

Endometriomas with low-risk malignancy potential in ultrasonography with high human epididymis protein 4 and risk of ovarian malignancy algorithm: a cases series

Tolga Karacan, Eser Ozyurek, Seyma Yesiralioglu, Huseyin Kiyak, Taner Usta & Engin Oral

To cite this article: Tolga Karacan, Eser Ozyurek, Seyma Yesiralioglu, Huseyin Kiyak, Taner Usta & Engin Oral (2019): Endometriomas with low-risk malignancy potential in ultrasonography with high human epididymis protein 4 and risk of ovarian malignancy algorithm: a cases series, Gynecological Endocrinology, DOI: [10.1080/09513590.2019.1653842](https://doi.org/10.1080/09513590.2019.1653842)

To link to this article: <https://doi.org/10.1080/09513590.2019.1653842>



Published online: 20 Aug 2019.



Submit your article to this journal [↗](#)



View related articles [↗](#)





View Crossmark data [↗](#)

CASE REPORT



Endometriomas with low-risk malignancy potential in ultrasonography with high human epididymis protein 4 and risk of ovarian malignancy algorithm: a cases series

Tolga Karacan^a, Eser Ozyurek^a , Seyma Yesiralioglu^a, Huseyin Kiyak^b , Taner Usta^c and Engin Oral^d

^aDepartment of Obstetrics and Gynecology, Bagcilar Research and Education Hospital, University of Health Sciences, Istanbul, Turkey;

^bDepartment of Obstetrics and Gynecology, Kanuni Sultan Suleyman Research and Education Hospital, University of Health Sciences, Istanbul, Turkey; ^cDepartment of Obstetrics and Gynecology, Altunizade Hospital, Acibadem University, Istanbul, Turkey; ^dDepartment of Obstetrics and Gynecology, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey

ABSTRACT

Endometriosis is an estrogen-dependent disease that affects 5 to 15% of women of reproductive age. Data from large-cohort and case-control studies indicate an increased risk for ovarian cancers in women with endometrioma. Recently, as an ovarian cancer biomarker, human epididymal secretory protein E4 (HE4) has been increasingly investigated in the differentiating of endometrioma from ovary malignancy and in confirming the benign structure of the endometrioma. This case series study describes women who underwent surgery due to increased serum HE4 levels and higher Risk of Ovarian Malignancy Algorithm (ROMA) index, in whom the final pathology was reported as benign, although, ultrasonography and magnetic resonance imaging (MRI) findings showed features of “typical” endometrioma.

ARTICLE HISTORY

Received 27 November 2018
Revised 16 July 2019
Accepted 4 August 2019
Published online 20 August 2019

KEYWORDS

Endometrioma; human epididymal secretory protein e4; risk of ovarian malignancy algorithm index

Introduction

Endometriosis is an estrogen-dependent disease that affects 5 to 15% of women of reproductive age. Between 17% and 44% of women with endometriosis have ovarian endometriomas. Data from large-cohort and case-control studies indicate an increased risk for ovarian cancers in women with endometrioma [1–3]. The biologic behavior of the malignant transformation of ovarian endometrioma (i.e. the pattern of disease progression and changes in gene expression during primary tumor development) remains unclear [4]. Typical sonographic appearances of endometriomas, a unilocular cyst with homogeneous low-level echogenicity or ground glass pattern, are demonstrated in only 50–65% of the cases; the remaining cases are atypical and often suspected of malignancy, resulting in over-preparation or unnecessary referrals for specialist opinions [5].

Considering the association of endometrioma with fertility, the right timing for surgery is crucial because surgery may cause accidental removal of part of the ovarian tissue containing primordial follicles, resulting in diminished ovarian reserve. Thus, correct diagnosis of endometrioma forms the basis for determining the best treatment strategy. Based on current knowledge, only women with atypical endometriosis should be considered as being at high risk, otherwise the frightening information of harboring a premalignant condition may induce many low-risk patients to request for unnecessary extirpative surgery [6].

Cancer antigen 125 (CA125) is the most extensively investigated and used peripheral biomarker of endometriosis. It is helpful in distinguishing endometriomas from other benign lesions. However, it has a limited role in the differentiation between

endometriosis and ovarian cancer owing to its lack of specificity. Human epididymal secretory protein 4 (HE4) is an ovarian cancer biomarker that has been recently implicated in differentiating endometrioma from ovary malignancy and in determining the benign structure of the endometrioma. Despite this, the behavior of this marker in cysts that exhibit typical endometrioma features is only superficially known [7].

