment.

## Disclosure statement

No potential conflict of interest was reported by the authors.

## References

- [1] Greene AD, Lang SA, Kendzierski JA. Endometriosis: where are we and where are we going? *Reproduction*. 2016;152:R63–78.
- [2] Zondervan KT, Becker CM, Koga K, et al. Endometriosis. *Nat Rev Dis Primers*. 2018;4:9.
- [3] Nnoaham KE, Hummelshoj L, Webster P, et al. World endometriosis research foundation global study of women's health consortium. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. *Fertil Steril*. 2011;96:366–373.
- [4] Petrelluzzi KF, Garcia MC, Petta CA, et al. Salivary cortisol concentrations, stress and quality of life in women with endometriosis and chronic pelvic pain. *Stress*. 2008;11:390–397.
- [5] Lazzeri L, Orlandini C, Vannuccini S, et al. Endometriosis and perceived stress: impact of surgical and medical treatment. *Gynecol Obstet Invest*. 2015;79:229–233.
- [6] Bedaiwy MA, Allaire C, Yong P, et al. Medical management of endometriosis in patients with chronic pelvic pain. *Semin Reprod Med*. 2017;35:38–53.
- [7] Vercellini P, Viganò P, Somigliana E, et al. Endometriosis: pathogenesis and treatment. *Nat Rev Endocrinol*. 2014;10:261–275.
- [8] Rafique S, Decherney AH. Medical management of endometriosis. *Clin Obstet Gynecol*. 2017;60:485–496.
- [9] Flyckt R, Kim S, Falcone T. Surgical management of endometriosis in patients with chronic pelvic pain. *Semin Reprod Med*. 2017;35:54–64.
- [10] Tanbo T, Fedorcsak P. Endometriosis-associated infertility: aspects of pathophysiological mechanisms and treatment options. *Acta Obstet Gynecol Scand*. 2017;96:659–667.
- [11] Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. *Obstet Gynecol Clin North Am*. 2012;39:535–549.
- [12] Singh SS, Suen MW. Surgery for endometriosis: beyond medical therapies. *Fertil Steril*. 2017;107:549–554.
- [13] Sibiude J, Santulli P, Marcellin L, et al. Association of history of surgery for endometriosis with severity of deeply infiltrating endometriosis. *Obstet Gynecol*. 2014;124:709–717.
- [14] Kuznetsov L, Dworzynski K, Davies M, et al. Diagnosis and management of endometriosis: summary of NICE guidance. *Br Med J*. 2017; 358:j3935.
- [15] Bozdag G. Recurrence of endometriosis: risk factors, mechanisms and biomarkers. *Womens Health (Lond)*. 2015;11:693–699.
- [16] Koga K, Takamura M, Fujii T, et al. Prevention of the recurrence of symptom and lesions after conservative surgery for endometriosis. *Fertil Steril*. 2015;104:793–801.
- [17] Alimi Y, Iwanaga J, Loukas M, et al. The clinical anatomy of endometriosis: a review. *Cureus*. 2018;10:e3361.
- [18] Guo SW. Recurrence of endometriosis and its control. *Hum Reprod Update*. 2009;15:441–461.
- [19] Arcoverde FVL, Andres MP, Borrelli GM, et al. Surgery for endometriosis improves major domains of quality of life: a systematic review and meta-analysis. *J Minim Invasive Gynecol*. 2019;26:266–278.
- [20] Centini G, Zannoni L, Lazzeri L, et al. Enhanced Endometriosis Archiving Software (ENEAS): an application for storing, retrieving, comparing, and sharing data of patients affected by endometriosis integrated in the daily practice. *J Minim Invasive Gynecol*. 2017;24: 494–500.
- [21] Tosti C, Pinzauti S, Santulli P, et al. Pathogenetic mechanisms of deep infiltrating endometriosis. *Reprod Sci*. 2015;22:1053–1059.
- [22] Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA project. *International quality of life assessment*. *J Clin Epidemiol*. 1998;51:1171–1178.
- [23] Cheong Y, Tay P, Luk F, et al. Laparoscopic surgery for endometriosis: how often do we need to re-operate? *J Obstet Gynaecol*. 2008; 28:82–85.
- [24] Shakiba K, Bena JF, McGill KM, et al. Surgical treatment of endometriosis: a 7-year follow-up on the requirement for further surgery. *Obstet Gynecol*. 2008;111:1285–1292.
- [25] Berlanda N, Vercellini P, Fedele L. The outcomes of repeat surgery for recurrent symptomatic endometriosis. *Curr Opin Obstet Gynecol*. 2010;22:320–325.
- [26] Kho RM, Andres MP, Borrelli GM, et al. Surgical treatment of different types of endometriosis: comparison of major society guidelines and preferred clinical algorithms. *Best Pract Res Clin Obstet Gynaecol*. 2018;51:102–110.
- [27] Nowak-Psiorz I, Ciecwiez SM, Brodowska A, et al. Treatment of ovarian endometrial cysts in the context of recurrence and fertility. *Adv Clin Exp Med*. 2019;28:407–413.
- [28] Santulli P, Lamau MC, Marcellin L, et al. Endometriosis-related infertility: ovarian endometrioma per se is not associated with presentation for infertility. *Hum Reprod*. 2016;31:1765–1775.

