Management of women with endometriosis

Guideline of the European Society of Human Reproduction and Embryology

ESHRE Endometriosis Guideline Development Group

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INTRODUCTION

Clinical need for the guideline

Endometriosis is defined as the presence of endometrial-like tissue outside the uterus, which induces a chronic, inflammatory reaction (Kennedy, et al., 2005). While some women with endometriosis experience painful symptoms and/or infertility, others have no symptoms at all. The exact prevalence of endometriosis is unknown but estimates range from 2 to 10% within the general female population but up to 50% in infertile women (Eskenazi and Warner, 1997, Meuleman, et al., 2009).

Endometriosis diagnosis is based on the women's history, symptoms and signs; the diagnosis is corroborated by physical examination and imaging techniques, and finally proven by histology of either a directly biopsied vaginal lesion, from a scar, or of tissue collected during laparoscopy. The visual recognition of endometriosis during laparoscopy alone is of limited value as it has a high false-positive rate. On the other hand, diagnosis during laparoscopy is dependent on the ability of the surgeon to recognize peritoneal disease in all its different appearances. If the surgeon performing the laparoscopy is not familiar with these appearances, endometriosis may be missed and left untreated — you see only what you recognize. This is especially relevant in deep infiltrating disease, where sometimes endometriosis is hidden beneath the peritoneal surface. Laparoscopy also allows direct surgical treatment and disease staging, which could for example be performed according to the ASRM classification system (Revised American Society for Reproductive Medicine classification of endometriosis: 1996, 1997). This classification system assigns points to the different locations of the disease thus resulting in four stages: minimal, mild, moderate and severe. These stages, however, poorly reflect the severity of endometriosis-associated pain and infertility. Furthermore, the classification system is of limited value in scoring deep endometriosis.

Due to the wide variety of clinical practice in the management of disease in these women, doctors frequently experience difficulties in establishing a final diagnosis of endometriosis. This results in many women receiving either delayed or suboptimal care (Kennedy, et al., 2005).

Recently, the World Endometriosis Research Foundation (WERF) EndoCost study has shown that the costs arising from women with endometriosis treated in referral centres are substantial, resulting in an economic burden that is at least comparable to the burden associated with other chronic diseases, like diabetes mellitus. The total annual societal burden of endometriosis-associated symptoms for Europe was estimated to be between 0.8 million and 12.5 billion euros, which was theoretically calculated from the annual average costs per woman treated in referral centres across Europe (Nnoaham, et al., 2011, Simoens, et al., 2012).

Apart from the economic burden, endometriosis has a significant effect on various aspects of womens' lives, including their social and sexual relationships, work and study (De Graaff, et al., 2013, Nnoaham, et al., 2011, Simoens, et al., 2012). Caretakers should be aware of these issues in order to adequately assist women with endometriosis in coping with these impacts of the disease on their daily lives. Furthermore, chronic illnesses, like endometriosis, are likely to affect patients' partners to some extent. In endometriosis, the effect of the disease on partners and on the couple unit are

especially pronounced given the absence of an obvious cause or cure, the likelihood of chronic, recurring symptoms and the potential impact on both sex and fertility.

Therefore, there is a significant need to optimise the management of women with endometriosis to improve diagnosis, endometriosis care and reduce both the personal and societal costs of this disease.

Previous guidelines

Guidelines have been developed by a number of national and international societies, including:

- European Society of Human Reproduction and Embryology:
  (http://guidelines.endometriosis.org/)
- American Society of Reproductive Medicine:
  (Practice Committee of the American Society for Reproductive, 2008, 2012)
- Royal College of Obstetricians and Gynaecologists:
  Green-top Guideline No. 24 (October 2006, Minor revisions October 2008) : The investigation and management of endometriosis. (http://www.rcog.org.uk/files/rcog-corp/GTG2410022011.pdf)
- Society of Obstetrics and Gynecology of Canada:
  (Leyland, et al., 2010)
- Collège National des Gynécologues et Obstétriciens Français (CNGOF):
  (Roman, 2007)
- Deutsche Gesellschaft für Gynäkologie und Geburtshilfe
  (http://www.awmf.org/leitlinien/detail/ll/015-045.html)

In 2005, the ESHRE guideline for the diagnosis and treatment of endometriosis, written by the ESHRE Special Interest Group for Endometriosis and Endometriosis Guideline Development Group, was published in Human Reproduction (Kennedy, et al., 2005). This guideline was also available at http://guidelines.endometriosis.org/, and was visited about 42,000 times a year between 2007 and 2011. The guideline was last updated on 30th of June 2007.

The guideline group members of the 2005 guideline decided that the guideline should be updated according to the ESHRE manual for guideline development, resulting in the current guideline.

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GUIDELINE SCOPE

This guideline offers best practice advice on the care of women with suspected endometriosis as well as with endometriosis diagnosed by laparoscopy/laparotomy and/or histology.

This clinical guideline provides recommendations on the diagnostic approach for endometriosis, including information on symptoms predictive of endometriosis and the utility of medical technologies and clinical examination for diagnosis. Treatments for endometriosis, such as medical treatment, non-pharmacological treatment as well as surgery, are discussed for both relief of painful symptoms and for infertility due to endometriosis. The effectiveness of medically assisted reproduction for endometriosis-associated infertility is discussed, as are therapies (medical treatment and surgery) adjunct to medically assisted reproduction.

Finally, information is provided for the management of patients in whom endometriosis is found incidentally (without pain or infertility), for primary prevention of endometriosis, for the treatment of menopausal symptoms in patients with a history of endometriosis and for women with questions about the possible association of endometriosis with malignancy.

Target users of the guideline

The guideline covers the care provided by secondary and tertiary healthcare professionals who have direct contact with, and make decisions concerning, the care of women with endometriosis. Although primary healthcare providers are not the main target users of this guideline, it may be of interest for them too.

This guideline is of relevance to European health care providers and women with endometriosis. To assist patient education and shared-decision making, a patient version of this guideline will be developed.

RECOMMENDATIONS

INTERPRETATION ON THE GRADES OF RECOMMENDATIONS

For each recommendation, a grade (A-D) were assigned based on the strength of the supporting evidence (scored from 1++ to 4). In case of absence of evidence, the GDG could decide on writing good practice points (GPP), based on clinical expertise.

Grades of recommendations	Supporting evidence
A	Meta-analysis, systematic review or multiple RCTs (high quality)
B	Meta-analysis, systematic review or multiple RCTs (moderate quality) Single RCT, large non-randomised trial, case-control or cohort studies (high quality)
C	Single RCT, large non-randomised trial, case-control or cohort studies (moderate quality)
D	Non-analytic studies, case reports or case series (high or moderate quality)
GPP	Expert opinion

Further information on the methodology is provided in Appendix 5.

1. DIAGNOSIS OF ENDOMETRIOSIS

Introduction

Several studies have reported large diagnostic delays in endometriosis. Recent studies report, specifically for Europe, an overall diagnostic delay of 10.4 years in Germany and Austria (Hudelist, et al., 2012), 8 years in the UK and Spain (Ballard, et al., 2006, Nnoaham, et al., 2011), 6.7 years in Norway (Ballard, et al., 2006), 7–10 years in Italy and 4–5 years in Ireland and Belgium (Nnoaham, et al., 2011).

In these studies, several causes for this delay in diagnosis were suggested, including intermittent use of contraceptives causing hormonal suppression of symptoms, the use of non-discriminatory examinations, misdiagnosis, attitude towards menstruation and normalisation of pain by the women, their mothers, family doctors, gynecologists or other "specialists" (Ballard, et al., 2006, Hudelist, et al., 2012, Nnoaham, et al., 2011).

In this section, the symptoms and signs of endometriosis are listed, and recommendations are provided on how the diagnosis of endometriosis should be established, in an attempt to improve the knowledge of gynecologists and other clinicians, and to decrease the diagnostic delay and the subsequent impact on the quality of life of women with endometriosis.

1.1 Symptoms and signs of endometriosis

Key question

WHICH SYMPTOMS ARE ASSOCIATED WITH ENDOMETRIOSIS?

Clinical evidence

Pelvic symptoms — cyclical pelvic pain, dysmenorrhea and dyspareunia — are some of the classic symptoms of endometriosis. However, systematic assessment of all endometriosis symptoms, preferably in a prospective study setting, is yet to be done. Dysmenorrhea, chronic pelvic pain, deep dyspareunia, cyclical intestinal complaints, fatigue/weariness and infertility continue to be the leading symptoms of endometriosis (Bellelis, et al., 2010, Davis, et al., 1993, Lemaire, 2004, Luscombe, et al., 2009). Dysmenorrhea was the chief complaint, reported by 62% of women with mainly peritoneal endometriosis in a Brazilian study (Bellelis, et al., 2010). In the same study, the prevalence of chronic pelvic pain was 57%, deep dyspareunia 55%, cyclic intestinal complaints 48%, infertility 40% and incapacitating dysmenorrhea 28%.

The symptoms of endometriosis depend on the location of the disease. Deep endometriosis of the posterior pelvis is associated with increased severity of dyschezia, in comparison to women with pelvic endometriosis without posterior deep endometriosis (Seracchioli, et al., 2008). Deep endometriosis of the rectovaginal septum is associated with the most severe forms of dyschezia and dyspareunia (Seracchioli, et al., 2008, Thomassin, et al., 2004).

Intestinal complaints — periodic bloating, diarrhea or constipation — are some of the unrecognized symptoms of endometriosis (Bellelis, et al., 2010, Davis, et al., 1993, Luscombe, et al., 2009). In a

prospective, controlled study, cyclic bloating was seen in 96%, diarrhea in 27% and constipation in 16% of the women with endometriosis (Luscombe, et al., 2009). The corresponding numbers in women with no endometriosis were 64, 9 and 0%, respectively.

Adolescent women with endometriosis report a high rate of symptoms. Uterine cramping has been reported by 100%, cyclic pain 67%, non-cyclic pain 39%, constipation/diarrhea 67%, and referred pain (legs, back) by 31% of adolescents with laparoscopically diagnosed endometriosis (Davis, et al., 1993).

Among infertile women undergoing laparoscopy, dysmenorrhea was the only symptom significantly predictive of endometriosis (Forman, et al., 1993). However, no differences in the rates of pelvic pain, dyspareunia or vaginal discharge were seen among women with endometriosis, compared to those with normal pelvis or adhesions (Forman, et al., 1993).

Conclusion and considerations

Several studies explored symptoms and signs associated with endometriosis, resulting in a long list of endometriosis-associated symptoms, including dysmenorrhea, chronic pelvic pain, deep dyspareunia, cyclical intestinal complaints, fatigue/weariness and infertility. However, the included studies all had retrospective design and did not show a predictive value of these symptoms for the presence of endometriosis.

Key question

WHICH SYMPTOMS ARE PREDICTIVE OF THE DIAGNOSIS OF ENDOMETRIOSIS?

Clinical evidence

Abdominopelvic pain, dysmenorrhea, heavy menstrual bleeding, infertility, dyspareunia and/or postcoital bleeding, as well as diagnosis of ovarian cyst, irritable bowel syndrome and pelvic inflammatory disease, are predictive of the diagnosis of endometriosis among patients seeking help from general practice.

In a large retrospective analysis of the UK general practice research database concerning the prevalent symptoms within 3 years before the diagnosis of endometriosis [n=5540, each matched (year-of-birth and practice) to four controls], women with subsequent diagnosis of endometriosis had higher proportions of abdominopelvic pain or heavy menstrual bleeding (73 vs. 20%) (Ballard, et al., 2008). When compared with controls, women with endometriosis had odds ratios [OR (95% CI)] for the following symptoms: abdominopelvic pain 5.2 (4.7–5.7), dysmenorrhea 8.1 (7.2–9.3), heavy menstrual bleeding 4.0 (3.5–4.5), infertility 8.2 (6.9–9.9), dyspareunia/postcoital bleeding 6.8 (5.7–8.2) and urinary tract symptoms 1.2 (1.0–1.3). In addition, history of diagnosis with ovarian cyst 7.3 (5.7–9.4), irritable bowel syndrome 1.6 (1.3–1.8), pelvic inflammatory disease 3.0 (2.5-3.6) and fibrocystic breast disease 1.4 (1.2–1.7) were risk factors for subsequent diagnosis of endometriosis. Increasing the number of symptoms increased the chance of having endometriosis. In addition, women with eventual diagnosis endometriosis had consulted the doctor more frequently, and were twice as likely to have had time off from work (Ballard, et al., 2008).

In the same study, women with endometriosis had a high incidence of having received a diagnosis of irritable bowel syndrome: OR (95% CI) for irritable bowel syndrome 3.5 (3.1–3.9) before and 2.5 (2.2–2.8) after the diagnosis of endometriosis. In addition, the incidence of having received the diagnosis of pelvic inflammatory disease is higher among women with endometriosis. In the UK general practice research database study the OR (95% CI) of pelvic inflammatory disease diagnosis was 5.9 (5.1–6.9) before and 3.8 (5.1–6.9) after the diagnosis of endometriosis (Ballard, et al., 2008).

In specialist health care, among infertile women undergoing laparoscopy, dysmenorrhea was the only symptom significantly predictive of endometriosis (Forman, et al., 1993). In a prospective Italian study, women scheduled to undergo various gynaecological operations were interviewed concerning infertility, dysmenorrhea, dyspareunia and non-cyclical pelvic pain. None of these was predictive of the diagnosis of endometriosis (Eskenazi, et al., 2001). However, women eventually surgically diagnosed with endometriosis reported more intensive dysmenorrhea than those with no diagnosis of endometriosis (Eskenazi, et al., 2001, Hsu, et al., 2011).

Conclusion and considerations

Overall, the evidence on symptoms that indicate a diagnosis of endometriosis is weak and incomplete. In women seeking help from general practitioners, the following symptoms were found to be risk factors for endometriosis: abdominopelvic pain, dysmenorrhea, heavy menstrual bleeding, infertility, dyspareunia, postcoital bleeding, a previous diagnosis of ovarian cyst, irritable bowel syndrome and pelvic inflammatory disease. Reporting multiple symptoms increases the chance of endometriosis. In specialist health care, severe dysmenorrhea was found to be predictive of a diagnosis of endometriosis in infertile women, but this was not found in all studies.

After the deadline for included papers, a prospective study was published on this topic, which confirms that menstrual dyschezia strongly predicts some stages of endometriosis (Nnoaham, et al., 2012).

Although the included evidence is limited, exploring the diagnosis of endometriosis in women seeking help with these symptoms could result in earlier diagnosis of endometriosis and improved quality of life for these patients. For reasons of clarity and clinical usefulness of the recommendations, the GDG decided on the following good practice points:

Recommendations

The GDG recommends that clinicians should consider the diagnosis of endometriosis in the presence of gynecological symptoms such as: dysmenorrhea, non-cyclical pelvic pain, deep dyspareunia, infertility, fatigue in the presence of any of the above.	**GPP**

The GDG recommends that clinicians should consider the diagnosis of endometriosis in women of reproductive age with non-gynecological cyclical symptoms (dyschezia, dysuria, hematuria, rectal bleeding, shoulder pain).	**GPP**

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1.2 Clinical examination in the diagnosis of endometriosis

Key question

WHAT FINDINGS DURING CLINICAL EXAMINATION ARE PREDICTIVE FOR THE PRESENCE AND LOCALIZATION OF PELVIC ENDOMETRIOSIS?

Clinical evidence

Clinical examination in endometriosis is aimed at facilitating diagnosis and treatment of the disease. It includes inspection of the vagina using a speculum as well as bimanual and rectovaginal palpation (Bazot, et al., 2009, Chapron, et al., 2002). Clinical examination in women suspected with endometriosis includes physical examination of the pelvis but also the inspection and palpation of the abdomen. Location and extent of disease can sometimes be determined by clinical examination

(Bazot, et al., 2009, Koninckx, et al., 1996, Ripps and Martin, 1992). There should be special emphasis on the visualization of deep endometriosis in the vagina by inspection of the posterior fornix of the vaginal wall (Bazot, et al., 2009).

Vaginal examination can facilitate the detection of infiltration or nodules of the vagina, uterosacral ligaments or pouch of Douglas (Bazot, et al., 2009).

Rectovaginal digital examination may allow the detection of infiltration or mass involving the rectosigmoidal colon or adnexal masses (Bazot, et al., 2009, Condous, et al., 2007, Eskenazi, et al., 2001, Koninckx, et al., 1996, Ripps and Martin, 1992).

A prospective study has demonstrated that reliability of the clinical examination in detecting pelvic endometriosis is improved during menstruation (Koninckx, et al., 1996).

The diagnostic accuracy of physical examination, transvaginal sonography (TVS), rectal endoscopic sonography (RES) and magnetic resonance imaging (MRI) in diagnosing deep endometriosis has been determined in a retrospective longitudinal study (Bazot, et al., 2009).

In a prospective study, the prevalence and accuracy of diagnosing endometriosis by clinical examination were investigated. The prevalences of endometriosis on the uterosacral ligaments, pouch of Douglas, vagina, bladder, rectovaginal space and rectosigmoid were 23.3, 16.3, 8.5, 3.1, 6.9 and 24%, respectively. Values for TVS were similar with regard to vaginal and rectovaginal space endometriosis, but were superior to vaginal examination in cases of ovarian, uterosacral ligament and rectosigmoidal endometriosis (Hudelist, et al., 2011).

In addition, clinical examination is less accurate than imaging using transvaginal or transrectal ultrasound or MRI in diagnosing endometrioma and/or deep endometriosis (Bazot, et al., 2009, Chapron, et al., 2002, Hudelist, et al., 2011).

Conclusion and considerations

Overall, the evidence on the value of clinical examination for the diagnosis of endometriosis is weak, mainly based on cohort studies.

For the good practice point, the GDG weight the benefits of clinical examination versus the burden for patients. Regarding the benefits, clinical examination is useful for a faster diagnosis of endometriosis and a more specific further diagnostic approach using medical technologies, but with several limitations, including the dependence on the skills and experience of the clinician performing the examination. The financial burden of clinical examination is minimal as it can be performed at low cost.

It has to be noted that vaginal examination might be inappropriate in adolescents and that it can be very painful in some women. In women with high burden/discomfort (adolescents, due to religion, painful examination, sexual abuse in the past) vaginal examination should be omitted, and other medical technologies, as described in the next sections, should be used as a first step towards diagnosis.

Recommendations

The GDG recommends that clinicians should perform clinical examination in all women suspected of endometriosis, although vaginal examination may be inappropriate for adolescents and/or women without previous sexual intercourse. In such cases, rectal examination can be helpful for the diagnosis of endometriosis.	**GPP**

Clinicians may consider the diagnosis of deep endometriosis in women with (painful) induration and/or nodules of the rectovaginal wall found during clinical examination, or visible vaginal nodules in the posterior vaginal fornix (Bazot, et al., 2009).	**C**

Clinicians may consider the diagnosis of ovarian endometrioma in women with adnexal masses detected during clinical examination (Bazot, et al., 2009, Condous, et al., 2007, Eskenazi, et al., 2001, Koninckx, et al., 1996, Ripps and Martin, 1992).	**C**

Clinicians may consider the diagnosis of endometriosis in women suspected of the disease even if the clinical examination is normal (Chapron, et al., 2002).	**C**

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1.3 Medical technologies in the diagnosis of endometriosis

Key question

CAN THE DIAGNOSIS OF ENDOMETRIOSIS BE MADE BY APPLICATION OF SPECIFIC MEDICAL TECHNOLOGIES?

The diagnosis of endometriosis is first suspected based on the history, the symptoms and signs, then corroborated by physical examination and imaging techniques and finally is proven by histological examination of specimens collected during laparoscopy. The combination of laparoscopy and the histological verification of endometrial glands and/or stroma is considered to be the gold standard for the diagnosis of the disease. In many cases the typical appearances of endometriotic implants in the abdominal cavity are regarded as proof that endometriosis is present. This section deals with the diagnostic value of laparoscopy, histology, ultrasound, MRI and biomarkers, to prove or rule out the presence of endometriosis.

Before the diagnosis of endometriosis is established by laparoscopy and/or histology, one could argue that empirical treatment can be started without a definitive diagnosis. This might be the case in young adolescents or in women that decide not to have a laparoscopy solely to know if the disease is there. Moreover, even if peritoneal disease is found it might not be the cause of pain, and if found and treated the treatment might not be successful in treating the pain symptoms. If medical pain treatment relieves pain, many women will not be interested whether or not their pain symptoms were due to peritoneal endometriosis (Kennedy, 2006). However, all this is highly dependent on proper history taking, physical examination and imaging to rule out ovarian disease and/or deep endometriosis.

More information on empirical treatment can be found in chapter 2.

1.3.1 Laparoscopy in the diagnosis of endometriosis

Clinical evidence

In women with symptoms and signs of endometriosis there is an argument for starting medical treatment before embarking on an invasive procedure like a laparoscopy to obtain histological proof of the disease (as mentioned above). Arguments to perform a laparoscopy include the woman's wish to have a definitive diagnosis, infertility and/or symptoms and signs of advanced disease (ovarian endometrioma and deep infiltrating disease). If signs of deep endometriosis or ovarian endometriosis are not present in physical examination and imaging, it can be argued that a diagnostic laparoscopy should not be performed just to find peritoneal disease and treat it, especially in adolescents and young adults. It has not been shown that treatment of peritoneal disease influences the natural course of the disease.