In women with isolated endometrioma with minimal-moderate pain, the main factor that leads to surgery is the malignant potential of the cyst. This case series study describes the features of ‘typical’ endometrioma in imaging modalities such as ultrasonography and magnetic resonance imaging (MRI) who underwent surgery due to increased serum HE4 levels and higher Risk of Ovarian Malignancy Algorithm (ROMA) index, in whom the final pathology was reported as benign.

Materials and methods

A single-center retrospective series including 8 women aged between 24 and 33 years was conducted at the University of Health Sciences, Bagcilar Training and Education Hospital, between January 2015 and July 2018. Variables including age at the time of surgery, body mass index (BMI; kg/m²), parity, smoking status, and medical histories were recorded. The severity of the pelvic pain (noncyclic chronic pelvic pain, dysmenorrhea and dyspareunia), size and laterality of ovarian endometriomas, and the uterine sliding sign were recorded. The severity of pelvic pain was evaluated using visual analog scale (VAS) scores. The largest diameter of the endometrioma on sonographic view was recorded as the size of the ovarian

endometrioma; if endometrioma was present in both ovaries, the total size was estimated by adding the largest diameters of the two endometriomas. Information regarding endometriosis score and stage was obtained from the surgical records (evaluated according to the revised American Society for Reproductive Medicine guidelines) [8].

This study included women who were considered as having typical endometrioma in preoperative transvaginal/transrectal ultrasonography, had elevated levels of HE4 and high ROMA index, and were pathologically diagnosed of having ovarian endometrioma. Standardized examination techniques, as well as standardized terms and definitions were used. The sonographic presence of endometriomas was determined in accordance with the recommendations of the International Ovarian Tumor Analysis (IOTA) group. All women underwent a speculum examination; rectal examinations were not performed on a routine basis. No bowel preparation was performed prior to sonography. The women underwent surgery within 30 days of the initial examination, following routine anesthesia preparation. Two experienced surgeons performed all laparoscopies.

Peripheral venous blood samples were collected during the follicular phase of the cycle from all patients before and after surgery to measure serum CA125 and HE4 levels. After centrifugation and separation of serum, HE4 and CA125 concentrations were determined in serum samples using enzyme-linked immunosorbent assay (ELISA) analysis (Fujirebio Diagnostics Inc., Malvern, PA, USA), according to the manufacturer's instructions. The Elecsys® HE4 and Elecsys® CA125 II assay reagents were used together with a Cobas® 6000 e601 analyzer (Roche Diagnostics, USA). The following formulae were used to calculate the predictive index (PI) and the predictive probability (ROMA value):

$$\text{Premenopausal PI} = -12.0 + 2.38 \times \text{LN}[\text{HE4}] + 0.0626 \times \text{LN}[\text{CA125}].$$

$$\text{ROMA index}[\%] = \exp(\text{PI}) / [1 + \exp(\text{PI})] \times 10.$$

The ROMA index value cutoff point in the Roche assays was 11.4% in premenopausal women. The 50th percentile value of the Elecsys® HE4 commercial kit for women aged under 40 years was 42 pmol/L, and the 95th percentile value was 60.5 pmol/L. Reference value for CA125 was <35 U/mL. All assays were run according to the manufacturer's instructions, and appropriate controls were within the ranges provided by the manufacturer for all runs.

Results

Serum HE4 levels and ROMA index values were high in all the eight premenopausal women with endometrioma (Table 1). Both the specialists who examined the women in the preoperative period considered the ovarian mass as endometrioma in both gray-scale and Doppler ultrasonography. All the endometriomas were considered to have low malignant potential. The indication for surgery was the suspicion of malignancy resulting from the elevated HE4 levels and high ROMA index. The lowest and highest levels of serum HE4 were 73.5 pmol/L and 150 pmol/L, and the lowest and highest levels ROMA indexes were 18.7% and 55.4%, respectively (Table 2).

Two of the eight women underwent endometriosis surgery due to endometrioma 4 years and 5 years previously, respectively. We identified one women with known chronic renal failure and ongoing hemodialysis. She had a 65-mm-sized bilateral

Table 1. Demographic characteristics and clinical examination findings of case series.