- [29] Chiang HJ, Lin PY, Huang FJ, et al. The impact of previous ovarian surgery on ovarian reserve in patients with endometriosis. *BMC Womens Health*. 2015;15:74.
- [30] Exacoustos C, Malzoni M, Di Giovanni A, et al. Ultrasound mapping system for the surgical management of deep infiltrating endometriosis. *Fertil Steril*. 2014;102:143–150. e142.
- [31] Guerriero S, Condous G, van den Bosch T, et al. Systematic approach to sonographic evaluation of the pelvis in women with suspected endometriosis, including terms, definitions and measurements: a consensus opinion from the International Deep Endometriosis Analysis (IDEA) group. *Ultrasound Obstet Gynecol*. 2016;48:318–332.
- [32] Nisenblat V, Bossuyt PM, Farquhar C, et al. Imaging modalities for the non-invasive diagnosis of endometriosis. *Cochrane Database Syst Rev*. 2016;2:Cd009591.
- [33] Vercellini P, Barbara G, Abbiati A, et al. Repetitive surgery for recurrent symptomatic endometriosis: what to do? *Eur J Obstet Gynecol Reprod Biol*. 2009;146:15–21.
- [34] Donnez J, Squifflet J. Complications, pregnancy and recurrence in a prospective series of 500 patients operated on by the shaving technique for deep rectovaginal endometriotic nodules. *Hum Reprod*. 2010;25:1949–1958.
- [35] Saraswat L, Ayansina D, Cooper KG, et al. Impact of endometriosis on risk of further gynaecological surgery and cancer: a national cohort study. *BJOG: Int J Obstet Gynecol*. 2018;125:64–72.
- [36] Culley L, Law C, Hudson N, et al. The social and psychological impact of endometriosis on women's lives: a critical narrative review. *Hum Reprod Update*. 2013;19:625–639.
- [37] Facchin F, Barbara G, Saita E, et al. Impact of endometriosis on quality of life and mental health: pelvic pain makes the difference. *J Psychosom Obstet Gynaecol*. 2015;36:135–141.
- [38] Vannuccini S, Lazzeri L, Orlandini C, et al. Mental health, pain symptoms and systemic comorbidities in women with endometriosis: a cross-sectional study. *J Psychosom Obstet Gynaecol*. 2018;39:315–320.
- [39] Vercellini P, Frontino G, De Giorgi O, et al. Endometriosis: preoperative and postoperative medical treatment. *Obstet Gynecol Clin North Am*. 2003;30:163–180.
- [40] Somigliana E, Vercellini P, Vigano P, et al. Postoperative medical therapy after surgical treatment of endometriosis: from adjuvant therapy to tertiary prevention. *J Minim Invasive Gynecol*. 2014;21:328–334.
- [41] Somigliana E, Busnelli A, Benaglia L, et al. Postoperative hormonal therapy after surgical excision of deep endometriosis. *Eur J Obstet Gynecol Reprod Biol*. 2017;209:77–80.
- [42] Rocha AL, Reis FM, Petraglia F. New trends for the medical treatment of endometriosis. *Expert Opin Investig Drugs*. 2012;21:905–919.
- [43] Wu B, Yang Z, Tobe RG, et al. Medical therapy for preventing recurrent endometriosis after conservative surgery: a cost-effectiveness analysis. *BJOG: Int J Obstet Gynecol*. 2018;125:469–477.
- [44] Tobiume T, Kotani Y, Takaya H, et al. Determinant factors of postoperative recurrence of endometriosis: difference between endometrioma and pain. *Eur J Obstet Gynecol Reprod Biol*. 2016;205:54–59.
- [45] Vercellini P, Buggio L, Frattaruolo MP, et al. Medical treatment of endometriosis-related pain. *Best Pract Res Clin Obstet Gynaecol*. 2018;51:68–91.
- [46] Belaisch J. Progestins and medical treatment of endometriosis – physiology, history and society. *Gynecol Endocrinol*. 2009;25:751–756.
- [47] Vercellini P, Buggio L, Berlanda N, et al. Estrogen-progestins and progestins for the management of endometriosis. *Fertil Steril*. 2016;106:1552–1571.e2.
- [48] Andres MDP, Lopes LA, Baracat EC, et al. Dienogest in the treatment of endometriosis: systematic review. *Arch Gynecol Obstet*. 2015;292:523–529.
- [49] Römer T. Long-term treatment of endometriosis with dienogest: retrospective analysis of efficacy and safety in clinical practice. *Arch Gynecol Obstet*. 2018;298:747–753.
- [50] Vercellini P, Bracco B, Mosconi P, et al. Norethindrone acetate or dienogest for the treatment of symptomatic endometriosis: a before and after study. *Fertil Steril*. 2016;105:734–743.e3.
- [51] Zheng Q, Mao H, Xu Y, et al. Can postoperative GnRH agonist treatment prevent endometriosis recurrence? A meta-analysis. *Arch Gynecol Obstet*. 2016;294:201–207.
- [52] Takaesu Y, Nishi H, Kojima J, et al. Dienogest compared with gonadotropin-releasing hormone agonist after conservative surgery for endometriosis. *J Obstet Gynaecol Res*. 2016;42:1152–1158.
- [53] Lovkvist L, Bostrom P, Edlund M, et al. Age-related differences in quality of life in Swedish women with endometriosis. *J Womens Health (Larchmt)*. 2016;25:646–653.
- [54] Pluchino N, Wenger JM, Petignat P, et al. Sexual function in endometriosis patients and their partners: effect of the disease and consequences of treatment. *Hum Reprod Update*. 2016;22:762–774.
- [55] American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril*. 1997;67:817–821.
- [56] Exacoustos C, Lazzeri L, Zupi E. Expert sonographers and surgeons are needed to manage deep infiltrating endometriosis. *Ultrasound Obstet Gynecol*. 2017;49:417.