A systematic review on the accuracy of laparoscopy to diagnose endometriosis (with biopsy and histology as the gold standard) showed that only limited reports of good quality exist (N=4), when assessing the value of visual diagnosis of endometriosis at laparoscopy. The accuracy of a diagnostic laparoscopy for endometriosis was evaluated in 433 patients. A negative diagnostic laparoscopy (i.e. a laparoscopy during which no endometriosis is identified) seems to be highly accurate for excluding

endometriosis and is therefore of use to the clinician in aiding decision-making. However, a positive laparoscopy (i.e. a laparoscopy during which endometriosis is identified) is less informative and of limited value when used in isolation (without histology); the positive likelihood ratio (LR+) (95% CI) is 4.30 (2.45–7.55), and the negative likelihood ratio (LR−) is 0.06 (0.01–0.47). With a prevalence of 20% the post-test probability is 51.8 (38.0–65.4) if the test is positive and 1.5 (0.2–10.5) if the test is negative (Wykes, et al., 2004).

The LR for a positive test on laparoscopy, 4.30 (2.45–7.45), is unlikely to raise the pre-test probability of endometriosis over a threshold for advanced management in most clinicians' practices, unless disease prevalence is very high (Wykes, et al., 2004).

A woman with a negative laparoscopy can be adequately reassured without the need for further testing.

However, the quality of both negative and positive laparoscopies depends highly on the abilities of the surgeon performing the laparoscopy. The experience, skill and knowledge of the surgeon determine whether endometriosis will be diagnosed if present. Retroperitoneally and vaginally localized endometriosis can be easily missed, especially if the patient has not been thoroughly examined preoperatively, preferably during anesthesia.

A good quality laparoscopy should include systematic checking of 1) the uterus and adnexa, 2) the peritoneum of ovarian fossae, vesico-uterine fold, Douglas and pararectal spaces, 3) the rectum and sigmoid (isolated sigmoid nodules), 4) the appendix and caecum and 5) the diaphragm. There should also be a speculum examination and palpation of the vagina and cervix under laparoscopic control, to check for 'buried' nodules. A good quality laparoscopy can only be performed by using at least one secondary port for a suitable grasper to clear the pelvis of obstruction from bowel loops, or fluid suction to ensure the whole pouch of Douglas is inspected.

The limited value of negative histology can also be explained partly by lack of knowledge of the clinician and/or the quality of the procedure, resulting in bad samples, squeezed samples or samples taken from the wrong location.

An appropriate preoperative clinical evaluation could prevent clinicians from overlooking deep endometriosis outside the peritoneal cavity or retroperitoneal lesions. Therefore, the GDG recommends that clinicians should assess ureter, bladder and bowel involvement by additional imaging if there is clinical suspicion of deep endometriosis, prior to further management. This recommendation is further explained in section 1.3g.

Conclusion and considerations

Laparoscopy with or without histological verification is widely used to diagnose and rule out the presence of endometriosis. However, the literature on the diagnostic value of a laparoscopy is very limited. Data on complications and adverse events are similarly limited, and one could expect a reporting bias. However, from the currently available data, laparoscopy (with histology) as a diagnostic intervention can be described as both successful and safe. A negative diagnostic laparoscopy in women with symptoms and signs of the disease is highly reliable for the exclusion of the diagnosis of endometriosis (Wykes, et al., 2004).

Recommendations

The GDG recommends that clinicians perform a laparoscopy to diagnose endometriosis, although evidence is lacking that a positive laparoscopy *without histology* proves the presence of disease.	**GPP**

The GDG recommends that clinicians confirm a positive laparoscopy by histology, since positive histology confirms the diagnosis of endometriosis, even though negative histology does not exclude it.	**GPP**

The GDG recommends that clinicians obtain tissue for histology in women undergoing surgery for ovarian endometrioma and/or deep infiltrating disease, to exclude rare instances of malignancy.	**GPP**

References

Kennedy S. Should a diagnosis of endometriosis be sought in all symptomatic women? *Fertil Steril* 2006; **86**:1312–1313; discussion 1317.

Wykes CB, Clark TJ and Khan KS. Accuracy of laparoscopy in the diagnosis of endometriosis: a systematic quantitative review. *BJOG* 2004; **111**:1204–1212.

1.3.2 Transvaginal sonography in the diagnosis of rectal endometriosis

Clinical evidence

In cases where there is a strong suspicion of endometriosis, especially in deep infiltrating disease, studies have been performed to evaluate the accuracy of transvaginal sonography (TVS) to diagnose rectal endometriosis.

In a systematic review, the diagnostic value of TVS for non-invasive, pre-surgical detection of bowel endometriosis was evaluated in 1105 women. In all but 32 women, histological verification (the gold standard) was obtained where diagnosis was made by laparoscopic visualisation. In the studies evaluated, the prevalence (95% CI) of bowel endometriosis was 47% (36.7–57.3). In these studies, the following characteristics were found for TVS diagnosis of bowel endometriosis: sensitivity 91% (88.1–93.5); specificity 98% (96.7–99.0); LR+ 30.36 (15.457–59.626); LR− 0.09 (0.046–0.188); PPV 98% (96.7–99.6); NPV 95% (92.1–97.7) (Hudelist, et al., 2011).

Conclusion and considerations

It can be concluded that TVS is useful for both identifying and ruling out rectal endometriosis.

It should be noted however that: 1) in most of these studies the surgeon was not blinded to the results of the test; 2) bowel surgery was not performed in all women, so it is difficult to confirm the presence/absence of disease; and 3) performing ultrasound is operator dependent.

Due to the operator dependency and the observation that in several European institutions clinicians are not experienced in performing TVS for the diagnosis of rectal endometriosis, the GDG feels that it cannot recommend TVS for the diagnosis of rectal endometriosis, unless performed by clinicians highly experienced in TVS.

Recommendation

In women with symptoms and signs of rectal endometriosis, transvaginal sonography is useful for identifying or ruling out rectal endometriosis (Hudelist, et al., 2011).	**A**

References

Hudelist G, English J, Thomas AE, Tinelli A, Singer CF and Keckstein J. Diagnostic accuracy of transvaginal ultrasound for non-invasive diagnosis of bowel endometriosis: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2011; **37**:257–263.

1.3.3 Transvaginal sonography in the diagnosis of ovarian endometriosis

Clinical evidence

In women with an adnexal mass with a suspicion of endometriosis, several studies were performed to evaluate the accuracy of TVS in ovarian endometriosis diagnosis.

In a systematic review, transvaginal and transabdominal ultrasound scanning (with or without Doppler) was evaluated as a diagnostic test for pelvic endometriosis. A total of 1257 adnexal masses were evaluated; histology was used in all but eight cases, where only cytology was performed. The prevalence of endometriosis was 13 to 38%. Diagnostic characteristics were: sensitivity 64 to 89%, specificity 89 to 100%, LR+ 7.6 to 29.8, and LR− 0.1 to 0.4 (Moore, et al., 2002).

It has to be noted that women with ovarian endometriosis have more pelvic and intestinal areas invaded by endometriosis, compared to women without ovarian endometriosis (Redwine, 1999). Ovarian endometrioma are only rarely sole findings. This implies that if an ovarian endometrioma is diagnosed by TVS, attention should be given to the possible existence of deep infiltrating disease; this should be further investigated by performing thorough vaginal and rectovaginal examinations and, where indicated, by more extensive imaging techniques like MRI.

Conclusion and considerations

It can be concluded that ovarian endometrioma can be diagnosed and excluded by TVS. One limitation is that small endometrioma could be missed. For the diagnosis of ovarian endometriosis, TVS is less operator-dependent and can be applied more widely. The GDG recommends that clinicians base diagnosis of ovarian endometriosis on the recently published ultrasound characteristics of ovarian endometrioma (Van Holsbeke, et al., 2010).

Recommendations

Clinicians are recommended to perform transvaginal sonography to diagnose or to exclude an ovarian endometrioma (Moore, et al., 2002).	**A**

The GDG recommends that clinicians base the diagnosis of ovarian endometrioma in premenopausal women on the following ultrasound characteristics: ground glass echogenicity and one to four compartments and no papillary structures with detectable blood flow.	**GPP**

References

Moore J, Copley S, Morris J, Lindsell D, Golding S and Kennedy S. A systematic review of the accuracy of ultrasound in the diagnosis of endometriosis. *Ultrasound Obstet Gynecol* 2002; **20**:630–634.

Redwine DB. Ovarian endometriosis: a marker for more extensive pelvic and intestinal disease. *Fertil Steril* 1999; **72**:310–315.

Van Holsbeke C, Van Calster B, Guerriero S, Savelli L, Paladini D, Lissoni AA, Czekierdowski A, Fischerova D, Zhang J, Mestdagh G et al. Endometriomas: their ultrasound characteristics. *Ultrasound Obstet Gynecol* 2010; **35**:730–740.

1.3.4 3D sonography in the diagnosis of rectovaginal endometriosis

Clinical evidence

The value of 3D sonography in detecting the presence of rectovaginal endometriosis was evaluated in a case series of 39 women with a clinical suspicion of rectovaginal endometriosis (Pascual, et al., 2010). The gold standard was laparoscopy, with the macroscopic and microscopic presence of rectovaginal endometriosis.

The prevalence of rectovaginal endometriosis was 50%, the investigators found: sensitivity (95% CI) 89.5% (73.3–94.5), specificity 94.7% (78,6–99,7), LR+ 17.2 (2.51–115) and LR− 0.11 (0.03–0.41). Given the pre-test probability of 50, this yields values of 94 (positive test) and 10 (negative test).

Conclusion and considerations

Since this is only a small case series and as 3D sonography has the inherent problem of all ultrasound diagnostic tests (i.e. operator dependency), the results of this study should be interpreted with caution, and diagnosis of rectal endometriosis based solely on 3D ultrasound should be limited to highly skilled ultrasound clinicians.

Recommendation

Clinicians should be aware that the usefulness of 3D sonography to diagnose rectovaginal endometriosis is not well established (Pascual, et al., 2010).	**D**

Reference

Pascual MA, Guerriero S, Hereter L, Barri-Soldevila P, Ajossa S, Graupera B and Rodriguez I. Diagnosis of endometriosis of the rectovaginal septum using introital three-dimensional ultrasonography. *Fertil Steril* 2010; **94**:2761–2765.

1.3.5 Magnetic resonance imaging in the diagnosis of peritoneal endometriosis

Clinical evidence

The value of magnetic resonance imaging (MRI) in detecting the presence of peritoneal endometriosis was evaluated by Stratton and co-workers in a case series of 44 women with a clinical suspicion of endometriosis. The gold standard was laparoscopy, with the macroscopic and microscopic presence of endometriosis. The prevalence of endometriosis was 86%; sensitivity was 69%, specificity was 75%, LR+ was 2.76, and LR− was 0.41. These LRs are too low to justify use of MRI to diagnose or exclude peritoneal disease. Overall, compared with biopsy results for each lesion, MRI had a diagnostic sensitivity of 38% and specificity of 74% (Stratton, et al., 2003).

Conclusion and considerations

In conclusion, MRI is not useful to diagnose or exclude peritoneal endometriosis. Furthermore, the authors noted that MRI is not a cost-effective diagnostic tool. The usefulness of MRI in establishing the extent of disease in women with deep endometriosis is discussed in section 1.3.7.

Recommendation

Clinicians should be aware that the usefulness of magnetic resonance imaging (MRI) to diagnose peritoneal endometriosis is not well established (Stratton, et al., 2003).	**D**

References

Stratton P, Winkel C, Premkumar A, Chow C, Wilson J, Hearns-Stokes R, Heo S, Merino M and Nieman LK. Diagnostic accuracy of laparoscopy, magnetic resonance imaging, and histopathologic examination for the detection of endometriosis. *Fertil Steril* 2003; **79**:1078–1085.

1.3.6 Biomarkers in the diagnosis of endometriosis

Clinical evidence

May and co-workers performed a systematic review to assess critically the clinical value of markers retrieved from endometrial tissue, menstrual fluid or uterine fluid to diagnose endometriosis in a non-invasive way. All 182 studies had visual and/or histological confirmation of endometriosis after laparoscopy or laparotomy, defined as the presence of peritoneal endometriotic lesions, endometrioma and/or rectovaginal endometriotic nodules (May, et al., 2011).

The overall conclusions of the authors were: 1) nine studies of high quality were identified, 2) in 32 studies sensitivity and specificity could be calculated, 3) the most promising markers were associated nerve fibres and cell-cycle molecules, and 4) whilst no marker was conclusively shown to diagnose endometriosis, several high-quality studies identified endometrial nerve fibres and molecules

involved in cell-cycle control, cell adhesion and angiogenesis as promising candidates for future biomarker research.

Serum CA-125 in the diagnosis of endometriosis

Serum CA-125 has been proposed as a candidate biomarker. Mol and co-workers (1998) performed a meta-analysis to assess critically the clinical value of serum CA-125 as a non-invasive diagnostic marker for endometriosis (Mol, et al., 1998).

The 2131 patients underwent laparoscopy because of pain and/or infertility. The prevalence of endometriosis was between 19 and 86%; the following characteristics were found: sensitivity 4 to 100%, specificity 38 to 100%, LR+ 2.8. A summary receiver operating characteristic (ROC) curve showed low diagnostic performance.

The overall conclusion was that the estimated summary ROC curves showed that the performance of serum CA-125 measurement in the diagnosis of endometriosis grade I/IV is limited, whereas its performance in the diagnosis of endometriosis grade III/IV is better.

Despite its limited diagnostic performance, Mol and co-workers believe that routine use of serum CA-125 measurement in patients with infertility might be justified, since it could identify a subgroup of patients who are more likely to benefit from early laparoscopy.

Immunological biomarkers in the diagnosis of endometriosis

May and co-workers performed a systematic review to critically assess the clinical value of all proposed immunological biomarkers for endometriosis in serum, plasma, and urine. All 161 studies had visual and/or histological confirmation of endometriosis after laparoscopy or laparotomy, defined as the presence of peritoneal endometriotic lesions, endometrioma and/or rectovaginal endometriotic nodules. The review did not report the total number of involved patients, the prevalence of the disease, or the sensitivity and specificity of the tests of the individual studies (May, et al., 2010).

Conclusion and considerations

The overall conclusions of the authors were 1) there is a lack of high quality studies investigating large numbers of well-phenotyped patients, and 2) the search identified over 200 investigated possible immunological biomarkers, but none had been clearly shown to be of clinical use.

From the included review, it can be concluded that serum CA-125 measurement has limited potential for the diagnosis of endometriosis. Future studies may show a potential of this biomarker in women with endometriosis, including prognosis, disease staging, identifying subgroups of patients and differentiation from other ovarian abnormalities.

There are currently no known immunological biomarkers that are able to diagnose endometriosis in a non-invasive way.

Recommendations

Clinicians are recommended not to use biomarkers in endometrial tissue, menstrual or uterine fluids to diagnose endometriosis (May, et al., 2011).	**A**

Clinicians are recommended not to use immunological biomarkers, including CA-125, in plasma, urine or serum to diagnose endometriosis (May, et al., 2010, Mol, et al., 1998).	**A**

References

May KE, Conduit-Hulbert SA, Villar J, Kirtley S, Kennedy SH and Becker CM. Peripheral biomarkers of endometriosis: a systematic review. *Hum Reprod Update* 2010; **16**:651–674.

May KE, Villar J, Kirtley S, Kennedy SH and Becker CM. Endometrial alterations in endometriosis: a systematic review of putative biomarkers. *Hum Reprod Update* 2011; **17**:637–653.

Mol BW, Bayram N, Lijmer JG, Wiegerinck MA, Bongers MY, van der Veen F and Bossuyt PM. The performance of CA-125 measurement in the detection of endometriosis: a meta-analysis. *Fertil Steril* 1998; **70**:1101–1108.

1.3.7 Barium enema, transvaginal sonography, transrectal sonography and MRI to establish the extent of disease in deep endometriosis

Where there is clinical suspicion of deep endometriosis, it is deemed beneficial to establish the extent of the disease. The key issue is whether it is possible to predict preoperatively in which patients there is involvement of the bowel wall, bladder or ureter.

Key question

CAN THE EXTENT OF DEEP ENDOMETRIOSIS BE ESTABLISHED BY APPLICATION OF SPECIFIC MEDICAL TECHNOLOGIES?

Clinical evidence

In six cohort studies, 575 patients with a high suspicion of deep endometriosis underwent several techniques in order to try to predict which patients had bowel involvement (barium enema, double contrast barium enema, transvaginal sonography, transrectal sonography) (Anaf, et al., 2009, Bergamini, et al., 2010, Faccioli, et al., 2008, Landi, et al., 2004, Ribeiro, et al., 2008, Savelli, et al., 2011).

The gold standard in these studies was laparoscopy and histology of resected endometriosis from the bowel wall. Since not all patients had a bowel resection, partial dissection or shaving without total bowel resection, histology was not available in all cases, thus reducing the quality of the studies. The prevalence of bowel wall involvement was between 48 and 100%. The sensitivity, specificity and positive and negative predictive values stated in the different studies were less reliable because of the lack of a histological gold standard.

From the results of these studies it is not possible to draw firm conclusions concerning to what extent a preoperative barium enema, transvaginal sonography or transrectal sonography are accurate in the diagnosis of bowel wall involvement in women with deep endometriosis.

Studies reporting on the value of MRI in predicting the extent of disease in deep endometriosis are either prospective (Abrao, et al., 2007) or retrospective (Bazot, et al., 2007, Chapron, et al., 2004). Only one study included women with surgically proven endometriosis (Chapron, et al., 2004). LR+ ranged from 12.0 to 41.7, indicating that MRI provides a good test to predict whether deep endometriosis has infiltrated the bowel wall. LR− ranged from 0.1 to 0.2, indicating a moderate test for excluding the presence of rectal infiltration.

Consideration should be given to performing MRI or sonography (transrectal and/or transvaginal and/or renal), with or without barium enema studies depending upon individual circumstances, to map the extent of the disease, which may be multifocal.

Bladder endometriosis can be suspected from patient history and diagnosed by transvaginal sonography, ideally while the patient has a full bladder. Conceivably, the detection rate of bladder endometriosis is related to the size of the endometriotic nodules (Savelli, et al., 2009). During cystoscopy a biopsy can be taken for histological confirmation. Endometriosis involving the ureter can be visualized by MRI or CT urogram.

Conclusion and considerations

From the evidence, it can be concluded that imaging techniques are helpful in estimating the extent of the disease in women with deep endometriosis. Since the focus is on predicting the extent of disease to target further management, these techniques should be sensitive rather than specific in diagnosing endometriosis.

Recommendation

The GDG recommends that clinicians should assess ureter, bladder, and bowel involvement by additional imaging if there is a suspicion based on history or physical examination of deep endometriosis, in preparation for further management.	**GPP**

References

Abrao MS, Goncalves MO, Dias JA, Jr., Podgaec S, Chamie LP and Blasbalg R. Comparison between clinical examination, transvaginal sonography and magnetic resonance imaging for the diagnosis of deep endometriosis. *Hum Reprod* 2007; **22**:3092–3097.

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Bazot M, Bornier C, Dubernard G, Roseau G, Cortez A and Darai E. Accuracy of magnetic resonance imaging and rectal endoscopic sonography for the prediction of location of deep pelvic endometriosis. *Hum Reprod* 2007; **22**:1457–1463.

Bergamini V, Ghezzi F, Scarperi S, Raffaelli R, Cromi A and Franchi M. Preoperative assessment of intestinal endometriosis: A comparison of transvaginal sonography with water-contrast in the rectum, transrectal sonography, and barium enema. *Abdom imaging* 2010; **35**:732–736.

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Savelli L, Manuzzi L, Pollastri P, Mabrouk M, Seracchioli R and Venturoli S. Diagnostic accuracy and potential limitations of transvaginal sonography for bladder endometriosis. *Ultrasound Obstet Gynecol* 2009; **34**:595–600.

2. TREATMENT OF ENDOMETRIOSIS-ASSOCIATED PAIN

Introduction

Women with endometriosis are confronted with one or both of two major problems: endometriosis-associated pain and infertility. This section focuses on pain treatment; chapter 3 addresses treatment of women suffering mainly from infertility.

Endometriosis-associated pain includes dysmenorrhea, dyspareunia, dysuria, dyschezia and non-menstrual pelvic pain, but the literature searches were not restricted to these terms. In the searches, quality of life was included, although this was found as an outcome in only a limited number of studies.

This chapter on the treatment of endometriosis-associated pain is subdivided into sections on empirical treatment, medical treatment, surgical treatment, pre- or postoperative medical treatment (including secondary prevention after surgery) and non-medical management strategies.

It has to be noted that endometriosis is a chronic and incurable disease in a significant number of women. The treatments described in this section can offer (partial) relief of pain symptoms, but symptoms often recur after discontinuation of therapy.

