Management of women with endometriosis

Draft version

Guideline of the European Society of Human Reproduction and Embryology

ESHRE endometriosis guideline development group

April 2013

Disclaimer

The European Society of Human Reproduction and Embryology develops clinical practice guidelines to provide clinical recommendations to improve the quality of health care delivery within the European field of human reproduction and embryology.

Clinical practice guidelines are defined as "systematically developed statements to assist care providers and patient decisions about appropriate health care for specific clinical circumstances". Clinical guidelines are intended as neither cookbook nor textbook, but should be helpful in everyday clinical medical decision-making about appropriate and effective care. The ultimate decision about a particular clinical procedure or treatment will always depend on each individual patient's condition, circumstances and wishes, and the clinical judgment of the healthcare team.

Clinical guidelines do not rob clinicians of their freedom, nor relieve them of their responsibility to make appropriate decisions based on their own knowledge and experience only.

While ESHRE takes every care to compile accurate information and to keep it up-to-date, we cannot guarantee its correctness and completeness. The information provided on this website does not constitute business, medical or other professional advice, and is subject to change. We do not accept responsibility for any loss, damage or expense resulting from the use of this information.

Please reference as:

CONTENTS

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). Women with endometriosis can experience painful symptoms and/or infertility, while some women have no symptoms at all.

The exact prevalence of endometriosis is unknown but estimates range from 2 to 10% within the general population to 50% in infertile women (Eskenazi and Warner, 1997; Meuleman e*t al.*, 2009).

Endometriosis is diagnosed based on the history, the signs and the symptoms; the diagnosis is corroborated by physical examination and imaging techniques and finally proven by histology either of a direct biopsy of a vaginal localisation or of tissue collected during laparoscopy. Due to a high false positive rate the visual recognition alone of endometriosis during laparoscopy is of limited value. Laparoscopy also allows for direct surgical treatment and for staging the disease preferably according to the ASRM classification system (American Society for Reproductive Medicine, 1997). This classification system objectively assigns points to the different localizations of the disease resulting in four stages, minimal, mild, moderate and severe. These stages however poorly reflect pain symptoms and infertility.

Due to the symptoms, affected women experience a significantly reduced quality of life, including restraint of normal activities, pain/discomfort and anxiety/depression (Simoens *et al.,* 2007; Nnoaham *et al.*, 2011; Simoens *et al.*, 2012). Furthermore, women with endometriosis and their docters experience difficulties in diagnosing the disease and with the wide variety of clinical practice in the management of women with the disease. This results in many women either being delayed in receiving care or receiving suboptimal care (Kennedy *et al.*, 2005).

Recently, the WERF EndoCost study has shown that the costs of 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 euro, which was theoretically calculated from the annual average costs per woman treated in referral centres across Europe (Simoens *et al.*, 2012).

Therefore, there is a significant need to optimize the management of women with endometriosis to improve 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:

- European Society for Human Reproduction and Embryology: *(http://guidelines.endometriosis.org/)*
- American Society of Reproductive Medicine: (*Practice Committee of the American Society for Reproductive Medicine 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)*

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 on http://guidelines.endometriosis.org/ and visited about 42000 times a year between 2007 and 2011. The guideline was last updated on 30 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.

References

American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril. 1997 May;67(5):817-21.

Eskenazi B, Warner ML. Epidemiology of endometriosis. Obstet Gynecol Clin North Am. 1997 Jun;24(2):235-58.

Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, Hummelshoj L, Prentice A, Saridogan E; ESHRE Special Interest Group for Endometriosis and Endometrium Guideline Development Group. ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod. 2005 Oct;20(10):2698-704.

Leyland N, Casper R, Laberge P, Singh SS; SOGC. Endometriosis: diagnosis and management. J Obstet Gynaecol Can. 2010 Jul;32(7 Suppl 2):S1-32.

Meuleman C, Vandenabeele B, Fieuws S, Spiessens C, Timmerman D, D'Hooghe T. High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. Fertil Steril. 2009 Jul;92(1):68-74.

