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CLINICAL PRACTICE

Evidence-based gynaecological practice: clinical review 1

Management of ovarian endometriomas

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Abstract In this review, the first of a series of evidence-based reviews of clinical practice commissioned by Gynaecological Surgery, we introduce the concept of applying the evidence to focused questions asked frequently by patients about specific treatment options. We pose the question about the appropriate treatment of ovarian endometriomas and search the readily available literature including systematic literature reviews, randomised controlled trials (RCTs) and observational studies. In addition to an overview of the pathophysiology and diagnosis of endometriomas we explore the search strategies used along with methods of focusing the clinical question into a question that can be asked of the literature. The treatment options identified are then used to inform any discussion that one might have with regards to the treatment of endometriomas. We conclude that endometriomas are best treated surgically by capsule stripping and that there is little evidence for the efficacy of adjuvant medical treatment either pre- or post-operatively. The risk of ovarian failure following surgical treatment appears to be small.

Keywords Endometriosis · Endometrioma · Evidence-based medicine · Review · Endoscopy · Ovarian diseases

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Introduction

Women seeking help with gynaecological problems are increasingly well informed and expect advice based not only on your personal experience, but also on the available evidence from the medical literature. Studies published in scientific journals are of varying quality. It is important to be able to establish the quality of evidence when giving advice and to be able to review literature that is being presented to you by a patient who has undertaken her own research on the internet. In this series of clinical reviews we will use evidence that is readily available to all practicing gynaecologists to answer a number of questions that patients frequently raise in clinical practice. We will also provide a systematic framework for searching for the evidence and appraising it in response to specific clinical questions. In this paper, the first of the series, we will describe the methodology in some detail to help you carry out your own searches. Let us suppose that our hypothetical patient has asked our advice on how best her endometrioma should be surgically managed to preserve ovarian function and fertility.

In order to put the treatment options into context, however, we will firstly outline the issues relating to the pathology and recognition of ovarian endometriomas.

Pathophysiology of endometriomas

The pathophysiology and aetiology of endometriomas has long been a subject of controversy. Hughesdon [1] and subsequently, Brosens et al. [2] suggested that endometriomas are formed as a result of the invagination of the ovarian cortex by parietal peritoneal deposits, thus explaining why they frequently rupture on mobilisation. However, endome-

triomas are frequently associated with endometriotic deposits elsewhere, usually deep infiltrating endometriosis of the utero-sacral ligaments and recto-vaginal space, suggesting that the pathological process is more widespread than the invagination of the ovarian cortex alone [3]. Nisolle and Donnez [4] proposed that invaginated ovarian cortical epithelium subsequently undergoes metaplasia to develop the typical glandular epithelial stroma of endometriosis. The most likely explanation, given the distribution of the disease, is that endometriosis is embryologically patterned, with the endometriotic deposits lying predominantly in the Mullerian developmental pathway. The remaining areas of cell rests in this pathway are stimulated by oestrogens [5]. Accepting differences in the theories about the aetiology of endometriomas, it is important to recognise that ovarian endometriomas rarely occur in isolation [3], and treatment, therefore must also be concerned with endometriosis elsewhere in the pelvis.

Diagnosis of endometriomas

Endometriomas are usually diagnosed following referral for either investigation of pain or infertility, the diagnosis often being made using transvaginal ultrasonology (TVS) examination. In their systematic review of the diagnosis of endometriomas using TVS, Moore et al. [6] reported positive likelihood ratios using gray-scale ultrasound of between 7.6 and 29.8 and negative likelihood ratios of 0.1 to 0.4. Likelihood ratios are derived from the sensitivity and specificity of diagnostic tests. The likelihood ratio can be combined with the pre-test probability of disease in a population to provide the post-test probability of disease for an individual patient. A positive likelihood ratio of greater than 10 indicates that the test is good at detecting disease and a negative likelihood ratio of less than 0.1 indicates that the test is good at excluding the disease [7]. Thus, for endometriomas, gray-scale ultrasound is a reasonably accurate test for their detection and exclusion. Whilst the ultrasound features of endometriomas are typical, there is a paucity of good quality published evidence to support the use of ultrasound in the diagnosis of endometriosis elsewhere in the pelvis [6].

Why should we treat endometriomas?