2.1 Empirical treatment of pain

In the section on medical treatment, we focus on women in pain due to diagnosed endometriosis. Studies assessing treatment of pain without a diagnosis of endometriosis were not assessed. However, it should be noted that women suffering from pelvic pain with a high suspicion of endometriosis use empirical analgesics and hormonal medication without a prior definitive laparoscopic diagnosis. This is in part due to the invasiveness of the laparoscopic procedure, but also due to the ease of prescribing hormonal contraceptives, which would be prescribed for prevention of pregnancy anyway. Before starting empirical treatment, other causes of pelvic pain symptoms should be ruled out, as far as possible. It is common practice for laparoscopy to be performed if the patient does not react favourably to the prescribed medical or hormonal pain treatment, to exclude or diagnose endometriosis (and possibly treat it at the same time). However, response to hormonal therapy does not always predict the presence or absence of endometriosis (Jenkins, et al., 2008, Ling, 1999). It has to be emphasized as well that prescribing oral contraceptives in adolescents with pelvic pain without a definitive diagnosis of endometriosis might contribute the well known delay in diagnosing the disease. It has been argued that starting oral contraception in young girls because of primary dysmenorrhea could be indicative of the diagnosis of deep endometriosis in later life (Chapron, et al., 2011).

Recommendation

The GDG recommends clinicians to counsel women with symptoms presumed to be due to endometriosis thoroughly, and to empirically treat them with adequate analgesia, combined hormonal contraceptives or progestagens.	**GPP**

References

Chapron C, Souza C, Borghese B, Lafay-Pillet MC, Santulli P, Bijaoui G, Goffinet F and de Ziegler D. Oral contraceptives and endometriosis: the past use of oral contraceptives for treating severe primary dysmenorrhea is associated with endometriosis, especially deep infiltrating endometriosis. *Hum Reprod* 2011; **26**:2028–2035.

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Ling FW. Randomized controlled trial of depot leuprolide in patients with chronic pelvic pain and clinically suspected endometriosis. Pelvic Pain Study Group. *Obstet Gynecol* 1999; **93**:51–58.

2.2 Hormonal therapies for treatment of endometriosis-associated pain

Key question

ARE HORMONAL THERAPIES EFFECTIVE FOR PAINFUL SYMPTOMS ASSOCIATED WITH ENDOMETRIOSIS?

Endometriosis is considered a predominantly estrogen-dependent disease. Thus, hormonal suppression might be an attractive medical approach to treat the disease and its symptoms. However, while, for example, combined hormonal contraceptives have been shown to reduce endometriosis-associated symptoms, it is conceivable that the estrogen component may mask the effect of the progestin, possibly by activating the disease. On the other hand, it is conceivable that the ethinylestradiol doses in modern combined hormonal contraceptives are too low to reach an activating threshold.

Many studies have compared various hormonal treatments. Early studies often failed to include a placebo or no treatment. As most of the hormonal treatments have been shown to be equally effective in treating endometriosis-associated symptoms, it would be ethically problematic to withhold treatment or use placebo in any future study. None of the hormones (or in fact any drug) is free of side effects, but severity and tolerability can vary quite significantly. In addition, significant cost differences exist between treatment groups. Finally, not all types of pain respond equally to hormonal treatment. In conclusion, all these factors should be taken into consideration when prescribing hormones to women suffering from endometriosis-associated pain.

Currently, hormonal contraceptives, progestagens, anti-progestagens, GnRH agonists and aromatase inhibitors are in clinical use. These compounds are discussed below. Data on selective estrogen receptor modulators (SERMs) and selective progesterone receptor modulators (SPRMs) was retrieved and assessed, but as there are insufficient data supporting a role for these in treatment of

pain in endometriosis, they are not discussed further. With no overwhelming evidence to support particular treatments over others, it is important to recognize that the decisions in any treatment plan are individual, and that a woman is able to make informed choices based on a good understanding of what is happening to her body.

Recommendations

Clinicians are recommended to prescribe hormonal treatment [hormonal contraceptives (level B), progestagens (level A), anti-progestagens (level A), or GnRH agonists (level A)] as one of the options, as it reduces endometriosis-associated pain (Vercellini, et al., 1993, Brown, et al., 2012, Brown, et al., 2010).	**A-B**

The GDG recommends that clinicians take patient preferences, side effects, efficacy, costs and availability into consideration when choosing hormonal treatment for endometriosis-associated pain.	**GPP**

2.2.1 Hormonal contraceptives

Clinical evidence

A systematic review investigated the results of four different comparisons with combined oral contraceptive pills (OCP) on endometriosis-related pain: 1) combined OCP versus placebo; 2) combined OCP versus no treatment ; 3) combined OCP versus other medical therapies (danazol, gonadotrophin releasing hormone analogues, progestagens, anti-progestagens, levonorgestrel-releasing intrauterine system); and 4) combined OCP versus conservative surgical treatment (Davis, et al., 2007).

Only one included study compared the GnRHa goserelin with low-dose combined OCP (20µg ethinylestradiol, 150µg desogestrel) (Vercellini, et al., 1993). At the end of a 6-month treatment period, non-menstrual pain, dyspareunia and dysmenorrhea were reduced in comparison with baseline, for both treatments. For dyspareunia, goserelin was superior to OCP, while for non-menstrual pain, there was no difference. During treatment with goserelin, amenorrhea occurred, so dysmenorrhea could not be compared between the groups at the end treatment.

At the end of a 6-month follow-up period, no difference in dysmenorrhea, non-menstrual pain or dyspareunia was seen between patients treated with low-dose combined OCP and those with goserelin. Furthermore, pain scores at the end of follow up did not differ significantly from pain scores at baseline, except for deep dyspareunia in patients that received goserelin (improvement).

One self-reported, prospective trial tested the effect of continuous use of a combined OCP (20µg ethinylestradiol, 150µg desogestrel) compared to conventional cyclic use (Vercellini, et al., 2003). Fifty women who had undergone surgery for endometriosis in the previous 12 months and experienced recurrent dysmenorrhea of more than 6 months were asked to take the same OCP continuously for an indefinite time. In the case of prolonged (more than 7 days) breakthrough

bleeding, women were advised to suspend treatment for one week. While moderate to severe side effects were reported in 14% of the women, 80% were very satisfied or satisfied after two years.

The same group investigated the tolerability to and effect of a contraceptive vaginal ring (15µg of ethinylestradiol and 120µg etonogestrel, the biologically active metabolite of desogestrel) and a transdermal patch (60µg of ethinylestradiol and 6mg of 17-deacetylnorgestimate, the primary active metabolite of norgestimate) in women with recurrent endometriosis-associated pain. During the 12-month study period, 36% of users of rings and 61% of users of the patch withdrew from treatment due various reasons, including side effects (mostly weight gain, headaches and bloating) and treatment inefficacy, or were lost to follow-up. In subjects who continued the study, both treatments for 12 months reduced dysmenorrhea, dyspareunia and chronic pelvic pain: 71% of vaginal ring users and 48% of transdermal patch users were satisfied after this time. The vaginal ring reduced dysmenorrhea significantly more in patients with rectovaginal endometriosis compared to women in the patch group. (Vercellini, et al., 2010).

Conclusion and considerations

In the Cochrane review, only one study was found and included on the use of hormonal contraceptives in treatment of pain in endometriosis. The authors of the study concluded that the use of this low-dose cyclic OCP is effective in reducing pain symptoms in patients with endometriosis, but they mentioned that the sample size for their study was limited and that data were limited to a 6-month period. They also stated that their study was underpowered to detect minor differences that might exist between OCP and goserelin. One study showed that continuous use of a combined OCP may be of benefit in patients suffering from dysmenorrhea. The GDG noted that although the evidence is limited, OCP is widely used as treatment for both endometriosis-associated pain and pain in women suspected of endometriosis. This may be due to practical advantages of OCP, including contraceptive protection, long term safety and control of menstrual cycle.

Recommendations

Clinicians can consider prescribing a combined hormonal contraceptive, as it reduces endometriosis-associated dyspareunia, dysmenorrhea and non-menstrual pain (Vercellini, et al., 1993).	**B**
Clinicians may consider the continuous use of a combined oral contraceptive pill in women suffering from endometriosis-associated dysmenorrhea (Vercellini, et al., 2003).	**C**
Clinicians may consider the use of a vaginal contraceptive ring or a transdermal (estrogen/progestin) patch to reduce endometriosis-associated dysmenorrhea, dyspareunia and chronic pelvic pain (Vercellini, et al., 2010).	**C**

References

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Vercellini P, Trespidi L, Colombo A, Vendola N, Marchini M and Crosignani PG. A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. *Fertil Steril* 1993; **60**:75–79.

2.2.2 Progestagens and anti-progestagens

Clinical evidence

A recent systematic Cochrane review investigated the effectiveness of progestagens and anti-progestagens in the treatment of endometriosis-associated pain (Brown, et al., 2012). Although published after the literature search, this Cochrane review replaces the initially included review by Kives, last edited in 2010 (Kives, et al., 2000). In this review, the authors included depot medroxyprogesterone acetate, cytoproterone acetate, medroxyprogesterone acetate, desogestrel and dienogest, as they were all evaluated in the literature as different progestagens for the treatment of endometriosis. Gestrinone was the only anti-progestagen (i.e. a substance that prevents cells from making or using progesterone) identified by the reviewers that has been evaluated for the treatment of endometriosis.

The review included two RCTs comparing progestagens with placebo and eight studies comparing progestagens with other treatments (two discussed depot progestagens, six discussed oral progestagens). Of the two studies on progestagens versus placebo, one small trial showed significant improvement of pain in women receiving progestagens (medroxyprogesterone acetate (MPA, 100mg) or danazol (200mg three times daily, for 6 months), compared to placebo. The second study showed no significant effect on pain. In this study, 12 days of 40 or 60mg of dydrogesterone was compared with placebo during the luteal phase in women with endometriosis who were trying to conceive.

Eight RCTs compared progestagens with other treatments. Two studies were included comparing depot progestagens to a cyclic monophasic OCP combined with danazol and leuprolide acetate. Six studies compared oral progestagens with other treatments: MPA was compared with danazol, and with intranasal nafarelin; cytoproterone acetate and desogestrel were compared with a combined oral contraceptive pill (2 studies); and dienogest was compared with buserelin acetate and with leuprolide acetate. Based on the eight included studies comparing progestagens with other medical treatments, the reviewers concluded that there was no evidence to suggest a benefit of progestagens over other treatments.

The anti-progestagen gestrinone was tested in 4 RCTs. Hornstein and co-workers showed, in a total of 12 patients, that twice-weekly oral intake of either 1.25mg or 2.5mg gestrinone were equally effective, but side effects were less common in the lower-dose group. Gestrinone and danazol were

compared by two groups, one Italian and the other British-led. Pelvic pain and deep dyspareunia (first study) and pelvic pain and dysmenorrhea (second study) were similarly reduced in both groups during treatment. Both treatments resulted in severe side effects, and several patients withdrew from the study. Finally, an Italian multicentre study compared the effect of oral gestrinone with intramuscular leuprolide acetate for 6 months in women with endometriosis-associated pelvic pain. Both treatments were effective in reducing dysmenorrhea, deep dyspareunia and non-menstrual pain during treatment and the 6-month follow-up.

The conclusion from this literature review is that both continuous progestagens and continuous gestrinone are effective therapies for the treatment of painful symptoms associated with endometriosis. However, this conclusion must be treated with caution due to the paucity of data and lack of placebo-controlled studies.

Another Cochrane review summarised studies comparing oral danazol with placebo or no treatment, and danazol vs. oral MPA vs. placebo (Farquhar, et al., 2007). Five studies met the inclusion criteria, but in three trials treatment was used in addition to surgery. The two remaining studies might have had some patient overlap. In these trials, patients were treated for 6 months. Endometriosis-associated pain, back pain and dyschezia scores were reduced at 6 and 12 months in those patients in both the danazol and MPA groups (compared to placebo), but had significant side effects (e.g. acne, oedema, vaginal spotting, weight gain and muscle cramps). Oral danazol has been withdrawn from the market in some countries due to its side-effect profile. Recent studies indicate that vaginal danazol may be better tolerated.

Three studies investigated the potential of a levonorgestrel-releasing intrauterine system (LNG-IUS) for endometriosis-associated symptoms. The first randomized, controlled, multicentre study by Petta and colleagues randomized 83 patients to either the LNG-IUS or monthly leuprolide acetate (Petta, et al., 2005). After 6 months of treatment both groups had significantly reduced visual analogue pain scores (VAS), but no difference was found between the groups. A second study aimed primarily to determine whether the levonorgestrel-releasing intrauterine system can influence ASRM staging scores, assessed by second-look laparoscopy, using a similar regimen as described above (Gomes, et al., 2007). They also found a significant decrease in pelvic pain scores after 6 months of treatment compared to baseline values, but again no intergroup differences. The same group published another study with slightly larger numbers of participants (Ferreira, et al., 2010). Similarly to both previous studies, pelvic pain scores were reduced in both groups, but no difference was found between groups. In general, all authors comment on the potential benefit of a levonorgestrel-releasing intrauterine system due to the better side-effect profile.

Conclusion and considerations

There is sufficient evidence on the effectiveness of progestagens and anti-progestagens, including the levonorgestrel-releasing intrauterine system, in reducing pain in women with endometriosis. The GDG stresses that clinicians should look at side-effect profiles, to tailor the medical treatment and improve the quality of life of the woman.

Regarding the use of danazol for treatment of endometriosis-associated pain, the GDG strongly believes that danazol should not be used if any other medical therapy is available, due to its severe side effects (acne, oedema, vaginal spotting, weight gain, muscle cramps).

Recommendations

Clinicians are recommended to use progestagens [medroxyprogesterone acetate (oral or depot), dienogest, cyproterone acetate, norethisterone acetate or danazol] or anti-progestagens (gestrinone) as one of the options, to reduce endometriosis-associated pain (Brown, et al., 2012).	**A**

The GDG recommends that clinicians take the different side-effect profiles of progestagens and anti-progestagens into account when prescribing these drugs, especially irreversible side effects (e.g. thrombosis, androgenic side effects).	**GPP**

Clinicians can consider prescribing a levonorgestrel-releasing intrauterine system as one of the options to reduce endometriosis-associated pain (Ferreira, et al., 2010, Gomes, et al., 2007, Petta, et al., 2005).	**B**

References

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Petta CA, Ferriani RA, Abrao MS, Hassan D, Rosa E Silva JC, Podgaec S and Bahamondes L. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. *Hum Reprod* 2005; **20**:1993–1998.

2.2.3 GnRH agonists

Clinical evidence

A Cochrane review compared GnRH agonist (GnRHa) at different doses, regimens and routes of administration, with danazol, with intrauterine progestagen, with placebo, and with analgesics for relieving endometriosis-associated pain symptoms (Brown, et al., 2010). The results suggest that GnRHa is more effective than placebo but inferior to the levonorgestrel-releasing intrauterine system or oral danazol. The review found a worse side effect profile for GnRHa in all studies. According to one study, there was no difference for dysmenorrhea, pelvic pain, tenderness and induration when women are treated for 3 or 6 months with GnRHa (leuprolide), but dyspareunia was decreased in the shorter protocol (Hornstein, et al., 1995). No difference in effectiveness exists when GnRHa is administered intramuscularly, subcutaneously or intranasally. Limited evidence suggests an improvement in quality of life for patients receiving nafarelin intranasally compared to intramuscular leuprolide acetate (Zhao, et al., 1999). No studies were available comparing GnRHa with analgesics.

Due to the common presence of hypoestrogenic side effects of GnRHa, efforts have been made to tackle this problem by adding estrogens and/or progestagens or tibolone to GnRHa therapy (add-back therapy). This is based on the threshold theory, by which lower estrogen levels are needed to protect the bone and cognitive function and to avoid/minimise menopausal symptoms such as hot flushes, sleep disturbance, mood swings, than to activate endometriotic tissue (Barbieri, 1992). Studies have explored whether such add-back therapy reduces side effects and whether it has an effect on the efficacy of GnRHa. Several studies reported a reduction in side effects by adding estrogens and/or progestagens to GnRHa therapy, as compared to GnRHa therapy alone: GnRHa plus MPA reduced hot flushes and sweating during treatment (Makarainen, et al., 1996), nafarelin plus norethisterone acetate (NEA, 1,2mg) decreased hot flushes and resulted in better bleeding control (Bergqvist, et al., 1997), goserelin plus tibolone reduced vasomotor symptoms and bone metabolism (Taskin, et al., 1997) and goserelin plus conjugated estrogen and MPA reduced bone loss (Moghissi, et al., 1998). None of these studies reported a negative effect of add-back therapy on the efficacy of treatment with GnRHa (compared to GnRHa alone). However, due to a lack of large RCTs it remains unclear as to which form of add-back therapy should be recommended for women with endometriosis treated with GnRHa.

A multicentre RCT compared a combined oral contraceptive pill (750µg gestroden and 30µg ethinylestradiol) for 12 months with 4 months of triptorelin (3.75mg slow release every 28 days) followed by 8 months of the combined OCP (Parazzini, et al., 2000). Both groups showed decreased dysmenorrhea and non-menstrual pain, although no statistical data were presented. No significant difference between groups was seen.

No evidence exists on the effectiveness of GnRHa for endometriosis-associated pain.

Conclusion and considerations

It can be concluded that GnRH agonists, with and without add-back therapy, are effective in the relief of endometriosis-associated pain, but evidence is limited regarding dosage or duration of treatment. No specific GnRHa can be recommended over another in relieving endometriosis-associated pain. No evidence exists on the efficacy of GnRH antagonists for endometriosis-associated pain. There is

evidence of severe side effects with GnRHa, which should be discussed with the woman when offering this treatment.

Recommendations

Clinicians are recommended to use GnRH agonists (nafarelin, leuprolide, buserelin, goserelin or triptorelin), as one of the options for reducing endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment (Brown, et al., 2010).	**A**

Clinicians are recommended to prescribe hormonal add-back therapy to coincide with the start of GnRH agonist therapy, to prevent bone loss and hypoestrogenic symptoms during treatment. This is not known to reduce the effect of treatment on pain relief (Bergqvist, et al., 1997, Makarainen, et al., 1996, Moghissi, et al., 1998, Taskin, et al., 1997).	**A**

The GDG recommends clinicians to give careful consideration to the use of GnRH agonists in young women and adolescents, since these women may not have reached maximum bone density.	**GPP**

References

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2.2.4 Aromatase inhibitors

Even though the evidence for increased expression of aromatase P450 in endometriotic tissue is still controversial, aromatase inhibitors (AIs) have been studied as treatment for pain symptoms in premenopausal women with endometriosis.

Clinical evidence

Two systematic reviews looked at the potential of aromatase inhibitors for the treatment of endometriosis-associated pain (Ferrero, et al., 2011, Nawathe, et al., 2008). Nawathe and co-workers identified five studies, all but one of which showed a significant benefit of aromatase inhibitors for endometriosis-associated pain. However, the review only found studies with small numbers and only included one RCT.

Recently, Ferrero and co-workers performed another systematic review including seven studies, two of which were from the authors' group. The minimum number of individuals in each trial was 10. The systematic review found that treatment with oral letrozole plus norethisterone acetate (NEA) or desogestrel, or anastrozole as vaginal suppository (250µg daily) or orally (1mg daily) in combination with OCP resulted in a significant decrease of endometriosis-associated pain in premenopausal women. The same appears to be true for letrozole plus either NEA or triptorelin, although letrozole plus triptorelin resulted in more side effects than NEA. The authors concluded that aromatase inhibitors should be investigated long-term to see if they are superior to currently available endocrine therapies in terms of improvement of pain, adverse effects and patient satisfaction.

Aromatase inhibitors are not available (even as an off-label drug) in some countries. The most common third-generation aromatase inhibitors letrozole and anastrozole are reversible inhibitors of the enzyme aromatase, competing with androgens for aromatase binding sites. The side effects are mostly hypoestrogenic in nature and include vaginal dryness, hot flushes and diminished bone mineral density. Because of the reduction of estrogen-driven negative feedback at the hypothalamic-pituitary axis, aromatase inhibitors are used for ovulation induction. Therefore, pregnancies with higher rates of multiples are a potential complication of this treatment. Earlier reports of increased cardiovascular risks have not been substantiated.

Conclusion and considerations

The evidence consists of two recent systematic reviews; both evaluated mostly non-randomized controlled studies and case reports, and show significant overlap in the included studies. They both conclude that the existing evidence is of moderate quality and that evidence on the long-term effects of aromatase inhibitors is lacking.

All evidence is based on studies in women with rectovaginal endometriosis or women that are refractory to previous surgical and medical treatment. Due to the severe side effects (vaginal dryness, hot flushes, diminished bone mineral density), aromatase inhibitors should only be prescribed to women after all other options for medical or surgical treatment are exhausted.

Furthermore, the systematic review on this topic is based on small studies and case reports. Therefore, the evidence level was downgraded to B.