Case No.	Age	BMI ^a	Parity	virgin	Delivery type	Infertility	Smoking	Comorbid disease	Dys-menorrhoea	Dys-pareunia	Chronic pelvic pain	Prior surgery	Elapsed time (months)	Medical treatment	First menstruation (years)	Bi-laterality	Side	Size (mm)	Mural nodule	Doppler USG	Sliding sign
1	27	21.3	2	virgin	-	-	-	-	3	-	5	yes	48	NSAID	13	No	Right	45	No	Negative	Yes
2	24	24.1	2	CS ^b	-	+	-	-	6	4	5	-	-	NSAID	17	No	Right	40	No	Negative	Yes
3	25	24.8	virgin	-	-	-	-	-	-	3	4	-	-	NSAID	40	No	Left	70	No	Negative	Yes
4	24	18.4	virgin	-	-	-	-	-	5	-	2	-	-	NSAID	12	No	Left	55	No	Negative	Yes
5	30	20	virgin	-	-	-	-	-	5	-	-	-	-	NSAID	13	No	Left	45	No	Negative	No
6	29	19.2	1	CS ^b	-	-	-	-	2	3	4	-	-	NSAID	13	No	Left	40	No	Negative	Yes
7	33	17.2	virgin	-	-	-	-	CRF ^c	-	-	2	-	-	-	13	Yes	-	65	No	Negative	Yes
8	31	20.9	1	CS ^b	-	-	-	-	6	2	4	yes	60	NSAID	12	No	Right	50	No	Negative	Yes

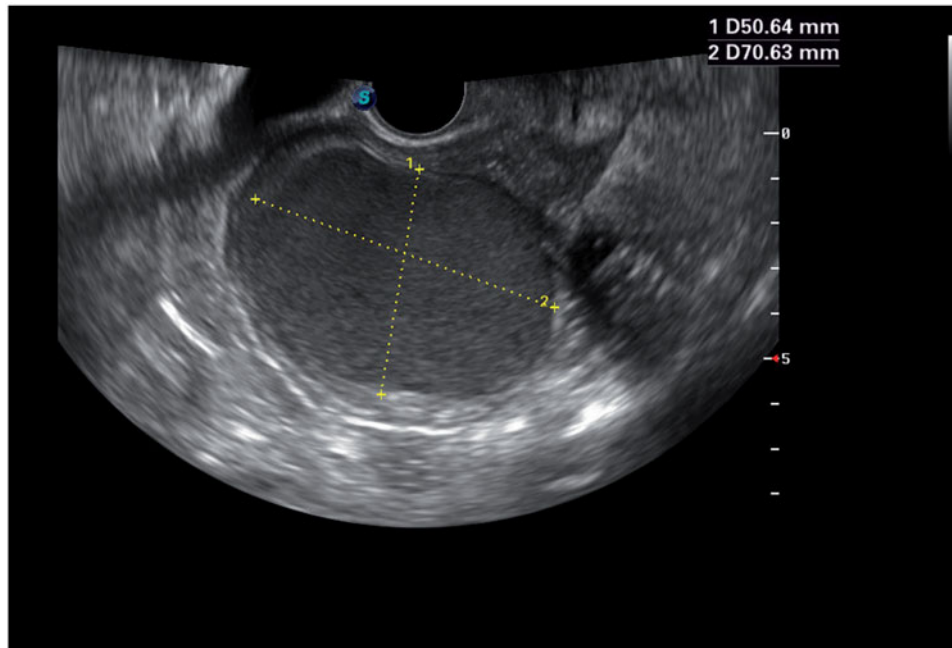
^akg/m².

^bCesarean Section.

^cChronic Renal Failure.

Table 2. Pre-operative and postoperative serum marker levels and surgery outcomes of patients.