Nnoaham KE, Hummelshoj L, Webster P, d'Hooghe T, de Cicco Nardone F, de Cicco Nardone C, Jenkinson C, Kennedy SH, Zondervan KT; World Endometriosis Research Foundation Global Study of Women's Health consortium. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril. 2011 Aug;96(2):366-373.e8.

Practice Committee of American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis. Fertil Steril. 2008 Nov;90(5 Suppl):S260-9.

80 Practice Committee of the American Society for Reproductive Medicine. Endometriosis and
81 infertility: a committee opinion. Fertil Steril. 2012 Sep;98(3):591-8.

82 Simoens S, Hummelshoj L, D'Hooghe T. Endometriosis: cost estimates and methodological
83 perspective. Hum Reprod Update. 2007 Jul-Aug;13(4):395-404.

84 Simoens S, Dunselman G, Dirksen C, Hummelshoj L, Bokor A, Brandes I, Brodszky V, Canis
85 M, Colombo GL, DeLeire T, Falcone T, Graham B, Halis G, Horne A, Kanj O, Kjer JJ,
86 Kristensen J, Lebovic D, Mueller M, Vigano P, Wullschleger M, D'Hooghe T. The burden of
87 endometriosis: costs and quality of life of women with endometriosis and treated in referral
88 centres. Hum Reprod. 2012 May;27(5):1292-9.

SUMMARY OF RECOMMENDATIONS

Chapter 1: Diagnosis of endometriosis

1.1 Symptoms and signs of endometriosis

Which symptoms are associated with endometriosis?

Rec 1.1	The GDG recommends that clinicians should consider the diagnosis of endometriosis in women of reproductive age with cyclical symptoms.	GPP
Rec 1.2	The GDG recommends that clinicians should consider the diagnosis of endometriosis in the presence of symptoms such as dysmenorrhea, non-menstrual pelvic pain, deep dyspareunia, infertility and fatigue.	GPP

Are there symptoms that are predictive of the diagnosis of endometriosis?

Rec 1.3	Clinicians may consider the diagnosis of endometriosis in infertile women with severe dysmenorrhea.	C
Rec 1.4	Clinicians may consider the diagnosis of endometriosis in women with abdominopelvic pain, dysmenorrhea, menorrhagia, infertility, dyspareunia, postcoital bleeding, and/or previous diagnosis of ovarian cyst, irritable bowel syndrome or pelvic inflammatory disease.	C

1.2 Clinical examination in the diagnosis of endometriosis

What findings during clinical examination are predictive for the presence and localization of pelvic endometriosis?

Rec 1.5	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.	GPP
Rec 1.6	Clinicians may consider the diagnosis of deep infiltrating endometriosis in women with induration and/or nodules of the uterosacral ligaments found during clinical examination.	C
Rec 1.7	Clinicians may consider the diagnosis of ovarian endometrioma in women with adnexal masses detected during clinical examination.	C
Rec 1.8	Clinicians may consider the diagnosis of endometriosis in women suspected of the disease even if the clinical examination is normal.	C

1.3 Medical technologies in the diagnosis of endometriosis

Can the diagnosis of endometriosis be made by application of specific medical technologies?

Laparoscopy in the diagnosis of endometriosis

Rec 1.9	The GDG recommends to perform a laparoscopy to diagnose endometriosis, although evidence is lacking that a positive laparoscopy truly proves the presence of disease.	GPP
Rec 1.10	A negative diagnostic laparoscopy in women with symptoms and signs of the disease is highly accurate for the exclusion of the diagnosis of endometriosis.	A
Rec 1.11	The GDG recommends that clinicians confirm a positive laparoscopy by histology, since positive histology confirms the diagnosis of endometriosis although negative histology does not exclude it.	GPP
Rec 1.12	The GDG recommends that clinicians obtain tissue for histology in women undergoing surgery for ovarian endometrioma (> 3 cm in diameter), and/or deep infiltrating disease, to exclude rare instances of malignancy.	GPP

Ultrasound in the diagnosis of rectal endometriosis

Rec 1.13	In women with symptoms and signs of rectal endometriosis, transvaginal sonography is useful for identifying or ruling out rectal endometriosis.	A