Recommendation

In women with pain from rectovaginal endometriosis refractory to other medical or surgical treatment, clinicians can consider prescribing aromatase inhibitors in combination with oral contraceptive pills, progestagens, or GnRH analogues, as they reduce endometriosis-associated pain (Ferrero, et al., 2011, Nawathe, et al., 2008).	**B**

References

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2.3 Analgesics for treatment of endometriosis-associated pain

Pain is a cardinal symptom of endometriosis. Studies have demonstrated elevated prostaglandin levels in peritoneal fluid and endometriotic tissue in women with endometriosis. As a result, non-steroidal anti-inflammatory drugs (NSAIDs) are widely used analgesics in clinical practice. Good evidence exists to support the use of NSAIDs for primary dysmenorrhea (Marjoribanks, et al., 2010). This chapter will assess the available data for endometriosis-associated pain.

Key question

ARE ANALGESICS EFFECTIVE FOR SYMPTOMATIC RELIEF OF PAIN ASSOCIATED WITH ENDOMETRIOSIS?

Clinical evidence

Only two studies were available that investigated the role of NSAIDs in the relief of endometriosis-associated pain. In a systematic review, three studies were identified, but one had to be excluded because of methodological flaws and another was excluded because the drug had to be withdrawn from the market (Allen, et al., 2009). Thus, the review included only one paper, reporting on a two-period, two-treatment crossover trial comparing naproxen sodium (275mg, 4 times per day) with placebo (4 times per day) in 24 women with stage II-IV endometriosis (for a total of 4 months) (Kauppila and Ronnberg, 1985). Using a self-reporting questionnaire after each menstrual cycle, pain relief and the effect on daily activities was tested. There was no significant evidence of a moderate to excellent pain relief or the need for additional analgesia in both groups. The review authors concluded that there is inconclusive evidence to determine whether NSAIDs (naproxen sodium) are effective for the treatment of pain caused by endometriosis (Allen, et al., 2009).

One study that was not included in the systematic review used an oral cyclooxygenase (COX)-2 inhibitor (rofecoxib) versus control for 6 months in 28 patients (Cobellis, et al., 2004). The authors reported that dysmenorrhea, dyspareunia and chronic pelvic pain were significantly reduced in the

COX-2 inhibitor group 6 months after the end of treatment versus placebo (p<0.001). No side effects were found.

To our knowledge, there are no other trials on analgesics (paracetamol, aspirin, ibuprofen, cyclooxygenase inhibitors, codeine, pethidine, narcotics, dentin desensitizing agents, morphine) in the treatment of endometriosis-associated pain.

Conclusion and considerations

Although widely used as a first line treatment of endometriosis-associated pain, there is virtually no evidence on the use of NSAIDS for endometriosis, except for one study published in 1985. A more recent study discussed the COX-2 inhibitor rofecoxib, but this has been withdrawn from the market in some European countries due to severe side effects. However, there is good evidence that NSAIDs have a favourable effect on primary dysmenorrhea (Marjoribanks, et al., 2010).

From a patient perspective, clinicians should discuss the use of NSAIDs for the management of pain with the women, especially pointing out some side effects associated with frequent use of NSAIDs, including inhibition of ovulation, risk of gastric ulceration and cardiovascular disease (Duffy and Stouffer, 2002, McGettigan and Henry, 2013).

In conclusion, the effectiveness of NSAIDs (naproxen) in treating endometriosis-associated dysmenorrhea is not well established owing to a lack of studies. Nevertheless, the GDG came to the following recommendation due to the known benefit of NSAIDs in primary dysmenorrhea.

Recommendation

The GDG recommends that clinicians should consider NSAIDs or other analgesics to reduce endometriosis-associated pain.	**GPP**

References

Allen C, Hopewell S, Prentice A and Gregory D. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. *Cochrane Database Syst Rev* 2009:CD004753.

Cobellis L, Razzi S, De Simone S, Sartini A, Fava A, Danero S, Gioffrè W, Mazzini M and Petraglia F. The treatment with a COX-2 specific inhibitor is effective in the management of pain related to endometriosis. *Eur J Obstet Gynecol Reprod Biol* 2004; **116**:100–102.

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2.4 Surgery for treatment of endometriosis-associated pain

Introduction

Surgical treatment — elimination of endometriotic lesions, division of adhesions and interruption of nerve pathways — has long been an important part of the management of endometriosis. Historically, surgical approaches were achieved at open surgery, but in recent decades, laparoscopy has dominated. Elimination of endometriosis may be achieved by excision, diathermy or ablation/evaporation. Division of adhesions aims to restore pelvic anatomy, and interruption of pelvic nerve pathways is carried out with the intention of improving pain control.

Key question

IS SURGERY EFFECTIVE FOR PAINFUL SYMPTOMS ASSOCIATED WITH ENDOMETRIOSIS?

2.4.1 Surgery for treatment of endometriosis-associated pain

Clinical evidence

A non-randomized report showed that laparoscopy and laparotomy were equally effective in the treatment of chronic pelvic pain related to severe endometriosis (Crosignani, et al., 1996). The efficacy of laparoscopic treatment of endometriosis has been compared against diagnostic laparoscopy or medical treatment. A Cochrane review summarised 5 RCTs that compared surgical treatment of endometriosis with diagnostic laparoscopy only or medical treatment (Jacobson, et al., 2009). The reviewers showed significant benefits of laparoscopic surgery 6 and 12 months after the operation; there was no significant difference at 3 months. In the five included trials the method of treatment was either excision, coagulation or laser vaporisation of endometriotic lesions. A study by Sutton also included laparoscopic uterosacral nerve ablation (LUNA) in addition to laser vaporisation of endometriotic lesions and adhesiolysis in the treatment arm (Sutton, et al., 1994). It is worth noting that there were relatively few patients with severe endometriosis in these trials. The studies included in this review reported no major complications.

Conclusion and considerations

Laparotomy and laparoscopy are equally effective in the treatment of endometriosis-associated pain. Operative laparoscopy (excision/ablation) is more effective for the treatment of pelvic pain associated with all stages of endometriosis, compared to diagnostic laparoscopy only. Laparoscopy is usually associated with less pain, shorter hospital stay, quicker recovery and better cosmesis, hence it is usually preferred to open surgery. If the relevant experience with laparoscopy is not available, the patient should be referred to a centre of expertise.

Recommendation

When endometriosis is identified at laparoscopy, clinicians are recommended to surgically treat endometriosis, as this is effective for reducing endometriosis-associated pain i.e. 'see and treat' (Jacobson, et al., 2009).	**A**

References

Crosignani PG, Vercellini P, Biffignandi F, Costantini W, Cortesi I and Imparato E. Laparoscopy versus laparotomy in conservative surgical treatment for severe endometriosis. *Fertil steril* 1996; **66**:706–711.

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Sutton CJ, Ewen SP, Whitelaw N and Haines P. Prospective, randomized, double-blind, controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal, mild, and moderate endometriosis. *Fertil steril* 1994; **62**:696–700.

2.4.2 Ablation versus excision of endometriosis

Clinical evidence

A small RCT showed that excision and ablation equally improved pelvic pain associated with mild endometriosis (Wright, et al., 2005). A more recent RCT including women with all stages of endometriosis showed that ablation was as effective as excision (Healey, et al., 2010). However, this study did not specify how ablation or excision was carried out or how ovarian cysts were treated. Furthermore, the excision group had higher American Fertility Society (AFS) staging system scores.

Conclusion and considerations

Ablation and excision of peritoneal disease are thought to be equally effective for treatment of endometriosis-associated pain. However, this information comes from one small study and a larger one with suboptimal design; hence their conclusions should be treated with caution. Excision of lesions could be preferred with regard to the possibility of retrieving samples for histology. Furthermore, ablative techniques are unlikely to be suitable for advanced forms of endometriosis with deep endometriosis component.

Recommendation

Clinicians may consider both ablation and excision of peritoneal endometriosis to reduce endometriosis-associated pain (Healey, et al., 2010, Wright, et al., 2005).	**C**

References

Healey M, Ang WC and Cheng C. Surgical treatment of endometriosis: a prospective randomized double-blinded trial comparing excision and ablation. *Fertil Steril* 2010; **94**:2536–2540.

Wright J, Lotfallah H, Jones K and Lovell D. A randomized trial of excision versus ablation for mild endometriosis. *Fertil Steril* 2005; **83**:1830–1836.

2.4.3 Surgical interruption of pelvic nerve pathways

Clinical evidence

The effectiveness of surgical interruption of pelvic nerve pathways in primary and secondary dysmenorrhea was analysed in a Cochrane review that included 6 RCTs on women with endometriosis (Proctor, et al., 2005). Three of these RCTs evaluated the effect of laparoscopic uterosacral nerve ablation (LUNA) together with conservative laparoscopic surgery for endometriosis; the other three studied the effects of presacral neurectomy (PSN) (two at laparotomy, one at laparoscopy) in addition to conservative surgery for endometriosis. The RCTs on LUNA showed that this technique did not offer any additional benefit as an adjunct to conservative surgery one year after surgery. The assessment at 6 months did not show any benefit either, but this included one additional trial studying patients who had fibroids. There were significant benefits of PSN at 6 months (1 RCT) and 12 months (2 RCTs). However, PSN is associated with increased risk of adverse effects such as bleeding, constipation, urinary urgency and painless first stage of labour (Proctor, et al., 2005). The data suggest that the effect of PSN may be specific to midline pain only.

Conclusion and considerations

It can be concluded that LUNA is not beneficial as an additional procedure to conservative surgery for endometriosis, as it offers no additional benefit over surgery alone (Proctor, et al., 2005).

PSN is beneficial for treatment of endometriosis-associated midline pain as an adjunct to conservative laparoscopic surgery, but it should be stressed that PSN requires a high degree of skill and is associated with increased risk of adverse effects such as bleeding, constipation, urinary urgency and painless first stage of labour.

Recommendations

Clinicians should not perform laparoscopic uterosacral nerve ablation (LUNA) as an additional procedure to conservative surgery to reduce endometriosis-associated pain (Proctor, et al., 2005).	**A**

Clinicians should be aware that presacral neurectomy (PSN) is effective as an additional procedure to conservative surgery to reduce endometriosis-associated midline pain, but it requires a high degree of skill and is a potentially hazardous procedure (Proctor, et al., 2005).	**A**

References

Proctor M, Latthe P, Farquhar C, Khan K and Johnson N. Surgical interruption of pelvic nerve pathways for primary and secondary dysmenorrhoea. *Cochrane Database Syst Rev* 2005:CD001896. [Edited (no change to conclusions), published in Issue 11, 2010.]

2.4.4 Surgery for treatment of pain associated with ovarian endometrioma

Clinical evidence

A Cochrane review by Hart and co-workers reviewed two RCTs comparing laparoscopic excision of ovarian endometriotic cysts (3 cm or larger) to drainage and coagulation by bipolar diathermy (Alborzi, et al., 2004, Beretta, et al., 1998, Hart, et al., 2008). Both studies demonstrated lower recurrence of dysmenorrhea and dyspareunia after cystectomy compared to drainage and coagulation only. There were fewer cyst recurrences with the excisional approach. Need for further surgery and recurrence of non-menstrual pain were less likely after cystectomy.

A more recent RCT that was not included in the Cochrane review compared cystectomy with CO_2 laser vaporization; this showed that recurrence of cysts was more common at 12 months, but not at 60 months, after laser vaporization, and that the time to recurrence was shorter, compared to cystectomy (Carmona, et al., 2011).

Another recent RCT looked at direct stripping of endometrioma at the original adhesion site compared to circular excision at the initial adhesion site followed by stripping (Mossa, et al., 2010). This trial showed that initial circular excision followed by stripping was quicker, had shorter haemostasis times and had higher complete excision rates. However, the recurrence rates were not different. The average cyst size was bigger in the direct stripping group and blinding was unclear, hence the results should be interpreted with caution. Risk of ovarian failure after bilateral ovarian endometrioma removal is reported to be 2.4% (Busacca, et al., 2006).

Conclusion and considerations

Cystectomy is superior to drainage and coagulation in women with ovarian endometrioma (≥ 3cm) with regard to the recurrence of endometriosis-associated pain and the recurrence of endometrioma. Cystectomy is probably more effective than CO_2 laser vaporization in women with ovarian endometrioma (≥3cm) with regard to recurrence of endometrioma.

Although the three RCTs on which the recommendations of this section are based (Alborzi, et al., 2004, Beretta, et al., 1998, Carmona, et al., 2011) included patients with endometriomas of 3cm or larger, surgical treatment of smaller endometriomas is also recommended for the treatment of pain, based on the studies included in section 2.4a (Jacobson, et al., 2009). Whilst superiority of excision over drainage and coagulation/ablation can be expected, possible difficulties in removal of very small endometriomas should be kept in mind due to lack of a clear surgical plane.

Recommendations

When performing surgery in women with ovarian endometrioma, clinicians should perform cystectomy instead of drainage and coagulation, as cystectomy reduces endometriosis-associated pain (Hart, et al., 2008).	**A**

Clinicians can consider performing cystectomy rather than CO2 laser vaporization in women with ovarian endometrioma, because of a lower recurrence rate of the endometrioma (Carmona, et al., 2011).	**B**

References

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2.4.5 Surgery for treatment of pain associated with deep endometriosis

Clinical evidence

Deep endometriosis extends beneath the peritoneum and may affect the uterosacral ligaments, pelvic side walls, rectovaginal septum, vagina, bowel, bladder or ureter. Excision of these nodules is usually performed when surgical treatment is chosen. Colorectal involvement is not rare with deep endometriosis, and the treatment approaches for this condition include superficial shaving, discoid resection and segmental resection of the bowel to remove the deep endometriosis nodules. A large number of case series have been published for these methods since the late 1980s. A systematic review by Meuleman and co-workers looked at 49 papers on this subject, including laparoscopic, laparotomic, transvaginal or combined approaches. They found that pain and quality of life improvement was reported in most studies, the complication rate was 0–3% and the recurrence rate was 5–25%. However, they noted that most data were collected retrospectively, and study designs and reporting methods were variable. As it was impossible to make comparisons between different surgical techniques, a checklist was developed to standardise the reports of surgical trials for deep infiltrating endometriosis (Meuleman, et al., 2011b) .

Another systematic review by De Cicco and co-workers included 34 articles on bowel resection for colorectal endometriosis. This review found excellent pain relief in most studies. They concluded that segmental bowel resection for deep endometriosis with colorectal involvement seemed to be a widely acceptable option. The decision to perform resection seemed to be based on preference rather than data; complication rates were similar to resections for other indications, and data on sexual dysfunction were lacking. They suggested that in order to permit meta-analysis, journals should adopt a standard way of reporting indications, surgery, outcome, size and localisation of nodules. The common use of bowel resection may be due to bowel surgeons who are used to resections for cancer treatment (De Cicco, et al., 2011).

A relatively small RCT (26 patients in each group) showed that laparoscopy was as effective as laparotomy for colorectal resection for endometriosis, in improving pain symptoms and quality of life. Furthermore, a subgroup analysis showed that spontaneous pregnancies occurred only in the laparoscopy group (Darai, et al., 2010, Darai, et al., 2011).

Surgery for deep endometriosis appears possible and effective, but this is associated with significant complication rates, particularly when rectal surgery is required. The reported total intraoperative complication rate was 2.1%, and the total postoperative complication rate was 13.9% (9.5% minor, 4.6% major) (Kondo, et al., 2011). There is an ongoing debate about the indication for shaving nodules as opposed to segmental resection (Donnez and Squifflet, 2010, Meuleman, et al., 2011a).

The reported recurrence rates following surgery for colorectal endometriosis in the studies with longer than 2 years follow up were 5–25% (Meuleman, et al., 2011b); the recurrence rates were higher in studies that reported symptomatic recurrence than in studies that reported histological recurrence (De Cicco, et al., 2011).

Surgical treatment of bladder endometriosis is usually excision of the lesion and primary closure of the bladder wall. Ureteral lesions may be excised after stenting the ureter; however, in the presence of intrinsic lesions or significant obstruction segmental excision with end-to-end anastomosis or reimplantation may be necessary.

Conclusion and considerations

Overall, it can be concluded that surgery improves pain and quality of life in women with deep endometriosis. However, surgery in women with deep endometriosis is associated with substantial intraoperative and postoperative complication rates.

There is a lack of consistency in the way the studies reported outcome, and the systematic review on this topic was based on small studies and case reports. Therefore, the evidence level was downgraded to B.

Recommendations

Clinicians can consider performing surgical removal of deep endometriosis, as it reduces endometriosis-associated pain and improves quality of life (De Cicco, et al., 2011, Meuleman, et al., 2011b).	**B**

The GDG recommends that clinicians refer women with suspected or diagnosed deep endometriosis to a centre of expertise that offers all available treatments in a multidisciplinary context.	**GPP**

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2.4.6 Hysterectomy for endometriosis-associated pain

Clinical evidence

There are no RCTs on hysterectomy (with or without oophorectomy) for the treatment of endometriosis-associated pain; most published articles are retrospective case series, and there are only a few prospective studies. A non-systematic review by Martin (2006) concluded that hysterectomy for chronic non-specified pelvic pain associated with endometriosis was a successful approach in many women. It also stated that some women did not obtain any relief of pain after hysterectomy and suggested focused prospective research to determine specific response patterns. This article listed a number of difficulties in evaluating hysterectomy for endometriosis-associated pain, including lack of differentiation between cyclical and non-cyclical pain, difficulty in establishing whether endometriosis is the cause of pain or a co-incidental finding in a woman with chronic pelvic pain, and high variability in the rates of success among the studies. Other important aspects to consider are effective removal of endometriotic lesions and removal of ovaries. Many clinicians believe that surgical castration would lead to regression of remaining endometriotic lesions. Furthermore, hysterectomy with ovarian conservation was reported to have a 6-fold risk for development of recurrent pain and an 8.1-times greater risk of reoperation (Martin, 2006).

Recommendation

The GDG recommends that clinicians consider hysterectomy with removal of the ovaries and all visible endometriosis lesions, in women who have completed their family and failed to respond to more conservative treatments. Women should be informed that hysterectomy will not necessarily cure the symptoms or the disease.	**GPP**

References

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2.4.7 Adhesion prevention after endometriosis surgery

Clinical evidence

There are a number of barrier, fluid and pharmacological agents that have been tried for adhesion prevention during gynaecological surgery. These include oxidised regenerated cellulose (Interceed®), polytetrafluoroethylene surgical membrane (Gore-Tex®), fibrin sheet, sodium hyaluronate and carboxymethylcellulose combination (Seprafilm®), polyethylene oxide and carboxymethylcellulose gel (Oxiplex/AP®), steroids, dextran, icodextrin 4% (Adept®), hyaluronic acid products and polyethylene glycol hydrogel (SprayGel®) (Ahmad, et al., 2008, Metwally, et al., 2006). Most of these agents have not been studied specifically for endometriosis; only a few studies reported outcome data separately for women with endometriosis.

A Cochrane review that analysed the studies on effectiveness of barrier adhesion methods after pelvic surgery included two RCTs on the place of oxidised regenerated cellulose after laparoscopic surgery for endometriosis compared with endometriosis surgery only (Ahmad, et al., 2008). Although both studies included relatively small numbers of patients, both showed significant reduction in adhesion formation rate at second-look laparoscopy 3-6 months after the original surgery. Neither of these studies gave fertility or pain outcome.

Another small RCT compared adhesion scores with or without the use of polyethylene oxide and carboxymethylcellulose gel before and after surgery for stage I-III endometriosis (diZerega, et al., 2007). This study concluded that endometriosis surgery alone increased adhesion scores, and that polyethylene oxide and carboxymethylcellulose gel either prevented increase in adhesion score or reduced it (stage II endometriosis only). However, control and treatment groups had different preoperative adhesion scores, and a direct comparison of postoperative scores between the control and treatment groups was not given, thus leaving an uncertainty as to whether the treatment was effective.

A multicentre RCT on the effectiveness of 4% Icodextrin versus lactated Ringer's solution (LRS) after laparoscopic adhesiolysis included 241 patients with endometriosis (out of a total of 401 patients) (Brown, et al., 2007). Clinical success was defined for a patient as a reduction of at least three sites or 30% of the number of pre-existing sites with adhesions, between initial surgery and the follow-up laparoscopy. In women with endometriosis, the difference between clinical success rates in both groups was only significant for patients with more than six sites treated for endometriosis (39% vs. 15%, p=0.036). For patients with primary diagnosis of infertility and endometriosis the AFS scores were reduced in 54% of the patients in the Icodextrin group and in 24% in the LRS group. However, clinical success and AFS category did not differ significantly between the two groups. Another multicentre RCT compared the effectiveness of 4% Icodextrin with LRS (Trew, et al., 2011). It was possible to assess the outcome in 330 patients, 76 of whom had endometriosis. This trial did not demonstrate any benefit of Icodextrin in adhesion prevention.

Conclusion and considerations

The use of oxidised regenerated cellulose in the prevention of adhesion formation after laparoscopic surgery for endometriosis can be effective. Although based on a systematic review, the evidence level was downgraded to B, since the systematic review was based on a small number of studies, with limited numbers of patients per study. The effect of adhesion prevention on fertility or pain is uncertain.