Endometriomas themselves may be asymptomatic and pelvic pain or dyspareunia that has triggered their diagnosis may be related to endometriosis elsewhere, such as deep infiltrating endometriosis of the utero-sacral ligaments to which the ovaries are adherent. The pathological nature of endometriomas where endometrium is trapped within the ovary, resulting in regular bleeding and shedding within an environment from which this tissue cannot escape, is likely to cause the endometriomas to grow over time, thus making some form of treatment necessary. In addition, since endometriomas frequently occur alongside deep infiltrating disease [3], the need for treatment of extra-ovarian deposits should be considered alongside any treatment for the endometrioma. Moreover, it has been shown that the presence of endometriomas reduces the probability of both natural and assisted conception [8].

It is also important to consider the risks of malignant transformation in approximately 0.7% of endometrioma cases [9, 10]. It is postulated that the relatively high levels of oestrogen from the ovary to which the endometriomas are exposed leads to epithelial hyperplasia or atypia and potentially to malignant transformation [10].

An evidence-based practice approach to the management of endometriomas

In considering the management of ovarian endometriomas, we need to start by deciding whether the treatment is medical, surgical or a combination of both.

The first thing that we need to do is to ensure that we have a focused question that can be asked of the literature. When carrying out a search of the evidence, it is very easy to get distracted, often retrieving interesting papers that do not actually answer your question. It is suggested, therefore, that your questions should consider the following aspects [11]:

- The **Population (P)** you are interested in
- The **Intervention (I)** that you are looking at
- The **Comparison (C)** group that you are considering (where relevant)
- The **Outcome (O)** which you are interested in.

For our first question, we want to ask:

In women with endometriomas, does pre- or post-operative adjuvant medical therapy, when compared to surgical treatment alone, reduce the risk of endometrioma recurrence and improve fertility?

To frame this question using the PICO structure:

- **P** = women with endometriomas
- **I** = adjuvant pre- or post-operative medical therapy
- **C** = surgical treatment alone
- **O** = reduced risk of endometrioma recurrence and improved fertility.

Our second question is:

In women with endometriomas, is excisional surgery, when compared with ablative surgery, more effective at preserving ovarian function and reducing endometrioma recurrence?

Again, to frame this question using the PICO structure:

- **P** = women with endometriomas
- **I** = excisional surgery
- **C** = ablative surgery
- **O** = preservation of ovarian function and reduction in endometrioma recurrence.

Levels of 'evidence' in medical research

When searching for the answer to our question of 'how' endometriomas should be treated to maximise fertility and preserve ovarian function, we need to consider studies that look at treatment effect. For questions of treatment effect, the highest level of evidence comes from the results of a well-conducted systematic literature review and meta-analysis of randomised controlled clinical trials (RCTs). Systematic literature reviews, such as those conducted by the Cochrane Collaboration (http://www.theCochraneLibrary.com) are designed to identify all studies of therapeutic efficacy published in any journal, in any language (regardless of whether the journals are indexed on databases such as Medline), and to identify unpublished studies and those that remain in the grey literature such as conference proceedings and dissertations. These systematic reviews aim to minimise the effects of publication bias to give a balanced 'answer' to a clinical question.

In the absence of well-conducted systematic literature reviews of RCTs, we then look to the results from individual well-conducted (and adequately powered) RCTs. RCTs are designed to minimise the effects of a number of types of bias (systematic errors) that might affect the results of the study. Randomisation minimises the effects of *confounding*—the chances of differences in treatment effect occurring because of differences between the baseline characteristics of the treatment groups. Blinding or masking in RCTs minimises the effects of bias introduced by the beliefs of the participants and investigators with regards to the comparative effectiveness of the two treatments. Although RCTs are regarded as the gold standard for determining treatment effectiveness, there is not always sufficient evidence from RCTs as there can be difficulties in recruitment of subjects and the results are not always generalisable to different populations. The questions asked in RCTs are frequently very specific because of tight control or exclusion criteria adding to the difficulties in their generalisability, in which case, the results of observational studies should also be considered.