Ultrasound in the diagnosis of ovarian endometriosis

Rec 1.14	Clinicians are recommended to perform transvaginal sonography to diagnose or to exclude an ovarian endometrioma.	A
Rec 1.15	The GDG recommends that clinicians base the diagnosis of ovarian endometrioma in premenopausal women on the following criteria: ground glass echogenicity and one to four compartments and no papillary structures with detectable blood flow.	GPP

3D ultrasound in the diagnosis of rectovaginal endometriosis

Rec 1.16	The usefulness of 3D ultrasound to diagnose rectovaginal endometriosis is not well established.	D

Magnetic resonance imaging in the diagnosis of endometriosis

Rec 1.17	Clinicians should be aware that the usefulness of magnetic resonance imaging (MRI) to diagnose peritoneal endometriosis is not well established.	D

Biomarkers in the diagnosis of endometriosis

Rec 1.18	Clinicians are recommended not to use biomarkers in endometrial tissue, menstrual or uterine fluids to diagnose endometriosis.	A
Rec 1.19	Clinicians are recommended not to use immunological biomarkers in plasma, urine or serum, including CA-125, to diagnose endometriosis.	A

Can the extent of deep infiltrating endometriosis be established by application of specific medical technologies?

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

Rec 1.20	The GDG recommends that clinicians should assess ureter, bladder, and bowel involvement by additional imaging if there is clinical suspicion of deep infiltrating endometriosis, in preparation for further management.	GPP

Chapter 2. Treatment of endometriosis-associated pain

Empirical treatment

Rec 2.1	Empirical treatment for painful symptoms presumed to be due to endometriosis without a definitive diagnosis includes counselling, adequate analgesia, progestagens, combined oral contraceptives (OCP) and nutritional therapy. It is unclear whether the OCP should be taken conventionally, continuously or in a tricycle regimen.	GPP

2.1 Medical therapies for treatment of endometriosis-associated pain

Are medical therapies effective for painful symptoms associated with endometriosis?

Rec 2.2	Clinicians are recommended to prescibe hormonal treatment (combined oral contraceptives, progestagens, gestrinone, danazol, or GnRH agonists) as one of the options, as it reduces endometriosis-associated pain.	A
Rec 2.3	The GDG recommends that clinicians take patient preferences, side effects, costs and availability into consideration when choosing medical treatment for endometriosis-associated pain.	GPP

Contraceptives

Rec 2.4	Clinicians can consider prescribing a low dose combined oral contraceptive, as it reduces endometriosis-associated dyspareunia, dysmenorrhea, and non-menstrual pain.	B

Progestagens and anti-progestagens

Rec 2.5	Clinicians are recommended to use progestagens (oral or depot medroxyprogesterone acetate, dienogest, cyproterone acetate or danazol) or anti-progestagens (gestrinone) as one of the options, as they reduce endometriosis-associated pain.	A
Rec 2.6	Clinicians should take the different side effect profiles of progestagens and anti-progestagens into account when prescribing these drugs.	GPP
Rec 2.7	Clinicians should consider prescribing a levonorgestrel-releasing intrauterine system as one of the options to reduce endometriosis-associated pain.	A

GnRH agonists

Rec 2.8	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.	A

Rec 2.9	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.	A
Rec 2.10	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 their maximum bone density.	GPP

Aromatase inhibitors

Rec 2.11	In women with pain from rectovaginal endometriosis, refractory to other medical or surgical treatment, clinicians can consider prescribing aromatase inhibitors in combination with progestagens, the oral contraceptive pill or GnRH analogues, as they reduce endometriosis-associated pain.	B

2.2 Analgesics for treatment of endometriosis-associated pain

Are analgesics effective for symptomatic relief of pain associated with endometriosis?

Rec 2.12	The GDG recommends that clinicians should consider NSAIDs or other analgesics to reduce endometriosis-associated pain.	GPP

2.3 Surgery for treatment of endometriosis-associated pain

Is surgery effective for painful symptoms associated with endometriosis?