The use of icodextrin in prevention of adhesion formation after laparoscopic surgery for endometriosis is probably not effective. In the study of Brown and colleagues, a moderate benefit of icodextrin was described, but this applied to only a specific small subgroup of patients (Brown, et al., 2007). A more recent trial did not show any benefit of icodextrin (Trew, et al., 2011). Furthermore, the studies were sponsored by the manufacturer. Hence, the GDG has decided not to recommend icodextrin for adhesion prevention.

Recommendations

Clinicians can use oxidised regenerated cellulose during operative laparoscopy for endometriosis, as it prevents adhesion formation (Ahmad, et al., 2008).	**B**

It is not reasonable for clinicians to use icodextrin after operative laparoscopy for endometriosis to prevent adhesion formation, as no benefit has been shown (Brown, et al., 2007, Trew, et al., 2011).	**B**

The GDG recommends that clinicians should be aware that other anti-adhesion agents (polytetrafluoroethylene surgical membrane, hyaluronic acid products) have been studied and proven effective for adhesion prevention in the context of pelvic surgery, although not specifically in women with endometriosis.	**GPP**

References

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2.5 Preoperative hormonal therapies for treatment of endometriosis-associated pain

Key question

ARE PREOPERATIVE HORMONAL THERAPIES EFFECTIVE FOR TREATMENT OF PAIN?

Clinical evidence

A Cochrane review considered both pre- and postoperative treatment in relation to the management of cyst, pain and infertility (Furness, et al., 2004).

With regard to preoperative treatment, the available literature was limited to two studies, both of which studied women of reproductive age (less than 35, and 18–50 years of age). The outcomes studied were AFS score in one study and AFS score, size of endometrioma, proportion who had complete excision of cysts and recurrence of cysts at 6 months in the second study. Both these studies were not truly just preoperative studies, as both study groups had undergone laparoscopy with endometrioma drainage prior to treatment, and the treatment was prior to a subsequent laparoscopy for further treatment of endometriomas. In both included studies, there was a mean difference in endometrioma size of 1–2cm (1.25cm and 1.8cm) between treated and non-treated groups, but the clinical benefit, if any, of this difference could not be evaluated. The studies differed in their findings with respect to AFS scores, with one reporting a reduction in scores in the treated group and the other showing no difference. One of the studies reported completeness of cyst removal; there was no difference (72% and 73%) between the treated and untreated groups, but there was a reduction in cyst recurrence in the treated group [10% (2/21) vs. 15% (4/27)]. The conclusion reached by Furness and colleagues was that there was no evidence of an additional benefit of preoperative treatment, but they did note that both trials were at high risk of bias and this may be reflected in their cautious conclusions (Furness, et al., 2004).

Conclusion and considerations

The role of preoperative hormonal treatment has been assessed in a Cochrane review that concluded that there was no evidence of a benefit of preoperative medical therapy on the outcome of surgery. This conclusion is shared by the GDG, but it also acknowledges that in clinical practice, surgeons prescribe preoperative medical treatment with GnRH analogues as this can facilitate surgery due to reduced inflammation, vascularisation of endometriosis lesions and adhesions. However, there are no controlled studies supporting this.

From a patient perspective, medical treatment should be offered before surgery to women with painful symptoms in the waiting period before the surgery can be performed, with the purpose of reducing pain before, not after, surgery.

Recommendation

Clinicians should not prescribe preoperative hormonal treatment to improve the outcome of surgery for pain in women with endometriosis (Furness, et al., 2004).	**A**

References

Furness S, Yap C, Farquhar C and Cheong YC. Pre and post-operative medical therapy for endometriosis surgery. *Cochrane Database Syst Rev* 2004:CD003678. [New search for studies, and content updated (no change to conclusions), published in Issue 1, 2011.]

2.6 Postoperative hormonal therapies for treatment of endometriosis-associated pain

Hormonal therapies after surgery for endometriosis can be prescribed in two situations: postoperative adjunctive hormonal therapy within 6 months after surgery can be prescribed with the aim of improving the outcome of surgery for pain; and secondary prevention, which is defined as prevention of the recurrence of pain symptoms or the recurrence of disease in the long-term (more than 6 months after surgery).

As the evidence from the literature is different for both outcomes, we have divided the section on postoperative hormonal therapies into short-term treatment (within 6 months of surgery) and treatment in the long-term (more than 6 months).

Recommendation

The GDG recommends that clinicians clearly distinguish adjunctive short-term (< 6 months) hormonal treatment after surgery from long-term (> 6 months) hormonal treatment; the latter is aimed at secondary prevention.	**GPP**

From the evidence on short-term postoperative hormonal treatment and hormonal treatment for secondary prevention summarized below, the following conclusion can be drawn: postoperative hormonal therapy may not improve the outcome of surgery but is an important adjunct to surgery to prolong the symptom-free interval and prevent recurrence of symptoms.

2.6.1 Short-term postoperative hormonal therapies

Key question

ARE POSTOPERATIVE HORMONAL THERAPIES EFFECTIVE FOR TREATMENT OF PAIN?

Clinical evidence

A Cochrane review considered 12 studies in the assessment of postoperative treatment in patients undergoing surgery for pain (Furness, et al., 2004). These comprised five studies with a postoperative placebo arm and seven with a postoperative no-treatment arm. The consensus from the included trials was that there was some reduction in pain at 12 months. However, due to heterogeneity in the assessment of pain, it was not possible to combine the studies in a meta-analysis. Pain recurrence within the first and second years was assessed in three trials and subjected to a meta-analysis. This demonstrated no benefit during either time period (1st year risk ratio (RR) (95% CI) 0.76 (0.52–1.1), 2nd year RR 0.70 (0.47–1.03)). Disease recurrence, assessed either by laparoscopy (one study) or clinical examination or scan (two studies), also demonstrated no benefit in postoperative hormonal treatment. One study documented increased patient satisfaction in both treatment arms, compared with placebo (Furness, et al., 2004).

In conclusion, despite the limitations regarding the quality of some of the included studies, there appears to be no strong evidence to support the use of either postoperative medical therapy in women undergoing surgery for endometriosis-associated pain.

Conclusion and considerations

The role of postoperative hormonal therapy has been assessed in a Cochrane review. The main strength of the review is that all included studies assessed women with laparoscopic diagnosis and staging of endometriosis. However, the major (acknowledged) weakness was that many of the included studies were of small size and were determined to be at risk of bias. The recommendations made here should be considered against this background.

Based on the current evidence (Cochrane review), the GDG concluded that there is no proven benefit of postoperative hormonal therapy (within 6 months after surgery) if this treatment is prescribed with the sole aim of improving the outcome of surgery. However, there is no proven harm, so postoperative hormonal therapy could be prescribed for other indications, such as contraception or secondary prevention.

Recommendation

Clinicians should not prescribe adjunctive hormonal treatment in women with endometriosis for endometriosis-associated pain after surgery, as it does not improve the outcome of surgery for pain (Furness, et al., 2004).	**A**

References

Furness S, Yap C, Farquhar C and Cheong YC. Pre and post-operative medical therapy for endometriosis surgery. *Cochrane database of systematic reviews* 2004:CD003678. [New search for studies, and content updated (no change to conclusions), published in Issue 1, 2011.].

2.6.2 Postoperative hormonal therapies aimed at secondary prevention of endometriosis

Introduction

Interventions for secondary prevention are defined as those aimed at stopping or slowing the progress of the disease after the diagnosis has been established. In the context of this guideline, secondary prevention was defined as prevention of the recurrence of pain symptoms (dysmenorrhea, dyspareunia, non-menstrual pelvic pain) or the recurrence of disease (recurrence of endometriosis lesions documented by ultrasound for ovarian endometrioma or by laparoscopy for all endometriosis lesions) in the long-term (more than 6 months after surgery). This is distinct from postoperative adjunctive hormonal therapy within 6 months after surgery, which was discussed in the previous section.

Key question

IS THERE A ROLE FOR SECONDARY PREVENTION OF DISEASE AND PAINFUL SYMPTOMS IN WOMEN TREATED FOR ENDOMETRIOSIS?

Clinical evidence

In women with moderate to severe dysmenorrhea receiving operative laparoscopy for endometriosis, recurrence of dysmenorrhea was lower in the group with a levonorgestrel-releasing intrauterine system (LNG-IUS) postoperatively than in the control group receiving expectant management (Abou-Setta, et al., 2006).

In women operated upon for endometriosis, postoperative pain recurrence is not different in women receiving GnRH agonists, danazol or medroxyprogesterone acetate (MPA) or pentoxifylline, when compared to placebo or no treatment (Furness, et al., 2004, Lv, et al., 2009).

In women operated upon for an endometrioma of 3 cm or more, when compared to drainage and electrocoagulation, ovarian cystectomy is associated with reduced recurrence of dysmenorrhea, dyspareunia and non-menstrual pelvic pain (Hart, et al., 2008).

In women with ovarian endometrioma surgically treated by cystectomy and not immediately seeking conception after surgery, the recurrence rate of ultrasound-diagnosed endometrioma is lower in women regularly using oral contraceptives (Vercellini, et al., 2010).

In women with surgically treated endometriosis, including ovarian cystectomy if an endometrioma was present, postoperative oral contraceptive for 6 to 24 months can be effective for the prevention of endometriosis-associated dysmenorrhea, but not for non-menstrual pelvic pain or dyspareunia. However, this effect is not sufficiently substantiated if postoperative oral contraceptives are used for only 6 months either cyclically (evidence not convincing) or continuously (evidence controversial) (Seracchioli, et al., 2009). Since both continuous and cyclic OCP administration regimens seem to have comparable effects, the choice of regimen can be made according to patient preferences. The protective effect seems to be related to the duration of treatment (Seracchioli, et al., 2009).

Conclusion and considerations

Secondary prevention of the recurrence of endometriosis and endometriosis-associated pain is clinically important in view of the recurrence rates reported after endometriosis surgery; there is sufficient evidence to make recommendations with respect to surgical technique and postoperative medical management.

In a specific population of women with an endometrioma of 3 cm or more, ovarian cystectomy, instead of drainage and electrocoagulation, can be used for the secondary prevention of dysmenorrhea, dyspareunia and non-menstrual pelvic pain. If they do not wish to conceive, women can use regular oral contraceptives for secondary prevention of endometrioma.

In the general population of women operated upon for endometriosis, including ovarian cystectomy for endometrioma, clinicians should advise postoperative use of a levonorgestrel-releasing intrauterine system, or combined oral contraceptives for at least 18–24 months, as one of the options for the secondary prevention of endometriosis-associated dysmenorrhea; this does not have proven benefit for the secondary prevention of non-menstrual pelvic pain or dyspareunia.

In conclusion, for patients not desiring to become pregnant after endometriosis surgery, secondary prevention of dysmenorrhea can be achieved by either postoperative use of a levonorgestrel-releasing intrauterine system, or combined oral contraceptives for at least 18–24 months.

Recommendations

The GDG states that there is a role for prevention of recurrence of disease and painful symptoms in women surgically treated for endometriosis. The choice of intervention depends on patient preference, cost, availability and side effects. For many interventions that might be considered here, there are limited data.	**GPP**

In women operated on for an endometrioma (≥ 3 cm), clinicians should perform ovarian cystectomy, instead of drainage and electrocoagulation, for the secondary prevention of endometriosis-associated dysmenorrhea, dyspareunia and non-menstrual pelvic pain (Hart, et al., 2008).	**A**

After cystectomy for ovarian endometrioma in women not immediately seeking conception, clinicians are recommended to prescribe hormonal contraceptives for the secondary prevention of endometrioma (Vercellini, et al., 2010).	**A**

In women operated on for endometriosis, clinicians are recommended to prescribe postoperative use of a levonorgestrel-releasing intrauterine system (LNG-IUS) or a combined hormonal contraceptive for at least 18–24 months, as one of the options for the secondary prevention of endometriosis-associated dysmenorrhea, but not for non-menstrual pelvic pain or dyspareunia (Abou-Setta, et al., 2006, Seracchioli, et al., 2009).	**A**

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2.7 Treatment of pain associated with extragenital endometriosis

Clinical evidence

Endometriosis has been found in almost every tissue type in the body. Symptoms depend on the site of the disease. Cyclicity of symptoms is usually present, at least in early stages, and may be the only clue that leads to the diagnosis of endometriosis. Diagnosis is usually made by histological confirmation, which is important to exclude other pathology, particularly malignancy. Additional imaging and endoscopic investigations specific to the location may also be used.

Treatment will also depend on the site. If complete excision is possible, this is the treatment of choice; when this is not possible, long-term medical treatment is necessary (Veeraswamy, et al., 2010). The principles of medical treatment for pelvic endometriosis will similarly apply for extragenital endometriosis (Bergqvist, 1992, Joseph and Sahn, 1996, Jubanyik and Comite, 1997, Nisolle, et al., 2007). Appendicular endometriosis is usually treated by appendectomy. Surgical treatment of bladder endometriosis usually takes the form of excision of the lesion and primary closure of the bladder wall. Ureteral lesions may be excised after stenting the ureter. In the presence of intrinsic lesions or significant obstruction, segmental excision with end-to-end anastomosis or reimplantation may be necessary. Abdominal wall and perineal endometriosis is usually treated by

complete excision of the nodule (Liang, et al., 1996, Marinis, et al., 2006, Nezhat, et al., 2011, Nissotakis, et al., 2010, Song, et al., 2011). For thoracic endometriosis, medical, surgical or combination treatment options are used. Immediate treatment of pneumothorax or haemothorax is by insertion of a chest tube drain. Hormonal treatment is known to be effective in a significant proportion of patients. In cases of recurrent pneumothorax or haemothorax, chemical pleurodesis, pleural abrasion or pleurectomy may be helpful. Persistent haemoptysis due to parenchymal lesions may be treated by lobectomy, segmentectomy or (rarely) tracheobronchoscopic laser ablation (Nisolle, et al., 2007).

Conclusion and considerations

There is limited evidence on endometriosis of tissues and body parts outside the genital tract. Pain is the most common presenting symptom, although a wide range of symptoms can manifest. Most of the rare cases of extragenital manifestations of endometriosis are published only as case reports, or not documented at all. The same applies for the treatment, either medical or surgical, of pain related to extragenital endometriosis.

Recommendations

Clinicians may consider surgical removal of symptomatic extragenital endometriosis, when possible, to relieve symptoms (Liang, et al., 1996, Marinis, et al., 2006, Nezhat, et al., 2011, Nissotakis, et al., 2010, Song, et al., 2011).	**D**

When surgical treatment is difficult or impossible, clinicians may consider medical treatment of extragenital endometriosis to relieve symptoms (Bergqvist, 1992, Joseph and Sahn, 1996, Jubanyik and Comite, 1997).	**D**

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2.8 Non-medical management strategies for treatment of endometriosis-associated pain

Introduction

Despite the growing popularity of complementary therapies, there is general lack of well-designed research to evaluate their effectiveness. As many as 30–50% of adults in western countries use some form of complementary medicine to prevent or treat health-related problems (Astin, et al., 1998). Complementary therapies are more commonly used by women of reproductive age, with almost half (49%) reporting use (Eisenberg, et al., 1998).

Several types of complementary and alternative therapies are used by patients to reduce pelvic pain, dysmenorrhea and improve quality of life. There is some evidence that these methods reduce pain.

Key question

WHAT OTHER PAIN MANAGEMENT STRATEGIES ARE EFFECTIVE FOR SYMPTOMATIC RELIEF OF PAIN ASSOCIATED WITH ENDOMETRIOSIS?

Clinical evidence

Whilst high-frequency transcutaneous electrical nerve stimulation (TENS) was shown to be effective for primary dysmenorrhea (dysmenorrhea in the absence of pelvic pathology), there are no data to suggest that it is helpful in the control of pain associated with endometriosis (Proctor, et al., 2002). Similarly, there are no data to indicate that dietary supplements are useful in controlling pain symptoms of endometriosis, although one low-quality RCT suggested that a combination diet had similar efficacy to GnRHa and the combined oral contraceptive pill in reducing non-menstrual pain (but not dysmenorrhea) (Sesti, et al., 2007).

A Cochrane review found no studies comparing traditional Chinese medicine (TCM) to placebo for the treatment of endometriosis-associated pain (Flower, et al., 2009). Two RCTs with poor methodological quality suggested that TCM may have similar efficacy to gestrinone or danazol in controlling pain after surgical treatment of endometriosis. Another Cochrane review looked at acupuncture in the treatment of pain in endometriosis. Only one small RCT was included, and this demonstrated that acupuncture may be of similar efficacy to TCM in the treatment of severe dysmenorrhea, but not in mild to moderate dysmenorrhea (Zhu, et al., 2011). Hence, this review concluded that evidence to support use of acupuncture for pain in endometriosis was limited.

To our knowledge, there is no literature on the use of neuromodulators, anesthesia, behavioural therapy, expert patient programmes, recreational drugs, reflexology, homeopathy, psychological therapy or exercise, for the management of pain in endometriosis.

Conclusion and considerations

Limited evidence exists on the usefulness of alternative and complementary medicine to reduce endometriosis-associated pain, especially since we have limited our searches to publications written in English. However, the literature searches were not limited with respect to the interventions. The following alternative and complementary therapies were included: neuromodulators, nerve blocks,

transcutaneous electrical nerve stimulation, acupuncture, behavioural therapy, nutritional supplements (including dietary supplements, vitamins, and minerals), expert patient programmes, recreational drugs, reflexology, homeopathy, psychological therapy, TCM, herbal medicine, sports and exercise. Furthermore, the inherent difference between the holistic Chinese approach and the scientific European approach makes it very difficult to integrate alternative and complementary therapies in evidence-based medicine.

From the limited included evidence, we conclude that the effectiveness of high-frequency TENS, dietary supplements, acupuncture and traditional Chinese medicine are not well established for pain management in women with endometriosis. However, the GDG acknowledges that alternative and complementary therapies are often used, in addition to traditional Western therapies, by women with endometriosis, in an attempt to increase their quality of life and that these women may benefit from it.

Taking these considerations into account, the GDG reached the following good practice point.

Recommendation

The GDG does not recommend the use of nutritional supplements, complementary or alternative medicine in the treatment of endometriosis-associated pain, because the potential benefits and/or harms are unclear. However, the GDG acknowledges that some women who seek complementary and alternative medicine may feel benefit from this.	**GPP**

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3. TREATMENT OF ENDOMETRIOSIS-ASSOCIATED INFERTILITY

Introduction

Women with endometriosis are confronted with one or both of two major problems: endometriosis-associated pain, infertility, or both. For the purpose of clarity, the GDG decided to separately discuss the evidence on pain as the outcome (chapter 2); infertility as an outcome is addressed in this chapter.

For the literature searches, the outcomes included were live birth rate, pregnancy, multiple pregnancy rate, miscarriage rate, ectopic pregnancy, teratogeneity and side effects of treatment. It should be noted that although live birth rate is the most relevant outcome, most studies only report on (biochemical or clinical) pregnancy rates. An increase in pregnancy rate could be an indication of live birth rate, but does not necessarily translate to an increase in this outcome.

This chapter deals with treatments (medical, surgical, medical adjunct to surgery and alternative treatments) for improving fertility in women with endometriosis, that is, treatments that improve the spontaneous pregnancy rate. Medically assisted reproduction and adjunctive treatments are discussed in chapter 4.

3.1 Hormonal therapies for treatment of endometriosis-associated infertility

Key question

ARE HORMONAL THERAPIES EFFECTIVE FOR INFERTILITY ASSOCIATED WITH ENDOMETRIOSIS?

Clinical evidence

The question as to whether hormonal therapy has a role in the treatment of endometriosis-associated infertility has been thoroughly evaluated in a systematic Cochrane review (Hughes, et al., 2007). The review does not evaluate individual hormonal treatments used in the treatment of pain associated with endometriosis but considers as a group all therapies that result in ovarian suppression. Thus, strictly speaking, the assessment is confined to the role of ovarian suppression as a therapeutic modality to improve fertility.

The Cochrane review included 18 studies, most of which reported conception, pregnancy or clinical pregnancy as surrogate markers for the now-accepted relevant end point: live birth rate. Thus, there are limited data on live birth rates, and the data that does exist are restricted to comparisons between different therapies. In 191 subjects, live births were reported for the comparison between other agents and danazol [OR (95% CI) 1.15 (0.57-2.32)]. In another comparison, gonadotrophin-releasing hormone analogues were compared to the combined oral contraceptive pill [n=86, OR 0.69 (0.26-1.85)]. Thus, in neither comparison was there a significant difference in live birth rates between agents. These outcomes are also reflected in comparisons where pregnancy is the clinical endpoint.

These comparisons however do not directly assess whether ovarian suppression *per se* is an effective intervention; they merely reflect the fact that there is no difference between different drugs in their effects on live birth rates (Hughes, et al., 2007).

Hughes and colleagues reported two comparisons of active drug against placebo or no treatment. The first included all drugs, and the second included all drugs with the exception of danazol. In both comparisons there was no significant difference in pregnancy rates [OR 1.02 (0.69-1.52) and OR 1.10 (0.70-1.73), respectively]. Thus, it is clear that as sole treatment for infertility, recognized medical therapies for endometriosis that suppress ovulation are an ineffective and should not be used.