Case No.	HE4 level (pmol/L)		CA-125 level (U/mL)		ROMA index value (%)		ASRM stage	Sacrouterine nodule	Rectovaginal nodule	Final pathology
	preop	postop	preop	postop	preop	postop				
1	79	34.9	108	70	21.3	3.6	Stage 3–4	No	No	Endometriotic csyt
2	100	95.3	25.9	18	29	27.4	Stage 3–4	Yes	No	Endometriotic csyt
3	105	73	160	57	35.1	17.7	Stage 3–4	Yes	No	Endometriotic csyt, sacrouterine endometriotic nodule
4	150	23.4	108	49.4	55.4	1.4	Stage 3–4	No	No	Endometriotic csyt
5	81	83	427	12.5	23.8	21	Stage 3–4	No	No	Endometriotic csyt, ureteral endometriosis (extrinsic)
6	88	79	1992	102	29.6	21.2	Stage 3–4	No	No	Endometriotic csyt
7	119	130	14	17	38.7	44.1	Stage 3–4	No	No	Endometriotic csyt
8	73.5	75.2	126.2	24.5	18.7	18	Stage 3–4	No	No	Endometriotic csyt

**Figure 1.** Transrectal gray-scale ultrasonography showed a 70-mm typical endometrioma in the left ovary (Case 3).

endometrioma and was not receiving any medical treatment (e.g. non-steroidal anti-inflammatory drugs) for her current illness. One patient was smoking 10 cigarettes per day.

The woman with the highest HE4 levels and highest ROMA index was aged 24 years. She was a virgin, and her BMI was 18.4 kg/m². Transrectal gray-scale ultrasonography and MRI findings showed a 70-mm endometrioma in the left ovary (Figure 1). No blood flow was detected in the cyst in Doppler USG. Preoperative VAS scores were eight for dysmenorrhea and two for chronic pelvic pain. Intraoperative cul-de-sac was partially obliterated and there were no pelvic adhesions. The level of serum HE4 (23.4 pmol/L) and ROMA index (1.4%) were decreased at postoperative 3 months. We observed this finding in three patients in this case series.

Two of the eight women had bilateral endometriomas. Two patients were considered as having adenomyosis based on the findings of ultrasonography and MRI. Two patients underwent nodule excision of the sacrouterine ligament. No intraoperative or postoperative complications were observed in any of the eight patients. All the women were discharged after they were cured.

Discussion

In recent years, interest in HE4 and the ROMA index, which are used as biomarkers to separate ovarian endometrioma from

ovarian malignancy, has been increasing [9]. Recently, HE4 has proved to be a promising marker for epithelial ovarian cancer with higher specificity and sensitivity than CA125 in distinguishing malignant tumors from benign pelvic masses [10]. However, current information about HE4 in patients with endometriosis is superficial, and in studies where this biomarker has been investigated, imaging features of ovarian endometriosis have not been adequately studied. Moreover, the use of HE4 as a biomarker in separating patients with endometriosis from healthy individuals is limited [10].

Montagnana et al. evaluated the diagnostic performance of serum HE4 and CA125 levels in 46 patients with ovarian cancer and 12 patients with endometrioma, among which, only one patient with endometriosis had elevated serum HE4 levels. The authors emphasized that HE4 was a promising biomarker in differentiating early ovarian cancer from endometrioma [11]. Huhtinen et al. revealed that neither serum concentration of HE4 nor encoding gene expression in endometriotic tissues was increased in endometriomas. Use of HE4 and CA125 together had the highest accuracy (94.0%) and sensitivity (78.6%) for the differential diagnosis of ovarian cancer from that of ovarian endometriosis [10]. In another study, Anastasi et al. [12] showed that serum HE4 level did not reach the upper limit in any of the 57 patients with ovarian endometriosis. Unlike previous studies, this study showed a cutoff value of HE4 of 150 pmol/L [13].