Laparotomy - laparoscopy for treatment of endometriosis-associated pain

Rec 2.13	When endometriosis is identified at laparoscopy, clinicians should consider surgical treatment as it is effective for reducing endometriosis-associated pain i.e. 'see and treat'.	A

Ablation versus excision of endometriosis

Rec 2.14	Clinicians may consider both ablation and excision of peritoneal endometriotic spots to reduce endometriosis-associated pain.	C

Surgical interruption of pelvic nerve pathways

Rec 2.15	Clinicians should not perform laparoscopic uterosacral nerve ablation (LUNA) as an additional procedure to conservative surgery to reduce endometriosis-associated pain.	A

Rec 2.16	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.	A

Surgery for treatment of pain associated with ovarian endometrioma

Rec 2.17	Clinicians should perform cystectomy in women with ovarian endometrioma (> 3cm) instead of drainage and coagulation, as it reduces endometriosis-associated pain.	A
Rec 2.18	Clinicians can consider performing cystectomy rather than CO_2 laser vaporization in women with ovarian endometrioma (> 3cm), because of a lower recurrence rate.	B

Surgery for treatment of pain associated with deep infiltrating endometriosis

Rec 2.19	Clinicians can consider performing surgical removal of deep infiltrating endometriosis, as it reduces endometriosis-associated pain and improves quality of life.	B
Rec 2.20	The GDG recommends that clinicians refer women with suspected or diagnosed deep infiltrating endometriosis to an expert centre that offers all available treatments in a multidisciplinary context, including advanced operative laparoscopy or laparotomy.	GPP

Surgery for treatment of extragenital endometriosis

Rec 2.21	Clinicians may consider surgical removal of symptomatic extragenital/ extrapelvic endometriosis to relieve symptoms.	D

Adhesion prevention after endometriosis surgery

Rec 2.22	Clinicians can use oxidised regenerated cellulose during operative laparoscopy for endometriosis, as it prevents adhesion formation.	B
Rec 2.23	It is not reasonable for clinicians to use icodextrin after operative laparoscopy for endometriosis to prevent adhesion formation, as no benefit has been shown.	B

2.4 Medical therapies adjunct to surgery for treatment of endometriosis-associated pain

Are medical therapies effective as an adjunct to surgical therapy for treatment of pain?

Rec 2.24	Clinicians should not prescribe preoperative hormonal treatment to improve the outcome of surgery for pain in women with endometriosis.	A

Rec 2.25	Clinicians should not prescribe adjunctive hormonal treatment in women with endometriosis, after surgery for endometriosis-associated pain, as it does not improve the outcome of surgery for pain.	A
Rec 2.26	The GDG recommends that clinicians clearly distinguish between relatively short-term adjunctive hormonal treatment within six months after surgery as opposed to longer-term hormonal treatment aimed at secondary prevention.	GPP

2.5 Secondary prevention of endometriosis

Is there a role for secondary prevention of disease and painful symptoms in women treated for endometriosis?

Rec 2.27	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 preferences, costs, availability and side effects. For many interventions that might be considered here, there are limited data.	GPP
Rec 2.28	In women operated for an endometrioma of 3 cm or more, clinicians should perform ovarian cystectomy, instead of drainage and electrocoagulation, for the secondary prevention of endometriosis-associateddysmenorrhea, dyspareunia and non-menstrual pelvic pain.	A
Rec 2.29	After cystectomy for ovarian endometrioma in women not immediately seeking conception, clinicians should consider prescribing oral contraceptives, for the secondary prevention of ultrasound-diagnosed endometrioma.	A
Rec 2.30	In women operated for endometriosis, including cystectomy for ovarian endometrioma, clinicians should consider prescribing postoperative use of a levonorgestrel releasing intrauterine system or combined oral 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.	A

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

What other pain management strategies are effective for symptomatic relief of pain associated with endometriosis?