Observational studies analyse the effects of treatment without the researchers having any control over treatment allocation. They are most useful for investigating 'risk factors' for disease, but can be used to describe differences between treatment outcomes. When reviewing the results of observational studies, the reader should be aware of the role of bias and confounding on the outcome of the study. For example, in an observational study comparing the efficacy of two treatments, it is likely that the demographic and disease-related characteristics of the participants in the two groups will be different, with, in many cases, those with more severe disease assigned to the treatment that is believed to be 'better'. Similarly, those patients at high risk are often assigned to the treatment that is believed to be 'safest'. In this context, the reader must remember that a more effective treatment may either do 'better' if it is given to patients with less severe disease or 'worse' because it is given to patients with more severe disease than in the comparator group. Similarly, a treatment may be seen to be less 'safe' because it may be perceived to be more effective and is therefore given to patients who are at high risk or have complicated disease. In terms of the hierarchy of evidence in observational studies, prospective cohort studies are the highest form of evidence, followed by retrospective cohort studies, case-control studies and then case series and case reports.

Identifying the evidence

As our aim was first to identify well-conducted systematic literature reviews of the treatment of endometriomas, we first searched the Cochrane Library, Medline and EMBASE for any such reviews. EMBASE is a database that is similar to Medline, but has a more European rather than North American emphasis. When searching specifically for RCTs, the most comprehensive single source is the Cochrane Collaboration Central Trials Register (CCTR). In Medline, EMBASE and in the Cochrane Library, all papers are indexed using standardised 'key words' called Medical Subject Headings (MeSH terms). These terms are organised in hierarchical 'trees', which allow you to carry out the most specific searches of the databases. However, if your aim is to identify all papers, a more sensitive search strategy would combine both MeSH terms and the use of text word searching. For help with searching Medline and the Cochrane Library either contact your local medical librarian or consult the help topics of these databases (under 'advanced searching').

Finding and appraising the evidence

We searched the Cochrane Library, Medline and EMBASE for systematic reviews of the treatment of endometriomas using the following search terms:

Search term	Comment
#1: Explode ENDOMETRIOSIS	MeSH term
#2: Endometriom*	Text search
#3: # 1 OR #2	
#4: Evidence-based medicine	MeSH term
#5: Review [publication type]	MeSH term
#6: Meta-analysis	MeSH term
#7: Systematic review	Text search
#8: #4 OR #5 OR #6 OR #7	
#9: #3 AND #8	Final search—we looked through the abstracts identified by this search

We did consider the use of other terms to identify studies of endometrioma, such as 'ovarian diseases'; however, these terms did not yield any further useful papers and were therefore excluded.

We identified two Cochrane reviews that addressed our specific question [12, 13]. In their review of pre- and post-operative medical therapy for endometriosis, though not specifically endometriomas, Yap and colleagues [12] identified five RCTs. From the meta-analysis of these studies, it was found that pre-treatment for all endometriosis significantly reduced the total r-AFS score [14], but concluded that this may not be of any benefit to the patient. Post-surgical medical therapy did not have any significant impact on pregnancy rates, recurrence of disease or r-AFS scores. The second review by Hart and colleagues [13] was on surgical treatment of endometriomas. This review contained only two RCTs [15, 16] that compared different surgical approaches for endometriomas. Both studies compared stripping of the capsule with tissue biopsy, drainage and ablation of the endometriomas with bipolar coagulation without adjuvant chemotherapy. Beretta's [15] study followed up patients for 2 years postoperatively, as did Alborzi's study [16], although fertility was only measured after 1 year, following which, women who did not achieve a spontaneous pregnancy underwent fertility intervention. Both studies had methodological problems with a lack of clarity surrounding blinding to the procedure, and neither study presented a power calculation prior to recruitment to explain their relatively small sample sizes (n=64 [15] and n=100 [16]). In Albazori's study [16] all of the women had severe disease elsewhere in the pelvis, but it was unclear whether or not they had received treatment for this disease at the time of surgery for their endometrioma and, if so, the nature of that surgery.

Despite the potential biases in these two studies, Hart [13] reports that excisional surgery of endometriomas appears to be more effective than drainage and ablation in terms of recurrence of the endometriomas [OR 0.41 (95% CI 0.18, 0.93)]. Excisional surgery, when compared with drainage and ablation was also more effective at reducing symptoms of dysmenorrhoea [OR 0.15 (95% CI 0.06, 0.38)], dyspareunia [OR 0.08 (95% CI 0.01, 0.51)] and non-menstrual pelvic pain [OR 0.10 (95% CI 0.02, 0.56)]. The odds of spontaneous pregnancy following excisional surgery was 5.21 (95% CI 2.04, 13.29) when compared with drainage and ablation. The methodological weaknesses in the primary studies, however, mean that they provide insufficient evidence on which to base clinical practice.