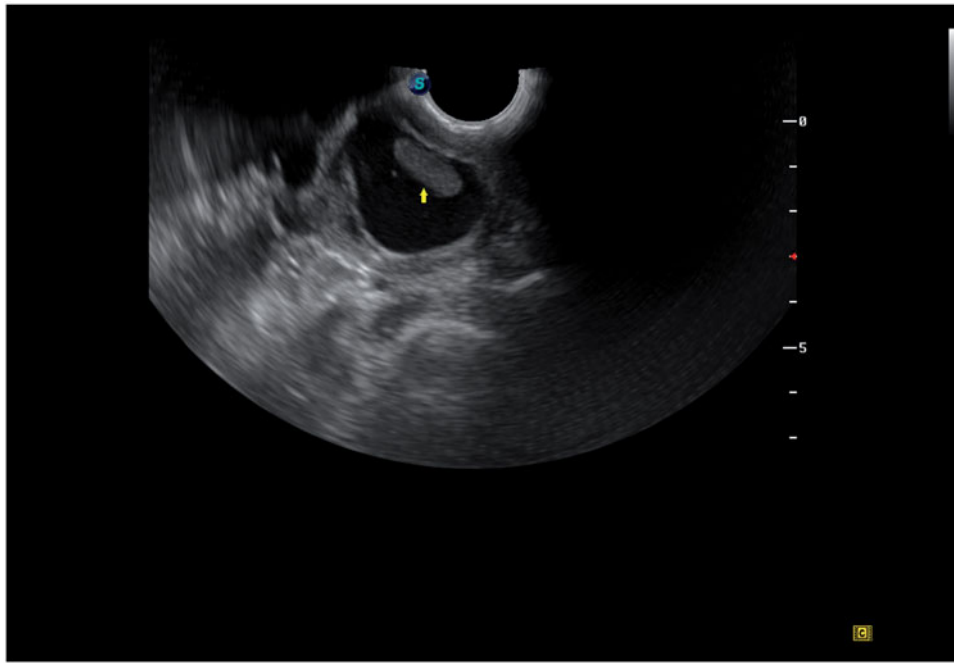


Figure 2. Atypical endometrioma in a 22-year-old woman. Transvaginal ultrasonography shows a well-defined round lesion within a homogeneously hypoechoic cyst (arrows). Doppler ultrasonography demonstrated no blood flow in the lesion, which proved to be a benign nature after surgical resection (not shown).

Moore et al. observed a marked difference between HE4 levels, which were increased in only 3% of cases, compared with CA125, which was elevated in 67% of cases. The researchers concluded that low serum levels of HE4 and high serum levels of CA125 are important indicators in confirming the benign nature of the cyst in patients with endometrioma [13].

In the aforementioned studies, patients with endometrioma showing typical sonographic characteristics who were considered to be at low risk for malignancy potential were not specifically studied. On the other hand, Jun Shin et al. found out a false positive high ROMA index in 15% of the patients with endometrioma, indicating that it is important to be careful to interpret these markers in patients with typical sonographic appearance of endometrioma [14]. Endometriomas may be misinterpreted, because of the complex echotexture, thick walls, and papillary projections (protrusion of solid tissue into the cyst lumen with a height of 3 mm or more) within the endometrioid cystic cavity, which mimics malignancy. In fact, these are not true papillations of solid tissue but images created from blood clots or fibrin lying adjacent to the cyst wall, showing a more regular surface and round shape of the protrusion (Figure 2). Approximately one-third of the endometriomas may show an atypical pattern that fits this definition. A study by Ubon Sang-Anan et al. demonstrated the usefulness of sonographic pattern recognition with 89.7% sensitivity and 97.1% specificity in distinguishing atypical endometriomas from malignant masses [4].

It is unclear why the ROMA indexes were elevated in some of the women with benign endometrioma. Although, women with endometriosis may have as high as a fourfold increased risk of developing epithelial ovarian cancer, this remains a tiny fraction of women with endometriosis [15]. Moreover, preventive screening with serum biomarkers such as CA125 for malignant transformation of endometrioma is not currently recommended [16]. Growing concerns of women with endometriosis might lead clinicians to consider non-evidence-based screening for ovarian cancer (e.g. serum CA125 measurements) [17].

The clinical management of endometrioma requires a clear understanding of the goals of surgery because surgical intervention can clearly cause more ovarian damage and further decrease ovarian reserve than other benign cysts. Moreover, the recurrence rate for ovarian endometriomas after surgical excision can be as high as 50% at 5 years, because it is not possible to remove all viable endometriotic cells. Repeat surgery for recurrent endometriomas is more harmful than the first surgery, as evaluated from the antral follicle count and ovarian volume. In addition, the complexity of the surgical procedure is often beyond simple excision of the endometriotic cyst and may require more extensive dissection and an interdisciplinary approach [18]. Therefore, diagnostic criteria for distinguishing ovarian endometriomas from other ovarian lesions seem to be of utmost importance, especially in patients with pregnancy intentions. There were some limitations in this retrospective study which may affect its interpretation. The most important limitation was the small number of cases. This makes it more difficult to generalize findings to the entire group of women with endometriomas.