Conclusion and considerations

Suppression of ovarian function (by means of danazol, GnRH analogues, OCP) to improve fertility in minimal to mild endometriosis is not effective and should not be offered for this indication alone. The published evidence does not report on more severe disease.

The best-quality evidence is a Cochrane review of high quality but limited by the underlying quality of the included trials, most of which (14/18) were published before 2000 and thus were conducted to the standards that were considered appropriate at that time. Nevertheless, they remain the best-quality data that exists to answer this question. The major deficiency in the reported data is paucity of data relating to live births, and thus the majority of conclusions is based on surrogate markers: conception, pregnancy or clinical pregnancy. Similarly, there is a significant lack of reported data on adverse pregnancy outcomes, such as miscarriage and ectopic pregnancy.

Recommendation

In infertile women with endometriosis, clinicians should not prescribe hormonal treatment for suppression of ovarian function to improve fertility (Hughes, et al., 2007).	**A**

References

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3.2 Surgery for treatment of endometriosis-associated infertility

Key question

IS SURGERY EFFECTIVE FOR INFERTILITY ASSOCIATED WITH ENDOMETRIOSIS?

Clinical evidence

In women with minimal to mild endometriosis (rASRM classification), operative laparoscopy including adhesiolysis is effective in increasing the pregnancy/live birth rate, compared to diagnostic laparoscopy (Jacobson, et al., 2010). Although treatment of minimal to mild lesions is associated with a (marginally) significant effect, no more than 50% of these women had this type of endometriosis. This translates into a number needed to treat of 25. These data are supported by the data from

another well-designed RCT (Nowroozi, et al., 1987), which was not included in the Jacobson Cochrane review because randomization was based on social security number.

In women with minimal to mild endometriosis wishing to conceive, the comparative effectiveness of different surgical techniques is unclear. In women with endometriosis as their major cause of infertility, postoperative cumulative pregnancy rate after 36 months was promising after treatment with CO_2 laser vaporization with or without resection of endometriosis (87%); this compares with monopolar electrocoagulation (71%), diagnostic laparoscopy (65%), and diagnostic laparoscopy followed by 3 months treatment with danazol 800mg/day (63%) (Chang, et al., 1997) (pseudo RCT considered as prospective controlled cohort study). There is a need for further data before firm conclusions are drawn.

In infertile women with laparoscopy-confirmed and Acosta-staged endometriosis and no other infertility factors (based on full fertility investigation), the spontaneous pregnancy rate after expectant management is just 30% (moderate endometriosis) or 0% (severe endometriosis) (Olive, et al., 1985). Among infertile women with surgically confirmed severe endometriosis (according to Acosta or AFS classification), the crude spontaneous pregnancy rate after laparoscopic surgery was reported to be 48% in a review (Acosta, et al., 1973, Candiani, et al., 1991). According to two prospective cohort studies in infertile women with moderate and severe endometriosis (AFS classification) receiving laparoscopic surgery with removal of lesions and adhesiolysis, the crude spontaneous pregnancy rate was 57–69% (moderate endometriosis) and 52–68% (severe endometriosis) (Nezhat, et al., 1989, Vercellini, et al., 2006a). The cumulative spontaneous pregnancy rate within 3 years (life table analysis) after surgery has been reported to vary between 46 and 77% for moderate endometriosis and between 44 and 74% for severe endometriosis (Nezhat, et al., 1989, Vercellini, et al., 2006a). Overall, these data suggest that laparoscopic surgery is effective for the treatment of infertility associated with moderate to severe endometriosis.

In patients with ovarian endometrioma receiving surgery for infertility or pain, excision of endometrioma capsule increases the postoperative spontaneous pregnancy rate, compared to drainage and electrocoagulation of the endometrioma wall (Hart, et al., 2008). Both techniques carry potential risks for the ovarian reserve, either by removal of normal ovarian tissue during excision or by thermal damage to the ovarian cortex during ablation. In women with infertility and severe pelvic pain who are resistant to medical treatment or severe bowel stenosis, radical excision of endometriosis combined with bowel segmental resection and anastomosis was associated with a higher postoperative pregnancy rate (17/48 or 35%; 12/30 for spontaneous pregnancies only) than radical excision of endometriosis without bowel resection in patients with surgical evidence of bowel endometriosis (8/39 or 21%; 7/23 for spontaneous pregnancies only). However, this difference was not significant (p=0.57 for all pregnancies; p=0.17 for spontaneous pregnancies only) (Stepniewska, et al., 2009, Stepniewska, et al., 2010; both retrospective controlled cohort studies).

In women with infertility and rectovaginal endometriosis, a prospective controlled study demonstrated no advantage of surgery by laparotomy when compared to expectant management with respect to reproductive outcome (Vercellini, et al., 2006b). However, this paper was not designed to make specific recommendations for infertility surgery in women with rectovaginal endometriosis for the following reasons: treatment allocation was based on shared decision making creating bias (more extensive endometriosis cases likely to have chosen surgery or to have been

counselled to surgery); pain was an important covariable in patient decision/counselling towards surgery or expectant management (no subanalysis was performed for women without pain); lack of comparison regarding pain quantity (VAS scores) or nodule size between both groups (could have been worse in surgery group); reproductive outcome was biased because it was affected not only by the treatment arm but also by use of other fertility treatment in both groups, without subanalysis for spontaneous conception; and, laparotomy was used, whereas most centres nowadays use laparoscopic approaches.

As mentioned in chapter 2 (treatment of pain), surgery for deep endometriosis is associated with significant complication rates (total postoperative complication rate 13.9%) (Kondo, et al., 2011).

Conclusion and considerations

In women with minimal to mild endometriosis, the evidence summarised in a Cochrane review, shows that operative laparoscopy is more effective than diagnostic laparoscopy in improving ongoing pregnancy rates.

The comparative effectiveness of different surgical techniques is less well studied.

In women with moderate to severe endometriosis, there are no controlled studies comparing reproductive outcome after surgery and after expectant management. The recommendations are based on evidence from two high-quality prospective cohort studies showing crude spontaneous pregnancy rates of 57–69% (moderate endometriosis) and 52–68% (severe endometriosis) after laparoscopic surgery, and on evidence from one high-quality prospective cohort study showing much lower crude pregnancy rates after expectant management: 33% (moderate endometriosis) and 0% (severe endometriosis).

Overall, the evidence for performing surgery with the sole intent of increasing live birth rate is limited. Especially for young women, intrauterine insemination with controlled ovarian stimulation could be a good alternative to surgery. Other treatment options with medically assisted reproduction are discussed in chapter 4.

Recommendations

In infertile women with AFS/ASRM stage I/II endometriosis, clinicians should perform operative laparoscopy (excision or ablation of the endometriosis lesions) including adhesiolysis, rather than performing diagnostic laparoscopy only, to increase ongoing pregnancy rates (Jacobson, et al., 2010, Nowroozi, et al., 1987).	**A**

In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may consider CO2 laser vaporization of endometriosis, instead of monopolar electrocoagulation, since laser vaporisation is associated with higher cumulative spontaneous pregnancy rates (Chang, et al., 1997).	**C**

In infertile women with ovarian endometrioma undergoing surgery, clinicians should perform excision of the endometrioma capsule, instead of drainage and electrocoagulation of the endometrioma wall, to increase spontaneous pregnancy rates (Hart, et al., 2008).	**A**

The GDG recommends that clinicians counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery.	**GPP**

In infertile women with AFS/ASRM stage III/IV endometriosis, clinicians can consider operative laparoscopy, instead of expectant management, to increase spontaneous pregnancy rates (Nezhat, et al., 1989, Vercellini, et al., 2006a).	**B**

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3.3 Hormonal therapies adjunct to surgery for treatment of endometriosis-associated infertility

Key question

ARE HORMONAL THERAPIES EFFECTIVE AS AN ADJUNCT TO SURGICAL THERAPY FOR TREATMENT OF INFERTILITY?

Clinical evidence

The roles of pre- and postoperative hormonal therapy in the management of cyst, pain and infertility has been assessed in a Cochrane review by Furness and colleagues (Furness, et al., 2004). Two studies on preoperative hormonal therapy were included in the review, although these studies did not evaluate any outcomes regarding infertility.

With regard to postoperative hormonal therapy in the infertile population, eight studies comprising 420 patients were included in a meta-analysis. No increase in pregnancy rates was demonstrated in those treated postoperatively (risk ratio (RR) (95% CI) 0.84 (0.59–1.18)). This finding is not surprising given the known lack of effect of hormonal therapy alone on endometriosis-associated infertility (see section 3.1).

Conclusion and considerations

For postoperative medical treatment, the evidence (mostly from low-quality studies) is summarised in a Cochrane review. In the same review, no studies were found on the effect of preoperative hormonal treatment on infertility after surgery. As hormonal treatments were found not to be effective for improving infertility without surgery and because they have severe side effects, pre- or postoperative hormonal treatments are not recommended for improving fertility. In conclusion, despite the limitations regarding the quality of the included studies, there appears to be no evidence to support the use of postoperative hormonal therapy in women undergoing surgery for endometriosis-associated infertility.

Recommendations

In infertile women with endometriosis, the GDG recommends clinicians not to prescribe adjunctive hormonal treatment before surgery to improve spontaneous pregnancy rates, as suitable evidence is lacking.	**GPP**

In infertile women with endometriosis, clinicians should not prescribe adjunctive hormonal treatment after surgery to improve spontaneous pregnancy rates (Furness, et al., 2004).	**A**

References

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3.4 Non-medical management strategies for treatment of endometriosis-associated infertility

Key question

WHAT OTHER MANAGEMENT STRATEGIES ARE EFFECTIVE FOR INFERTILITY ASSOCIATED WITH ENDOMETRIOSIS?

Clinical evidence

Complementary and alternative medicine is increasingly being used in pursuit of health and well being (Harris and Rees, 2000). Examples of complementary and alternative medicine are acupuncture, meditation, massage and herbal medicines. Most studies on the efficacy of complementary and alternative medicine are of poor quality, as well being within the field of endometriosis (Chan, 2008). Furthermore, reports on a possible role for recreational drugs, physical exercise, behavioural and psychological treatment as management strategies for endometriosis-associated infertility are also lacking.

Therefore, randomized controlled trials of good quality are needed to investigate a possible role for complementary and alternative medicine in the treatment of endometriosis-related infertility. Based on a literature search, the following interventions can be considered for future study: antioxidant therapy (Agarwal, et al., 2005), Chinese herbal medicine (Burks-Wicks, et al., 2005, Xu, et al., 2003, Zhou and Qu, 2009), acupuncture (Gerhard and Postneek, 1992) and manual physical therapy (Wurn, et al., 2008).

Conclusion and considerations

An extensive literature search was conducted on alternative and complementary therapies as treatment for endometriosis-associated infertility. The search terms included: nerve blocks, neuromodulators, transcutaneous electrical nerve stimulation, acupuncture, behavioural therapy, nutritional supplements (including dietary supplements, vitamins, minerals,..), expert patient programmes, recreational drugs, reflexology, homeopathy, psychological therapy, Traditional Chinese Medicine, herbal medicine, sports and exercise. We found no evidence of a beneficial effect of different types of nutritional supplements, complementary and alternative treatments for improving infertility in women with endometriosis. However, women with endometriosis often use these therapies in addition to traditional medical and/or surgical treatment, in an attempt to improve quality of life and to cope with the disease and the traditional treatments.

Recommendation

The GDG does not recommend the use of nutritional supplements, complementary or alternative medicine in the treatment of endometriosis-associated infertility, because the potential benefits and/or harms are unclear. However the GDG acknowledges that some women who seek complementary and alternative medicine may feel benefit from this.	**GPP**

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4. MEDICALLY ASSISTED REPRODUCTION

Introduction

In this chapter, we use the WHO ICMART definitions for the terms medically assisted reproduction and assisted reproductive technology (Zegers-Hochschild, et al., 2009).

Medically assisted reproduction (MAR) is defined as “Reproduction brought about through ovulation induction, controlled ovarian stimulation, ovulation triggering, ART [assisted reproductive technology] procedures, and intrauterine, intracervical, and intravaginal insemination with semen of husband/partner or donor”. Therefore, MAR includes intrauterine insemination and assisted reproductive technology.

Assisted reproductive technology (ART) is defined as “All treatments or procedures that include the in vitro handling of both human oocytes and sperm or of embryos for the purpose of establishing a pregnancy. This includes, but is not limited to, in vitro fertilization and embryo transfer, gamete intrafallopian transfer, zygote intrafallopian transfer, tubal embryo transfer, gamete and embryo cryopreservation, oocyte and embryo donation, and gestational surrogacy. ART does not include assisted insemination (artificial insemination) using sperm from either a woman's partner or a sperm donor”.

Intrauterine insemination (IUI) has been used in the treatment of couples with infertility associated with endometriosis, especially of minimal or mild stage. Its efficacy and the comparative results in unexplained infertility couples are debated.

An important proportion of women with moderate or severe endometriosis will need ART when they decide to become pregnant. The influence, if any, of the disease on the final outcome and the implications on the details of the treatment are important topics.

In the second part of this chapter, we discuss whether medical or surgical treatment prior to the initiation of ART in women with endometriosis increases the chance of pregnancy and the live birth rate.

References

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4.1 Medically assisted reproduction in women with endometriosis

Key question

IS MEDICALLY ASSISTED REPRODUCTION EFFECTIVE FOR INFERTILITY ASSOCIATED WITH ENDOMETRIOSIS?

4.1.1 Intrauterine insemination in women with endometriosis

Clinical evidence

The efficacy of controlled ovarian stimulation (COS) with gonadotrophins and IUI was assessed in a RCT including 103 couples with minimal to mild endometriosis, 53 under treatment and 50 in the expectant management group. The live birth rate was 5.6-times higher in the treated couples than in the control group (95% CI 1.18-17.4) (Tummon, et al., 1997). In an initially randomized and subsequently longitudinal study, Nulsen and co-workers compared gonadotrophins + IUI with urine LH-timed IUI alone. In 57 couples with minimal or mild endometriosis the pregnancy rate (PR) was 5.1-times higher than with IUI alone (95% CI 1.1–22.5) (Nulsen, et al., 1993).

Do infertile couples with minimal or mild endometriosis behave as couples with unexplained infertility? In a cohort study, Omland and colleagues compared one cycle of clomiphene citrate + HMG/FSH against HMG/FSH with artificial insemination by husband (IUI with or without intraperitoneal insemination) in couples with unexplained infertility (119 couples) or with minimal or mild endometriosis (49 couples, diagnostic laparoscopy only). PRs were 33.6 and 16.3%, respectively ($p<0.05$) (Omland, et al., 1998). In a case control study PRs following COS + homologous insemination were as high in women with minimal or mild endometriosis within 6 months of surgical treatment as in women with unexplained infertility (PR/cycle 20 vs. 20.5%) (Werbrouck, et al., 2006).

Kim and co-workers, in a RCT, compared the use of long protocol (LP) and ultralong protocol (ULP) of GnRH agonist in the COS prior to IUI in 80 women (all stages of endometriosis). No difference in the clinical PR was found between protocols in women with minimal or mild endometriosis. In women with stage III or IV endometriosis, the clinical PR per cycle was significantly higher in the ULP group (50.0% (10/20)) compared with the LP group (19.0% (4/21)) (Kim, et al., 1996).

The significance of minimal endometriosis in the results of artificial insemination with donor sperm is unclear. Classical papers suggest a negative influence, but in a double-blinded cohort study (24 women with minimal endometriosis , 51 without endometriosis) the pregnancy rates were, respectively, 8.6 and 13.3% per cycle of artificial insemination with donor sperm and 37.5 vs. 51.0% per woman. However, the number of included patients was lower than the calculated sample size (Matorras, et al., 2010).

Conclusion and considerations

In women with minimal to mild endometriosis, IUI with controlled ovarian stimulation may be effective in increasing live birth rate, compared with expectant management. Furthermore, IUI with controlled ovarian stimulation may be more effective in increasing pregnancy rate than IUI alone, and may be as effective in women with minimal or mild endometriosis within 6 months of surgical treatment as in women with unexplained infertility.

Recommendations

In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may perform intrauterine insemination with controlled ovarian stimulation, instead of expectant management, as it increases live birth rates (Tummon, et al., 1997).	**C**

In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may perform intrauterine insemination with controlled ovarian stimulation, instead of intrauterine insemination alone, as it increases pregnancy rates (Nulsen, et al., 1993).	**C**

In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may consider performing intrauterine insemination with controlled ovarian stimulation within 6 months after surgical treatment, since pregnancy rates are similar to those achieved in unexplained infertility (Werbrouck, et al., 2006).	**C**

The GDG recommends the use of assisted reproductive technologies for infertility associated with endometriosis, especially if tubal function is compromised or if there is male factor infertility, and/or other treatments have failed.	**GPP**

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4.1.2 Assisted reproductive technology in women with endometriosis

Clinical evidence

Implications of endometriosis in the success rate after IVF/ICSI:

In a small cohort study evaluating the results of natural cycle IVF (no ovarian stimulation) the clinical PRs per initiated cycle, per succesful oocyte retrieval and per embryo transfer were similar in endometriosis and tubal factor couples and significantly higher than those for couples with unexplained infertility (Omland, et al., 2001).

A systematic review indicated that pregnancy rates are lower in women with endometriosis undergoing IVF treatment (with ovarian stimulation) than in women with tubal infertility (Barnhart, et al., 2002). The review included 22 studies, consisting of 2,377 cycles in women with endometriosis and 4,383 in women without the disease. After adjusting for confounding variables, the PRs for women with stage I/II were not significantly different from those for women with tubal factor (OR (95% CI) 0.79 (0.60–1.03)). However, the PRs for women with stage III/IV were significantly lower than for tubal factor (OR 0.46 (0.28–0.74)) (Barnhart, et al., 2002).

This is the only systematic review in this area, and some caution must be applied in the interpretation of the results, since the search period was Jan 1980 to May 1999 (when different drugs were used and the technical conditions were significantly different), no correction was made for medical or surgical treatment before initiation of IVF and pregnancy was defined as detectable HCG. In addition, the GDG noted that endometriosis does not adversely affect pregnancy rates in some large databases [e.g. the Society for Assisted Reproductive Technology (SART) and the Human Fertilisation and Embryology Authority (HFEA)].

An RCT including 246 women with minimal to mild endometriosis and endometrioma showed that the implantation rate and clinical PR after COS with GnRH antagonist were not inferior to those for a GnRH agonist protocol (Pabuccu, et al., 2007).

Two studies of possible implications of deep endometriosis on the efficacy of IVF/ICSI showed conflicting results.

Risks of ovarian stimulation for IVF/ICSI in women with endometriosis:

Four studies evaluated the recurrence rate of disease in women with endometriosis submitted to MAR treatments. Although using different criteria of recurrence and different follow-up periods, all reached the conclusion that gonadotrophin ovarian stimulation for IVF/ICSI was not associated with increased risk of recurrence of the disease (Benaglia, et al., 2011, Benaglia, et al., 2010, Coccia, et al., 2010, D'Hooghe, et al., 2006).

In a series of 214 women with endometriomas undergoing oocyte retrieval for IVF/ICSI under antibiotic prophylaxis, no pelvic abcess was recorded (Benaglia, et al., 2008).

Conclusion and considerations

There is inconsistency regarding the implications of endometriosis on success rate after IVF/ICSI. PRs after IVF/ICSI were reported to be lower in patients with stage III and IV endometriosis, compared with those with tubal factor. GnRH antagonist protocol may be not inferior to GnRH agonist protocol

in women with minimal to mild endometriosis and endometrioma. No evidence was found relating deep endometriosis with the efficacy of IVF/ICSI.

There is no evidence of increased cumulative endometriosis recurrence rates after ovarian stimulation for IVF/ICSI in women with endometriosis.

The use of antibiotic prophylaxis at the time of oocyte retrieval in women with endometriomas seems reasonable.

Recommendations

The GDG recommends the use of assisted reproductive technologies for infertility associated with endometriosis, especially if tubal function is compromised or if there is male factor infertility, and/or other treatments have failed.	**GPP**

In infertile women with endometriosis, clinicians may offer treatment with assisted reproductive technologies after surgery, since cumulative endometriosis recurrence rates are not increased after controlled ovarian stimulation for IVF/ICSI (Benaglia, et al., 2011, Benaglia, et al., 2010, Coccia, et al., 2010, D'Hooghe, et al., 2006).	**C**

In women with endometrioma, clinicians may use antibiotic prophylaxis at the time of oocyte retrieval, although the risk of ovarian abscess following follicle aspiration is low (Benaglia, et al., 2008).	**D**

References

Barnhart K, Dunsmoor-Su R and Coutifaris C. Effect of endometriosis on in vitro fertilization. *Fertil Steril* 2002; **77**:1148–1155.

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Coccia ME, Rizzello F and Gianfranco S. Does controlled ovarian hyperstimulation in women with a history of endometriosis influence recurrence rate? *J Womens Health* 2010; **19**:2063–2069.

D'Hooghe TM, Denys B, Spiessens C, Meuleman C and Debrock S. Is the endometriosis recurrence rate increased after ovarian hyperstimulation? *Fertil Steril* 2006; **86**:283–290.