Rec 2.31	The GDG does not recommend the use of nutrition, complementary and alternative medicine in the treatment of endometriosis-associated pain, because potential benefits and/or harms are unclear. However the GDG acknowledges that some women who seek complementary and alternative medicine may benefit from this.	GPP

Chapter 3. Treatment of endometriosis-associated infertility

3.1 Medical therapies for treatment of endometriosis-associated infertility

Are medical therapies effective for infertility associated with endometriosis?

Rec 3.1	In infertile women with endometriosis, clinicians should not prescribe medical treatment for suppression of ovarian function to improve fertility.	A

3.2 Surgery for treatment of endometriosis-associated infertility

Is surgery effective for infertility associated with endometriosis?

Rec 3.2	In infertile women with AFS/ASRM stage I/II endometriosis, clinicians should perform operative laparoscopy (excision or ablation of the endometriotic lesions) including adhesiolysis, rather than performing diagnostic laparoscopy only, to increase the live birth rate.	A
Rec 3.3	In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may consider CO_2 laser vaporization of endometriosis, instead of monopolar electrocoagulation, since this is associated with higher cumulative spontaneous pregnancy rates.	C
Rec 3.4	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 the spontaneous pregnancy rate.	A
Rec 3.5	In infertile women with AFS/ASRM stage III/IV endometriosis, clinicians can consider operative laparoscopy, instead of expectant management, to increase spontaneous pregnancy rates.	B

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

Are medical therapies effective as an adjunct to surgical therapy for treatment of infertility?

Rec 3.6	In infertile women with endometriosis, the GDG recommends clinicians not to prescribe adjunctive hormonal treatment before surgery, as suitable evidence is lacking.	GPP

Rec 3.7	In infertile women with endometriosis, clinicians should not prescribe adjunctive hormonal treatment after surgery to improve spontaneous pregnancy rates.	A

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

What other management strategies are effective for infertility associated with endometriosis?

Rec 3.8	The GDG does not recommend the use of nutrition, complementary and alternative medicine in the treatment of endometriosis-associated infertility, because potential benefits and/or harms are unclear. However, the GDG acknowledges that some women who seek complementary and alternative medicine may benefit from this.	GPP

Chapter 4. Medically assisted reproduction

4.1 Medically assisted reproduction in women with endometriosis

Is medically assisted reproduction effective for infertility associated with endometriosis?

Intrauterine insemination in women with endometriosis

Rec 4.1	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 rate.	C
Rec 4.2	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.	C
Rec 4.3	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.	C

Assisted reproductive technologies in women with endometriosis

Rec 4.4	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
Rec 4.5	In infertile women with AFS/ASRM stage III/IV 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.	C
Rec 4.6	In women with endometriomas, clinicians may use antibiotic prophylaxis at the time of oocyte retrieval, although the risk for ovarian abscess following follicle aspiration is low.	D

4.2 Medical therapies as an adjunct to assisted reproductive technologies in women with endometriosis

Are medical therapies effective as an adjunct to treatment with ART for endometriosis-associated infertility?

Rec 4.7	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.	B

4.3 Surgical therapies as an adjunct to assisted reproductive technologies in women with endometriosis

Should surgery be performed prior to treatment with ART to improve reproductive outcomes?

Surgery prior to treatment with assisted reproductive technologies in women with peritoneal endometriosis

Rec 4.8	In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may consider complete surgical removal of endometriosis prior to treatment with assisted reproductive technologies to improve live birth rate.	C

Surgery prior to treatment with assisted reproductive technologies in women with ovarian endometrioma

Rec 4.9	In infertile women with endometriomas, clinicians should not perform cystectomy prior to treatment with assisted reproductive technology if the only aim is to improve pregnancy rates.	B
Rec 4.10	In women with an ovarian endometrioma, the GDG recommends clinicians to consider cystectomy prior to treatment with assisted reproductive technologies to confirm the diagnosis histologically, reduce the risk of infection after oocyte retrieval, improve accessibility of follicles or improve endometriosis-associated pain, although it does not improve pregnancy rates.	GPP
Rec 4.11	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

Surgery prior to treatment with assisted reproductive technologies in women with deep infiltrating endometriosis

Rec 4.12	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.	C

Chapter 5. Menopause in women with endometriosis

How should menopausal symptoms be treated in women with a history of endometriosis?