The aim of this case series was not to underestimate significance of the HE4 and ROMA index values, which have high specificity in ovarian cancer, but to put more emphasis on the typical features of endometrioma detected in diagnostic tools such as ultrasonography and MRI for the surgical indication in patients with endometrioma who may have fertility expectations. A potential perplexity for physicians may be the risk of malignant transformation of endometriomas in young women. These kind of circumstances might pose management challenges and have significant public health implications. The most important question is whether young women with endometrioma should undergo surgery based on elevated serum HE4 levels and high ROMA index, despite being at low risk for malignancy according to the findings from the imaging tools. To resolve this dilemma in clinical management, studies on HE4 and the ROMA index are needed in patients with endometriosis, who have otherwise low risk for malignancy.

Acknowledgment

We would like to thank David F. Chapman, BSc, for editing the article.

Disclosure statement

The authors declare that there is no conflict of interest regarding the publication of this article.

ORCID

Eser Ozyurek  <http://orcid.org/0000-0002-5373-3991>
 Huseyin Kiyak  <http://orcid.org/0000-0001-7580-9179>

References

- [1] Heidemann LN, Hartwell D, Heidemann CH, et al. The relation between endometriosis and ovarian cancer—a review. *Acta Obstet Gynecol Scand.* 2014;93:20–31.
- [2] Nishida M, Watanabe K, Sato N, et al. Malignant transformation of ovarian endometriosis. *Gynecol Obstet Invest.* 2000;50:18–25.
- [3] Munksgaard PS, Blaakaer J. The association between endometriosis and ovarian cancer: a review of histological, genetic and molecular alterations. *Gynecol Oncol.* 2012;124:164–169.
- [4] Kawaguchi R, Tsuji Y, Haruta S. Clinicopathologic features of ovarian cancer in patients with ovarian endometrioma. *J Obstet Gynaecol Res.* 2008;34:872–877.
- [5] Saeng-Anan U, Pantasri T, Neeyalavira V, et al. Sonographic pattern recognition of endometriomas mimicking ovarian cancer. *Asian Pac J Cancer Prev.* 2013;14:5409–5413.
- [6] Vercellini P, Buggio L, Frattaruolo MP, et al. Medical treatment of endometriosis-related pain. *Best Pract Res Clin Obstet Gynaecol.* 2018;51:68–91.
- [7] Escudero JM, Auge JM, Filella X, et al. Comparison of serum human epididymis protein 4 with cancer antigen 125 as a tumor marker in patients with malignant and nonmalignant diseases. *Clin Chem.* 2011; 57:1534–1544.
- [8] Johnson NP, Hummelshoj L, Adamson GD, et al. World Endometriosis Society consensus on the classification of endometriosis. *Hum Reprod.* 2017;32:315–324.
- [9] Zapardiel L, Gorostidi M, Ravaggi A, et al. Utility serum marker HE4 for the differential diagnosis between endometriosis and adnexal malignancy. *Int J Gynecol Cancer.* 2016;26:52–55.
- [10] Huhtinen K, Suvitie P, Hiissa J, et al. Serum HE4 concentration differentiates malignant ovarian tumours from ovarian endometriotic cysts. *Br J Cancer.* 2009;100:1315–1319.
- [11] Montagnana M, Lippi G, Danese E, et al. Usefulness of serum HE4 in endometriotic cysts. *Br J Cancer.* 2009;101:548.
- [12] Anastasi E, Granato T, Falzarano R, et al. The use of HE4, CA125 and CA72-4 biomarkers for differential diagnosis between ovarian endometrioma and epithelial ovarian cancer. *J Ovarian Res.* 2013;6:44.
- [13] Moore RG, McMeekin DS, Brown AK, et al. A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. *Gynecol Oncol.* 2009;112:40–46.
- [14] Shin JJ, Lee YJ, Kim R, et al. Analysis of falsely elevated risk of ovarian malignancy algorithm in women with ovarian endometrioma. *Obstet Gynecol Sci.* 2016;59:295–302.
- [15] Falcone T, Flyckt R. Clinical management of endometriosis. *Obstet Gynecol.* 2018;131:557–571.
- [16] Dunselman GA, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. *Hum Reprod.* 2014;29: 400–412.
- [17] Kvaskoff M, Horne AW, Missmer SA. Informing women with endometriosis about ovarian cancer risk. *Lancet.* 2017;390:2433–2434.
- [18] Somigliana E, Berlanda N, Benaglia L, et al. Surgical excision of endometriomas and ovarian reserve: a systematic review on serum antimüllerian hormone level modifications. *Fertil Steril.* 2012;98: 1531–1538.