Omland AK, Fedorcsák P, Storeng R, Dale PO, Abyholm T and Tanbo T. Natural cycle IVF in unexplained, endometriosis-associated and tubal factor infertility. *Hum Reprod* 2001; **16**:2587–2592.

Pabuccu R, Onalan G and Kaya C. GnRH agonist and antagonist protocols for stage I-II endometriosis and endometrioma in in vitro fertilization/intracytoplasmic sperm injection cycles. *Fertil Steril* 2007; **88**:832–839.

4.2 Medical therapies as an adjunct to treatment with ART in women with endometriosis

Key question

ARE MEDICAL THERAPIES EFFECTIVE AS AN ADJUNCT TO TREATMENT WITH ART FOR ENDOMETRIOSIS-ASSOCIATED INFERTILITY?

Clinical evidence

The role of medically assisted reproduction (MAR) in the treatment of endometriosis-associated infertility is addressed in the previous section and its role is well established. It has been proposed, following numerous non-randomized studies, that medical treatment of endometriosis prior to MAR may result in improved outcome, either because of improving oocyte quality or endometrial receptivity. The specific question of GnRHa treatment has been addressed in a Cochrane review (Sallam, et al., 2006); the use of other medical therapies has not been fully investigated. In this review, three individual studies comprising of a total of 228 patients were considered. The authors note that the quality of the studies was poor and thus are potentially at risk of methodological bias. Consequently, they state in their conclusions that there remains a need for high quality randomized studies using up-to-date assisted conception techniques. Nevertheless, they conclude that clinically downregulation for 3–6 months with a GnRHa in women with endometriosis increases the odds of clinical pregnancy by more than 4-fold. The odds of live birth are also improved, but the magnitude of this is unreliable due to the poor quality of the single study that included this as an outcome. This review and its included studies fail to address the potential adverse effects of the intervention and specifically do not consider miscarriage rates, multiple pregnancy rates or ectopic pregnancy rates.

Conclusion and considerations

The question as to whether medical treatment of endometriosis prior to ART is effective in improving fertility treatment outcomes was assessed in a high-quality Cochrane review. Regarding the quality of the included evidence, it should be noted that the number of studies, the number of included patients and the quality of the included studies were low. However, the results of these studies concur: a beneficial effect of GnRH agonists on the outcome of ART in women with endometriosis. Hence, the following B-level recommendation was drafted.

Recommendation

Clinicians can prescribe GnRH agonists for a period of 3 to 6 months prior to treatment with assisted reproductive technologies to improve clinical pregnancy rates in infertile women with endometriosis (Sallam, et al., 2006).	**B**

References

Sallam HN, Garcia-Velasco JA, Dias S and Arici A. Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. *Cochrane Database Syst Rev* 2006:CD004635. [Edited (no change to conclusions), published in Issue 1, 2010.]

4.3 Surgical therapies as an adjunct to treatment with ART in women with endometriosis

Key question

SHOULD SURGERY BE PERFORMED PRIOR TO TREATMENT WITH ART TO IMPROVE REPRODUCTIVE OUTCOMES?

It was mentioned (section 3.2) that surgery could have a beneficial effect on spontaneous pregnancy rates in women with endometriosis. Thus, one could speculate that surgical treatment of endometriosis prior to treatment with ART could be effective in improving reproductive outcome.

This section is subdivided into surgical therapy for peritoneal endometriosis, for ovarian endometrioma (ablation, cystectomy, aspiration) and for deep endometriosis prior to ART.

4.3.1 Surgery prior to treatment with ART in women with peritoneal endometriosis

Clinical evidence

With regard to the effect of surgical therapy on peritoneal endometriosis, a retrospective cohort study reported that surgery might be useful to enhance the success of ART. In a group of 399 women with minimal to mild endometriosis, all visible endometriosis was completely removed prior to ART. In the control group (262 women) only a diagnostic laparoscopy was performed. In the group in which surgery had taken place prior to ART, significant higher implantation, pregnancy and live birth rates were found. Moreover, the investigators reported a shorter time to first pregnancy and a higher cumulative pregnancy rate after surgical removal of endometriosis prior to ART (Opoien, et al., 2011). However, this does not imply that a laparascopy should be performed prior to ART in all asymptomatic women with the only aim to diagnose and subsequently treat peritoneal endometriosis in order to improve the result of the ART treatment.

Conclusion and considerations

The evidence regarding surgery prior to treatment with ART in women with minimal to mild endometriosis is of moderate quality, and has led to the following recommendation:

Recommendation

In infertile women with AFS/ASRM stage I/II endometriosis undergoing laparoscopy prior to treatment with assisted reproductive technologies, clinicians may consider the complete surgical removal of endometriosis to improve live birth rate, although the benefit is not well established (Opoien, et al., 2011).	**C**

References

Opøien HK, Fedorcsak P, Byholm T and Tanbo T. Complete surgical removal of minimal and mild endometriosis improves outcome of subsequent IVF/ICSI treatment. *Reprod Biomed Online* 2011; **23**:389–395.

4.3.2 Surgery prior to treatment with ART in women with ovarian endometrioma

Clinical evidence

With regard to the surgical therapy for cysts, a Cochrane review based on four randomized trials involving 312 women, concluded that laparoscopic aspiration or cystectomy of endometrioma prior to ART does not show evidence of benefit over expectant management with regard to the clinical pregnancy rate (Benschop, et al., 2010).

A systematic review confirms these results, but states that excision is more favourable than drainage with regard to recurrence of the endometrioma and of pain, and with regard to spontaneous pregnancy (Hart, et al., 2008). Other smaller cohort studies show partly contradictory results. In one cohort study the conclusion was drawn that cyst wall vaporisation does not impair IVF outcome (Donnez, et al., 2001). There is a need for more randomized controlled trials in order to answer the question as to whether small ovarian endometriotic cysts should be removed prior to ART.

Conclusion and considerations

Laparoscopic ovarian cystectomy in women with unilateral endometriomas before ART may not be useful in improving cycle outcome. This conclusion is drawn from several studies but is weak because of limited consistency in the interpretation of the results. Based on no difference in pregnancy rate, some authors advise cystectomy, whereas others advise caution with surgery because of the possible harmful effect on ovarian reserve.

Clinical evidence and recommendations on surgery for pain in women with ovarian endometrioma are discussed in section 2.4d.

Recommendations

In infertile women with endometrioma larger than 3 cm there is no evidence that cystectomy prior to treatment with assisted reproductive technologies improves pregnancy rates. (Benschop, et al., 2010, Donnez, et al., 2001, Hart, et al., 2008).	**A**
In women with endometrioma larger than 3 cm, the GDG recommends clinicians only to consider cystectomy prior to assisted reproductive technologies to improve endometriosis-associated pain or the accessibility of follicles.	**GPP**
The GDG recommends that clinicians counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery.	**GPP**

References

Benschop L, Farquhar C, van der Poel N and Heineman MJ. Interventions for women with endometrioma prior to assisted reproductive technology. *Cochrane Database Syst Rev* 2010:CD008571.

Donnez J, Wyns C and Nisolle M. Does ovarian surgery for endometriomas impair the ovarian response to gonadotropin? *Fertil Steril* 2001; **76**:662-665.

Hart RJ, Hickey M, Maouris P and Buckett W. Excisional surgery versus ablative surgery for ovarian endometriomata. *Cochrane Database Syst Rev* 2008:CD004992. [Edited (no change to conclusions), published in Issue 5, 2011.]

4.3.3 Surgery prior to treatment with ART in women with deep endometriosis

Clinical evidence

Surgical therapy for deep endometriosis is predominantly performed because of pain rather than infertility. One cohort study in which women with deep endometriosis could choose between surgery prior to ART or ART directly reports higher pregnancy rates after surgery and ART (Bianchi, et al., 2009). However, the numbers of live births did not differ between groups. Another cohort study did not find a beneficial effect of surgery prior to ART in women with deep endometriosis (Papaleo, et al., 2011).

Conclusion and considerations

From the literature, there is no evidence to recommend performing surgical excision of deep nodular lesions prior to ART in infertile women with endometriosis, to improve reproductive outcomes. However, these women often suffer from pain, requiring surgical treatment.

More information on surgery for pain in women with deep endometriosis, including the complication rates, is discussed in section 2.4e.

Recommendation

The effectiveness of surgical excision of deep nodular lesions before treatment with assisted reproductive technologies in women with endometriosis-associated infertility is not well established with regard to reproductive outcome (Bianchi, et al., 2009, Papaleo, et al., 2011).	**C**

References

Bianchi PH, Pereira RM, Zanatta A, Alegretti JR, Motta EL and Serafini PC. Extensive excision of deep infiltrative endometriosis before in vitro fertilization significantly improves pregnancy rates. *J Minim Invasive Gynecol* 2009; **16**:174–180.

Papaleo E, Ottolina J, Viganò P, Brigante C, Marsiglio E, De Michele F and Candiani M. Deep pelvic endometriosis negatively affects ovarian reserve and the number of oocytes retrieved for in vitro fertilization. *Acta Obstet Gynecol Scand* 2011; **90**:878–884.

5. MENOPAUSE IN WOMEN WITH ENDOMETRIOSIS

Introduction

Hormonal treatment is widely used in women suffering from menopausal symptoms. As endometriosis is an estrogen-depending condition, the use of hormonal therapy in women with menopausal symptoms and a history of endometriosis may reactivate residual disease or produce new lesions. However, denying these women hormonal therapy may worsen the longterm consequences of hypoestrogenism resulting from previous medical treatments with GnRH agonists and/or bilateral oophorectomy at early age.

The potential of malignant transformation of endometriosis and the regimen of hormonal therapy to be applied to women with a history of endometriosis experiencing menopausal symptoms are other relevant issues are discussed.

Key question

HOW SHOULD MENOPAUSAL SYMPTOMS BE TREATED IN WOMEN WITH A HISTORY OF ENDOMETRIOSIS?

Clinical evidence

The literature search revealed a systematic review that included two randomized controlled trials regarding recurrence of pain and endometriosis lesions in patients submitted to bilateral oophorectomy (Al Kadri, et al., 2009). In the first, 10 patients received continuous transdermal estrogen plus cyclical oral progestagen, and 11 received tibolone. After 12 months, 4 patients in the first group and 1 in the second experienced moderate pelvic pain. In the second study, 115 patients received continuous transdermal estrogen plus cyclical oral progesterone, and 57 received no hormonal treatment. After 45 months, 4 of the patients in the treated arm and none in the non-treated arm reported recurrence of pain. The authors found recurrence of the endometriosis in 2/115 treated patients and none in the control group. (The 2 patients had to be re-operated.) The differences were not statistically significant, but the authors highlighted residual disease as a risk factor to recurrence (Al Kadri, et al., 2009).

Neither of the included studies reported on malignant transformations or mortality.

No data are available for the regimen of hormone replacement therapy. Considering basic knowledge about eutopic and ectopic endometrial tissue, it seems advisable to use continuous combined estrogen-progestagen regimes in those patients requiring estrogen-containing treatment. Data suggesting that unopposed estrogens might be a risk factor for ovarian malignancy in endometriosis patients with high body mass index are also very limited.

The ideal interval to start hormonal therapy after surgical menopause is also not known, and decisions in this cannot be made on the basis of available evidence.

No information exists on possible consequences of the use of non-hormonal pharmacological treatments in this context.

Conclusion and considerations

We conclude that although it is not possible to rule out the possibility that hormone replacement therapy could result in pain and/or disease recurrence, the evidence in the literature is not strong enough to deny this treatment to severely symptomatic women in order to relieve menopausal symptoms.

We found no high-quality evidence on the recurrence of disease in menopausal endometriosis patients treated with hormone replacement therapy. In general, the different reports used different regimens.

Although the literature search included women with endometriosis after both surgical menopause and natural menopause, no evidence could be retrieved on the latter. The recommendations on surgical menopause could be extrapolated to women with endometriosis and natural menopause, bearing in mind the differences between both patient groups (e.g. age, gradual vs. abrupt onset of menopausal symptoms).

Recommendations

In women with surgically induced menopause because of endometriosis, estrogen/progestagen therapy or tibolone can be effective for the treatment of menopausal symptoms (Al Kadri, et al., 2009).	**B**

The GDG recommends that in postmenopausal women after hysterectomy and with a history of endometriosis, clinicians should avoid unopposed estrogen treatment. However, the theoretical benefit of avoiding disease reactivation and malignant transformation of residual disease should be balanced against the increased systemic risks associated with combined estrogen/progestagen or tibolone.	**GPP**

The GDG recommends that clinicians continue to treat women with a history of endometriosis after surgical menopause with combined estrogen/progestagen or tibolone, at least up to the age of natural menopause.	**GPP**

References

Al Kadri H, Hassan S, Al-Fozan HM and Hajeer A. Hormone therapy for endometriosis and surgical menopause. *Cochrane Database Syst Rev* 2009:CD005997.

6. ASYMPTOMATIC ENDOMETRIOSIS

Introduction

Asymptomatic endometriosis is defined as the incidental finding of peritoneal, ovarian or deep endometriosis without pelvic pain and/or infertility. The true prevalence of asymptomatic peritoneal endometriosis is not known, but between 3 and 45% of women undergoing laparoscopic sterilisation have been observed to have the disease (Gylfason, et al., 2010, Rawson, 1991).

Key question

IS SURGERY BENEFICIAL FOR INCIDENTAL FINDING OF ASYMPTOMATIC ENDOMETRIOSIS?

Clinical evidence

Surgical excision or ablation (and its inherent risks of damage to the bowel, bladder, ureter and blood vessels) for an incidental finding of asymptomatic endometriosis cannot be endorsed, because no clinical trials have been performed to date to assess whether surgery is beneficial, Furthermore, the risk that asymptomatic minimal disease will become symptomatic is low (Moen and Stokstad, 2002). However, in view of other possible negative consequences of endometriosis (e.g. effects on fertility, increased risk of ovarian carcinoma), there is a need for RCTs/cohort studies to determine whether surgery should be recommended (Pearce, et al., 2012).

Conclusion and considerations

Based on the lack of evidence, the guideline development group reached the following good practice point for an incidental finding of asymptomatic endometriosis at time of surgery. The GDG recommends that clinicians follow national guidelines for the management of ovarian cysts detected incidentally on ultrasound scan.

As the natural course of the disease is unknown and despite the small risk that asymptomatic minimal disease will become symptomatic, the general consensus from the guideline group is that clinicians have a duty of care to inform patients about an incidental finding of endometriosis.

Recommendations

The GDG recommends that clinicians should not routinely perform surgical excision and ablation for an incidental finding of asymptomatic endometriosis at the time of surgery, since the natural course of the disease is not clear.	**GPP**

The GDG recommends that clinicians fully inform and counsel women about any incidental finding of endometriosis.	**GPP**

References

Gylfason JT, Kristjansson KA, Sverrisdottir G, Jonsdottir K, Rafnsson V and Geirsson RT. Pelvic endometriosis diagnosed in an entire nation over 20 years. *Am J Epidemiol* 2010; **172**:237–243.

Moen MH and Stokstad T. A long-term follow-up study of women with asymptomatic endometriosis diagnosed incidentally at sterilization. *Fertil Steril* 2002; **78**:773–776.

Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, Nagle CM, Doherty JA, Cushing-Haugen KL, Wicklund KG et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. *Lancet Oncol* 2012; **13**:385–394.

Rawson JM. Prevalence of endometriosis in asymptomatic women. *J Reprod Med* 1991; **36**:513–515.

7. PREVENTION OF ENDOMETRIOSIS

Introduction

Primary prevention is aimed at protecting healthy, asymptomatic women from developing endometriosis.

Since the cause of endometriosis is unknown, the potential of primary prevention is limited. One of the risk factors for endometriosis seems to be having a first-degree family member with the disease, although the specific genetic origin of this association is still unknown. The increased disease prevalence which has been found in first-degree relatives of women with endometriosis results in questions from patients and family members on how they can prevent the development of endometriosis. Therefore, we performed a literature search for interventions that could influence the development of endometriosis, although not specifically for women with increased risk for endometriosis. However, interventions for prevention of disease development could be beneficial for these women as well.

Key question

IS THERE A ROLE FOR PRIMARY PREVENTION OF ENDOMETRIOSIS?

Clinical evidence

When comparing women with surgically diagnosed endometriosis to women without a diagnosis of endometriosis, there is evidence that current use of oral contraceptives has a protective effect against the development of endometriosis, but this effect is not observed in past or ever contraceptive users (Vercellini, et al., 2011). However, the protective effect observed in current users can be related to the postponement of surgical evaluation due to temporary suppression of pain (Vercellini, et al., 2011).

After adjustment for confounding variables, a slight reduction in the incidence of endometriosis was observed in premenopausal women with a high level of activity (≥42 metabolic equivalent (MET)-hours/week) compared to those with a low level (<3 MET-hours/week) [rate ratio (95% CI) 0.89 (0.77–1.03)]. Forty-two MET-hours corresponds to 6 hours jogging or 8 hours bicycling. The association was limited to participants with no past or current infertility (p=0.002, test for heterogeneity). No associations were seen with inactivity (Vitonis, et al., 2010).

Conclusion and considerations

We performed a broad literature search on endometriosis and primary prevention, and also searched for factors associated with the occurrence, prevalence and development of endometriosis. We only found evidence on oral contraceptives and physical exercise:

Recommendations

The usefulness of oral contraceptives for the primary prevention of endometriosis is uncertain (Vercellini, et al., 2011).	**C**

The usefulness of physical exercise for the primary prevention of endometriosis is uncertain (Vitonis, et al., 2010).	**C**

References

Vercellini P, Eskenazi B, Consonni D, Somigliana E, Parazzini F, Abbiati A and Fedele L. Oral contraceptives and risk of endometriosis: a systematic review and meta-analysis. *Hum Reprod Update* 2011; **17**:159–170.

Vitonis AF, Hankinson SE, Hornstein MD and Missmer SA. Adult physical activity and endometriosis risk. *Epidemiology* 2010; **21**:16–23.

8. ENDOMETRIOSIS AND CANCER

Introduction

The association between endometriosis and cancer has been assessed in several cohort and case control studies. There is controversy concerning the relationship between different forms of cancer, and the nature of the association. No consensus exists concerning means to affect the risk of cancer in women with endometriosis.

Key question

WHAT INFORMATION COULD BE PROVIDED TO WOMEN WITH ENDOMETRIOSIS REGARDING THE DEVELOPMENT OF CANCER?

Clinical evidence

Endometriosis is not associated with an overall increased risk of cancer (Somigliana, et al., 2006).

The diagnosis of endometriosis is associated with an increased risk of ovarian cancer. The odds ratios (OR), relative risks (RR) or standardized incidence ratios (SIR) in all case-control studies (n=6) and most (5/6) cohort studies have varied between 1.3 and 1.9. The association is strongest in cases of endometrioid and clear-cell ovarian cancer histologies (RR ≈ 3) (Munksgaard and Blaakaer, 2011, Sayasneh, et al., 2011).

Although the SIR is increased in endometriosis patients compared to control populations, the incidence of ovarian cancer is low in both groups. The cohort study of Melin and co-workers, for instance, reported an SIR of 1.43 (95% CI 1.19–1.71). The risk of developing cancer in this study (follow-up of 12.7 years) was 0.027 in endometriosis patients and 0.019 in control group, meaning that over 12.7 years, an average of 3 out of 100 endometriosis patients, compared to 2 out of 100 controls developed ovarian cancer (Melin, et al., 2006).

In cohort studies (n=3) the incidence of non-Hodgkin's lymphoma was increased in women with endometriosis (Somigliana, et al., 2006).

The relationship between endometriosis and breast cancer is uncertain. The risk for breast cancer was found to be increased in women with endometriosis in 3 out of 8 cohort studies (not increased in 5) and in 4 out of 5 case control studies (decreased in 1) (Munksgaard and Blaakaer, 2011).

Endometriosis is not associated with an altered risk of uterine cancer (Munksgaard and Blaakaer, 2011)

Endometriosis is associated with a lower risk of cervical cancer in most (2/3) cohort studies and one case control study (Munksgaard and Blaakaer, 2011).

Conclusion and considerations

A causative relationship between endometriosis and ovarian cancer has not been demonstrated. There is no evidence on how to lower the increased risk of ovarian cancer and non-Hodgkin's lymphoma in women with endometriosis. The lower risk of cervical cancer has been attributed to

increased referral and cervical surveillance among women with endometriosis. More evidence is needed before suggesting a change in the current overall management of endometriosis.

Recommendations

The GDG recommends that clinicians inform women with endometriosis requesting information on their risk of developing cancer that 1) there is no evidence that endometriosis causes cancer, 2) there is no increase in overall incidence of cancer in women with endometriosis, and 3) some cancers (ovarian cancer and non-Hodgkin's lymphoma) are slightly more common in women with endometriosis.	**GPP**

The GDG recommends that clinicians explain the incidence of some cancers in women with endometriosis in absolute numbers.	**GPP**

The GDG recommends no change in the current overall management of endometriosis in relation to malignancies, since there are no clinical data on how to lower the slightly increased risk of ovarian cancer or non-Hodgkin's lymphoma in women with endometriosis.	**GPP**

References

Melin A, Sparén P, Persson I and Bergqvist A. Endometriosis and the risk of cancer with special emphasis on ovarian cancer. *Hum Reprod* 2006; **21**:1237–1242.