Since the systematic review by Hart et al. [13] had identified papers published up to November 2004, we searched the CCTR for RCTs published between November 2004 and January 2007 using the following search terms: (Endometriosis OR Endometrioma*). As all of the studies on the CCTR are RCTs there was no need to use any further search terms to narrow the search. If we had used Medline and EMBASE, the following terms could be used to identify RCTs: Randomized Controlled Trials OR Random Allocation OR Double-Blind Method OR Single-Blind Method OR Clinical Trials. We identified one further study that related to our specific question, by Muzii et al. [17], comparing circular excision with subsequent stripping with immediate stripping. They found that with both techniques some ovarian tissue was excised with the endometrioma wall, but that the stripped tissue histologically showed very little functioning ovarian cortex suggesting that stripping was a safe procedure.

We searched Medline for further systematic reviews including observational studies using the following terms: (Endometriosis or Endometrioma*) AND Review. We identified three systematic reviews of the treatment of endometriomas [18–20]. Farquhar and Sutton [18] found that medical treatment for endometriomas reduced the cyst size by between 40 and 57%, but that there was a rapid return to the original size following the cessation of treatment. Whilst Farquhar and Sutton did not look at the impact of endometrioma size on subsequent surgery, it has been argued that a three-stage approach is sensible, i.e., initial drainage of the cyst and treatment with GnRH analogues to suppress function of the cyst wall followed by coagulation [21]. This does not seem to be based on any strong evidence of effectiveness given that evidence of pre-operative medical treatment is not associated with a lower recurrence rate, although it has been argued that this may make surgery easier [21].

Farquhar and Sutton [18] also reviewed a number of studies looking at the treatment of endometriomas using KTP laser and found there was a low endometrioma recurrence rate and also pregnancy rates of between 37.5% and 57% amongst those attempting to conceive, with the lower rates possibly being among those with more severe disease. In their systematic review of excision versus ablation for endometriomas including observational studies, Vercellini et al. [20] found that the treatment of endometromias using fenestration, coagulation or laser vapourisation was associated with an increase in recurrence compared with excision [OR 3.09 (95% CI 1.78, 5.36)]. In one of the observational studies included in the review [22], the 36-month pregnancy rate of 60% was higher in the group treated with coagulation compared with 47% in the excision group, with those undergoing coagulation also having a shorter time from treatment to pregnancy (1.4 years vs 2.3 years). However, in the RCT included in the review [15], the opposite was found, with coagulation leading to only a 24% pregnancy rate compared with 67% in the excision arm. This finding was also supported by the later study by Alborzi [16]. Finally, in their systematic review of fertility following laparoscopic treatment for endometriomas, Jones and Sutton [19] concluded that there was insufficient information available to determine whether there are significant differences between the outcome of ablation versus excision of endometriomas.

We were only able to find one retrospective observational study looking at ovarian failure following surgical treatment of endometriomas [23]. This study followed up 126 women who had undergone extensive resection of bilateral endometriomas and found that only 3 women [2.4% (95% CI 0.5, 6.8%)] experienced ovarian failure.

Recommendations based on the available evidence

Our patient wants to know how she should have her endometrioma surgically treated and which approach would maximise her likelihood of conception, preserve her ovarian function and reduce her likelihood of recurrence of disease. It would seem from the limited available evidence that there is minimal risk of reduced ovarian reserve and an early menopause following surgical treatment of endometriomas . Whilst theoretically, pre-operative ovarian suppression may make surgery easier, there appears to be no reported evidence to support this. Postoperative ovarian suppression would merely delay pregnancy. The treatment of choice, both in terms of future fecundity and cyst recurrence, appears to be ovarian capsule stripping. If the patient is suffering from significant pelvic pain it would be appropriate to treat areas of deep infiltrating endometriosis. We would advise that this treatment is carried out in a centre with appropriate technical expertise to undertake ovarian stripping with minimal trauma to the healthy ovarian tissue and to offer the appropriate treatment of deep infiltrating disease as is recommended in the RCOG 'Green Top' guidelines [24].

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