Munksgaard PS and Blaakaer J. The association between endometriosis and gynecological cancers and breast cancer: a review of epidemiological data. *Gynecol Oncol* 2011; **123**:157–163.

Sayasneh A, Tsivos D and Crawford R. Endometriosis and ovarian cancer: a systematic review. *ISRN Obstet Gynecol* 2011; **2011**:140310.

Somigliana E, Vigano P, Parazzini F, Stoppelli S, Giambattista E and Vercellini P. Association between endometriosis and cancer: a comprehensive review and a critical analysis of clinical and epidemiological evidence. *Gynecol Oncol* 2006; **101**:331–341.

APPENDIX 1–6

APPENDIX 1: ABBREVIATIONS

AFS	American Fertility Society
ART	Assisted reproductive technology
ASRM	American Society for Reproductive Medicine
CI	Confidence interval
COS	Controlled ovarian stimulation
FSH	Follicle stimulating hormone
GDG	Guideline development group
GIN	Guidelines international network
GnRHa	Gonadotrophin releasing hormone analogue
GPP	Good practice point
HCG	Human chorionic gonadotrophin
HMG	Human menopausal gonadotrophin
HRT	Hormone replacement therapy
ICSI	Intracytoplasmic sperm injection
IUI	Intrauterine insemination
IVF	In vitro fertilization
LH	Luteinising hormone
LNG-IUS	Levonorgestrel-releasing intrauterine system
LR	Likelihood ratio
LUNA	Laparoscopic uterosacral nerve ablation
MAR	Medically assisted reproduction
MET	Metabolic equivalent
MPA	Medroxyprogesterone acetate
MRI	Magnetic resonance imaging
NEA	Norethisterone acetate
NPV	Negative predictive value
NSAID	Nonsteroidal anti-inflammatory drug
OCP	Oral contraceptive pill
OR	Odds ratio
PPV	Positive predictive value
PR	Pregnancy rate
PSN	Pre-sacral neurectomy
RCT	Randomized controlled trial
RES	Rectal endoscopic sonography
RR	Relative risk
SIR	Standardized incidence ratio
TCM	Traditional Chinese medicine
TENS	Transcutaneous electrical nerve stimulation
TVS	Transvaginal sonography
VAS	visual analogue pain scores
WERF	World Endometriosis Research Foundation

APPENDIX 2: GLOSSARY

Assisted reproductive technology (ART): All treatments or procedures that include the in vitro handling of both human oocytes and sperm or of embryos for the purpose of establishing a pregnancy. This includes, but is not limited to, in vitro fertilization and embryo transfer, gamete intrafallopian transfer, zygote intrafallopian transfer, tubal embryo transfer, gamete and embryo cryopreservation, oocyte and embryo donation, and gestational surrogacy. ART does not include assisted insemination (artificial insemination) using sperm from either a woman's partner or a sperm donor (Zegers-Hochschild, et al., 2009).

Controlled ovarian stimulation (COS): For ART: pharmacologic treatment in which women are stimulated to induce the development of multiple ovarian follicles to obtain multiple oocytes at follicular aspiration (Zegers-Hochschild, et al., 2009).

Dyschezia: Painful or difficult defecation.

Dysmenorrhea: Painful menstruation.

Dyspareunia: Painful sexual intercourse.

Dysuria: Painful urination.

Hematuria: Presence of blood in the urine.

Heavy menstrual bleeding: Abnormally heavy and prolonged menstruation at regular intervals. (menorrhagia)

In vitro fertilization (IVF): An ART procedure that involves extracorporeal fertilization (Zegers-Hochschild, et al., 2009).

Infertility (clinical definition): A disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (Zegers-Hochschild, et al., 2009).

Intracytoplasmic sperm injection (ICSI): A procedure in which a single spermatozoon is injected into the oocyte cytoplasm (Zegers-Hochschild, et al., 2009).

Medically assisted reproduction (MAR): Reproduction brought about through ovulation induction, controlled ovarian stimulation, ovulation triggering, ART procedures, and intrauterine, intracervical, and intravaginal insemination with semen of husband/partner or donor (Zegers-Hochschild, et al., 2009).

Natural cycle IVF: An IVF procedure in which one or more oocytes are collected from the ovaries during a spontaneous menstrual cycle without any drug use (Zegers-Hochschild, et al., 2009).

Reproductive surgery: Surgical procedures performed to diagnose, conserve, correct and/or improve reproductive function (Zegers-Hochschild, et al., 2009).

References

Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, Sullivan E, van der Poel S, International Committee for Monitoring Assisted Reproductive T and World Health O. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology, 2009. *Human reproduction* 2009; **24**:2683-2687.

APPENDIX 3: GUIDELINE GROUP

This guideline was developed by a guideline development group (GDG) set up by the ESHRE Special Interest Group Endometriosis and Endometrium. The GDG constituted clinicians with special interest in women with endometriosis, a literature methodology expert and a patient representative.

Chair of the GDG

Dr. Gerard A.J. Dunselman	Academic Hospital Maastricht (The Netherlands)

GDG members

Dr. Christian Becker	Nuffield Department of Obstetrics and Gynaecology, University of Oxford (UK)
Prof. Dr. Carlos Calhaz-Jorge	Faculdade de Medicina de Lisboa (Portugal)
Prof. Thomas D'Hooghe	University Hospitals Gasthuisberg, University of Leuven (Belgium)
Dr. M. Oskari Heikinheimo	Helsinki University Central Hospital (Finland)
Dr. Andrew W. Horne	MRC Centre for Reproductive Health, University of Edinburgh (UK)
Prof. Dr. med. Ludwig Kiesel	University Hospital of Münster (Germany)
Dr. Annemiek Nap	Rijnstate Arnhem (The Netherlands)
Dr. Willianne Nelen	Radboud University Nijmegen Medical Centre (The Netherlands)
Dr. Andrew Prentice	University of Cambridge (UK)
Dr. Ertan Saridogan	University College London Hospital (UK)
Dr. David Soriano	Endometriosis Center, Sheba Medical Center, Tel-Hashomer (Israel)

Patient representative

Ms. Bianca De Bie	Endometriose Stichting (The Netherlands)

Methodology expert

Dr. Nathalie Vermeulen	European Society of Human Reproduction and Embryology

Representative of the ESHRE executive committee

Prof. Dr. Carlos Calhaz-Jorge

Declarations of interest

All members of the guideline development group were asked to declare possible conflicts of interest by means of the disclosure forms (see ESHRE manual for guideline development).

Name	Conflict of interest
Dr. Gerard A.J. Dunselman	*Consulting fees from Abbott*
Dr. Christian Becker	*Research grant from Bayer.*
Prof. Dr. Carlos Calhaz-Jorge	*Consulting fees and speaker's fees from MSD, Gedeon Richter*
Prof. Thomas D'Hooghe	*Research grants from Merck Serono, Schering Plough, Ferring, Bayer Healthcare. Consulting fees from Merck Serono, Schering Plough, Ferring, Bayer Healthcare, Astellas, Preglem, Roche, Proteomika.*
Ms. Bianca De Bie	*None declared.*
Dr. M. Oskari Heikinheimo	*Consulting and speaker's fees from Bayer AG and MSD.*
Dr. Andrew W. Horne	*None declared.*
Dr. Ludwig Kiesel	*Research grants, consulting fees and speaker's fees from Bayer-Schering.*
Dr. Annemiek Nap	*Consulting fees from Merck-Serono.*
Dr. Willianne Nelen	*Speaker's fees from RCOG.*
Dr. Andrew Prentice	*None declared.*
Dr. Ertan Saridogan	*Consulting fees from Bayer-Schering. Speaker's fees from Ethicon, Karl Storz and Gedeon Richter.*
Dr. David Soriano	*Consulting fees from Bayer.*
Dr. Nathalie Vermeulen	*None declared.*

To further minimise potential conflicts of interest, the synthesis of the evidence was performed by the expert GDG member and the methodology expert (with no conflicts of interest). The possible influence of conflicts of interest was taken into account in the division of key questions among GDG members. Conflicts of interest were further limited by the discussion of the evidence and draft recommendations in the GDG, until consensus of the GDG was reached.

APPENDIX 4: RESEARCH RECOMMENDATIONS

During the literature searches and discussion of the availability and strength of the evidence, several topics were found for which there is insufficient evidence to answer the key questions. For the benefit of women with endometriosis, the GDG recommends that future research in the field of endometriosis is focussed on these research gaps and that researchers attempt to perform high-quality randomized controlled trials and/or cohort studies, to answer the following clinical issues.

Key issues as topics for further research in endometriosis:

- The effectiveness of surgical excision of AFS/ASRM stage III-IV endometriosis in comparison to direct referral to ART.
- The diagnostic value of laparoscopy with or without histological verification
- Secondary prevention of endometriosis
- The best management, with respect to reproductive outcome after ART, of an ovarian endometriotic cysts of 3 cm or more in women with an indication for treatment with assisted reproductive technology: need to compare three groups: direct ART, 6 month GnRH agonist treatment before ART, and ovarian cystectomy before ART.

Other important topics for further research:

- The natural course of endometriosis.
- Prospective cohort studies on the signs and symptoms of endometriosis.
- The use of biomarkers for diagnosis and disease monitoring in endometriosis.
- The usefulness of oral contraceptives for treatment of endometriosis-associated pain.
- The usefulness of analgesics for treatment of pain in women with endometriosis.
- The role for complementary and alternative medicine in the treatment of endometriosis-associated pain and endometriosis-associated infertility.
- The benefit of anti-adhesion agents in surgery for endometriosis-associated pain.
- Primary prevention of endometriosis.
- Clinical management of endometriosis in adolescents.
- The effectiveness of surgical excision of deep nodular lesions in symptomatic endometriosis patients before assisted reproductive technologies, with regard to reproductive outcome.
- In women with endometriosis and an indication for ART: compare direct ART with 6/12 months GnRH agonist downregulation, as the current recommendation is based on a low number of RCTs and a low number of patients.
- The use of HRT for treatment of menopausal symptoms in women with endometriosis, with regard to effectiveness, disease and pain recurrence and regimen to be used.
- The benefit of surgery in cases of incidental finding of asymptomatic endometriosis.
- The psychosocial impact of endometriosis and how this should be addressed: patient-centred care, couple-centred interventions, interventions to improve quality of life.

- Implementation of awareness and earlier diagnosis of disease, i.e. efforts to raise awareness amongst primary care specialists, gastroenterologists and internal medicine specialists.

APPENDIX 5: METHODOLOGY

Guideline development

European Society of Human Reproduction and Embryology (ESHRE) guidelines are developed based on the Manual for ESHRE guideline development (W.L.D.M. Nelen, C. Bergh, P. de Sutter, K.G. Nygren, J.A.M. Kremer Manual for ESHRE guideline development 2009), which can be consulted at the ESHRE website (www.eshre.eu). The principal aim of this manual is to provide stepwise advice on ESHRE guideline development for members of ESHRE guideline development groups. Additionally, the expectation is that this approach will improve the methodological quality of ESHRE guidelines and will have a positive impact on the quality of European reproductive healthcare delivery. The manual has been developed by the Special Interest Group Safety and Quality in ART and has been approved by the Executive Committee. This manual describes a 12-step procedure for writing clinical management guidelines by the guideline development group, supported by the ESHRE methodological expert:

1. guideline topic selection
2. formation of the guideline development group
3. scoping of the guideline
4. formulation of the key questions
5. search of evidence
6. synthesis of evidence
7. formulation of recommendations
8. writing the guideline's draft version
9. consultation and review
10. guideline dissemination
11. guideline implementation and evaluation and
12. guideline updating.

The current guideline was developed and funded by ESHRE, which covered expenses associated with the guideline meetings (travel, hotel and catering expenses) associated with the literature searches (library costs, costs associated with the retrieval of papers) and with the implementation of the guideline (printing, online web tool, publication costs). Except for reimbursement of their travel expenses, GDG members did not receive any payment for their participation in the guideline development process.

During an ESHRE campus course entitled "Guideline development" in Nijmegen, The Netherlands, it was proposed to update the ESHRE endometriosis guideline (2005) by the methodology described in the ESHRE guideline manual. The GDG was composed of experts in endometriosis. We strived for balances in gender and location within Europe.

After defining the scope of the guideline, Dr A. Prentice, as a clinical expert, undertook to outline the key questions that needed to be addressed in the guideline. Ms L. Hummelshoj contacted different patient groups, inviting them to submit questions to be answered in the guideline. Dr A. Prentice and Ms L. Hummelshoj arranged a meeting to compare the received questions, which resulted in a

provisional list of 22 questions. A meeting of the GDG was set up to discuss these provisional questions and refine them through the PICO process (patients – interventions – comparison – outcome). From this analysis, key words were defined for each question, thus allowing the methodology expert (Dr. N. Vermeulen) to start a literature search.

Key words were sorted by importance and used for searches in PUBMED and the Cochrane library. The literature searches included studies published before January 1, 2012 or indexed in PUBMED before January 1, 2012. Literature searches were performed as an iterative process. In a first step, systematic reviews and meta-analyses were collected. If no results were found, the search was extended to randomized controlled trials, and further to cohort studies and case reports. Preliminary searches were pre-sifted by the methodology expert, based on title and abstract. An expert GDG member, to whom a specific question was assigned, continued sifting the literature search results, based on title, abstract and his/her knowledge of the existing literature. If necessary, additional searches were performed in order to get the final list of papers. The quality of the selected papers was assessed by means of the quality assessment checklist, defined in the ESHRE guideline manual. The evidence was collected and summarized in an evidence table, according to the GIN format (http://www.g-i-n.net/activities/etwg). The quality assessment and evidence tables were constructed by the methodology expert and an expert GDG member. A second GDG member checked the evidence table.

Based on the collected evidence, draft recommendations were written by the assigned expert GDG member in collaboration with the methodology expert. Two 2-day meetings and a 1-day GDG meeting were organized to discuss the draft recommendations and the supporting evidence, and to reach consensus on the final formulation of the recommendations. The guideline chair and methodology expert collected all recommendations and combined them into the ESHRE guideline "Management of women with endometriosis."

Grades of recommendations

All included studies were assessed to determine the quality of evidence. Based on the study type and quality, studies were scored from 1++ to 4. The combined evidence to answer a specific clinical key questions was scored from A to D, based on the included studies and their quality. Finally, the recommendations were formulated based on a standard phrasing, so they reflect the strength of the evidence. It is important to note that the grade of a recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation. This information is summarized in the table below.

Study type	Level of evidence	Study quality	Grades of recommendations	Phrasing
Meta-analysis **Multiple randomized trials**	**1**	High (++)	**A**	(clinicians) should/ are recommended to is recommended/ indicated is useful/effective
		Moderate (+)	**B**	(clinicians) can is reasonable can be useful/ effective is probably recommended /indicated
Single randomized trial **Large non-randomized trial(s)**	**2**	High (++)	**B**	(clinicians) can is reasonable can be useful/ effective is probably recommended /indicated
Case control / cohort studies		Moderate (+)	**C**	(clinicians) may may/might be considered the usefulness/effectiveness is not well established/ is unclear/uncertain
Non-analytic studies **case reports / case series**	**3**	High (++) / Moderate (+)	**D**	(clinicians) may may/might be considered the usefulness/effectiveness is not well established/ is unclear/uncertain
Experts' opinions	**4**	/	**GPP**	the GDG recommends
All other studies		Low (-)	**Excluded from the guideline**	

Adapted from SIGN (Scottish Intercollegiate Guidelines Network, 2010)

Strategy for review of the Guideline draft

After finalisation of the guideline draft, the review process was started.

The draft guideline was published on the ESHRE website, accompanied by the reviewers' comments form and a short explanation of the review process. The guideline was open for review between 15/02/2013 and 01/04/2013.

To notify interested clinicians, we sent out an invitation to review the guideline by email to all members of the ESHRE SIG of Endometriosis and Endometrium, and published an invitation for review in the ESHRE e-newsletter, ESHRE update, edition March 2013.

Selected reviewers were invited personally by email. These reviewers included:

- GDG members who wrote the guideline in 2005 and did not participate in the current guideline development.
- Coordinators and deputies of the ESHRE SIG of Endometriosis and Endometrium and the ESHRE SIG Quality and Safety in ART.
- Non-expert gynecologists. Every GDG member suggested two gynecologists as reviewers, to assemble a group of non-expert balanced across Europe.
- Contact persons of patient organisations across Europe.
- Contact persons of national societies on endometriosis across Europe.

All reviewers are listed in appendix 6. The Reviewer comments processing report, including further information on the review and a list of all comments per reviewer with the response formulated by the GDG will be published on the ESHRE website.

Guideline Implementation strategy

The standard dissemination procedure for all ESHRE guidelines comprises publishing (3 steps) and announcement (6 steps).

Each guideline is published on the ESHRE Website and in Human Reproduction. The announcement procedure includes an announcement in "Focus on Reproduction", a newsflash on the ESHRE website homepage and a news item in the monthly digital ESHRE newsletter. All participants in the annual ESHRE meeting will be informed about the development and release of new guidelines during a specific guideline session; all related national societies and patient organisations are separately informed about the guideline release. They are asked to encourage local implementation by, for instance, translations or condensed versions, but they are also offered a website link to the original document. Finally, all appropriate remaining stakeholders will be informed.

A patient version of the guideline will be developed by a subgroup of the GDG together with patient representatives. This is a translation of the recommendations in everyday language, with emphasis on questions important to questions. It aims to help patients understand the guideline's recommendations and facilitates clinical decision-making.

To further enhance implementation of the guideline, the members of the GDG, as experts in the field, will be asked to select 5 recommendations for which they believe implementation will be difficult. They will be asked to elaborate on the barriers to implementation for each selected recommendation (variance in practice, costs, need for resources, contradictory evidence, etc.) and make suggestions for tailor-made implementation interventions (e.g. option grids, flow-charts, additional recommendations, addition of graphic/visual material to the guideline). Based on this, 2 or 3 tools for implementation tailored to the specific guideline will be developed.

Schedule for updating the guideline

Guidelines should be kept up to date. They should be considered for revision four years after publication. Two years after publication, a search for new evidence will be performed by the methodology expert. In the case of important new findings, the methodology expert will contact the chair of the GDG and decide the necessity of an updated version of the guideline.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found at www.eshre.eu.

Reference

Scottish Intercollegiate Guidelines Network EH, 8-10 Hillside Crescent, Edinburgh EH7 5EA. www.sign.ac.uk. 2010.

APPENDIX 6: REVIEWERS OF THE GUIDELINE DRAFT

As mentioned in the methodology, the guideline draft was open for review for 6 weeks, between 15/02/2013 and 01/04/2013. All reviewers, their comments and the reply of the guideline development group are summarized in the review report, which is published on the ESHRE website as supporting documentation to the guideline.

The list of experts in the field that provided comments to the guideline and their nationality are summarized below.

Petra De Sutter	Belgium
Jan Bosteels	Belgium
Carla Tomassetti	Belgium
Michelle Nisolle	Belgium
Axel Forman	Denmark
Dominic Byrne	England
Lone Hummelshoj	England
Päivi Härkki	Finland
Herve Dechaud	France
Emile Daraï	France
Daniela Hornung	Germany
Robert Greb	Germany
Thomas Faustmann	Germany
Stefan P. Renner	Germany
Maria Goudakou	Greece
Ioannis E. Messinis	Greece
George Pados	Greece
Grigoris F. Grimbizis	Greece
Berglind Ósk	Iceland
P.G. Crosignani	Italy
Paolo Vercellini	Italy
Nicola Surico	Italy
Jone Trovik	Norway
Hans Kristian Opøien	Norway
Samuel Santos Ribeiro	Portugal
Fernanda Águas	Portugal
Teresa Almeida-Santos	Portugal
Ana Aguiar	Portugal
Florin Stamatian	Romania
Paul Mills	Scotland
Hilary Critchley	Scotland
Juan Antonio García Velasco	Spain
Francisco Gonzalez-Gomez	Spain
Ben Cohlen	The Netherlands
M.A. Spath	The Netherlands
JCM van Huisseling	The Netherlands
Peter Hompes	The Netherlands
Velja Mijatovic	The Netherlands
S.M.Mourad	The Netherlands
Harold Verhoeve	The Netherlands
Jacques WM Maas	The Netherlands
Arrianna D'Angelo	UK
Philip Owen	UK
Luca Fusi	UK
Lorraine Culley	UK
Ganeshselvi Premkumar	UK
Andreas Stavroulis	UK
Ying Cheong	UK
Bee Kang Tan	UK
Cindy Farquhar	UK
Martyn Stafford-Bell	Australia
Kate Young	Australia
Luk Rombauts	Australia
Paulo C. Serafini	Brazil
Keiji Kuroda	Japan
Mukhri Hamdan	Malaysia
Kamthorn Pruksananonda	Thailand
Linda Giudice	USA
G. David Adamson	USA
Tommaso Falcone	USA
Dr. Miguel A. Marrero	USA