Rec 5.1	In women with surgically induced menopause because of endometriosis, estrogen/progestagen therapy or tibolone can be effective for treatment of menopausal symptoms.	B
Rec 5.2	The GDG recommends that in postmenopausal hysterectomised women with a history of endometriosis, clinicians should consider avoiding 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
Rec 5.3	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

Chapter 6. Asymptomatic endometriosis

Is surgery beneficial for incidental finding of asymptomatic endometriosis?

Rec 6.1	The GDG recommends that clinicians should not routinely perform surgical excision and ablation for an incidental finding of asymptomatic endometriosis, since the natural course of the disease is not clear.	GPP
Rec 6.2	The GDG recommends that clinicians fully inform and counsel women about any incidental finding of endometriosis.	GPP

Chapter 7. Prevention of endometriosis

Is there a role for primary prevention of endometriosis?

Rec 7.1	The usefulness of oral contraceptives for the primary prevention of endometriosis is uncertain.	C
Rec 7.2	The usefulness of physical exercise for the primary prevention of endometriosis is uncertain.	C

Chapter 8. Endometriosis and Cancer

What information could be provided to women with endometriosis regarding the development of cancer?

Rec 8.1	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, (3) some cancers (ovarian cancer and non-Hodgkin's lymphoma) are slightly more common in women with endometriosis.	GPP
Rec 8.2	The GDG recommends that clinicians explain the incidence of some cancers in women with endometriosis in absolute numbers.	GPP
Rec 8.3	The GDG recommends no change in the current overall management of endometriosis in relation to malignancies, since there is no clinical data on how to lower the slightly increased risk of ovarian cancer, or non-Hodgkin's lymphoma in women with endometriosis.	GPP

GUIDELINE SCOPE

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

This clinical guideline provides recommendations on the diagnostic approach for endometriosis, including the symptoms predictive of endometriosis, the utility of medical technologies and of clinical examination. Treatments for endometriosis, 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 also provided for the management of patients in whom endometriosis is found incidentally (without pain or infertility), for prevention of recurrence of disease and/or painful symptoms, for the treatment of menopausal symptoms in patients with a history of endometriosis and for patients questioning about the possible association of endometriosis and 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. For the benefit of patient education and shared-decision making, a patient version of this guideline will be developed.

METHODOLOGY

Guideline development

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 (GDG). 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 the European Society of Human Reproduction and Embryology. ESHRE 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 associated with the implementation of the guideline (printing, online web tool, publication costs). Except for reimbursement of their travel expenses, the guideline development group 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 means of the methodology described in the ESHRE guideline manual. The guideline development group was composed of experts in endometriosis. We strived for a balance in gender and location within Europe.

After defining the scope of the guideline, Dr A. Prentice, as a clinical expert, undertook an attempt 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 blueprint each process against the other. This resulted in a list of 22 provisional questions. A meeting of the guideline development group was set up to discuss these provisional questions and redefine them through the PICO process (patients – interventions – comparison – outcome). From this analysis, key words were defined for each question, allowing the methodological expert (Dr. N. Vermeulen) to start a literature search.

Key words were sorted to importance and used for searches in PUBMED/MEDLINE and the Cochrane library. The literature searches included studies published 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 randomised controlled trials, and further to cohort studies and case reports. Preliminary searches were pre-sifted by the methodological expert based on title and abstract. An expert GDG member, to whom a specific question was assigned, continued with sifting the literature search results, based on title, abstract and his 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. Furthermore, the evidence was collected and summarized in an evidence table according to GIN format (http://www.g-i-n.net/activities/etwg). The quality assessment and evidence tables were constructed by the methodological 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 methodological expert. Two 2-day 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 methodological expert collected all recommendations and combined them into the ESHRE guideline entitled: "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 randomised 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 randomised trial **large non-randomised trial(s)**	2	High (++)	**B**	
case control / cohort studies		Moderate (+)	**C**	(clinicians) may may/might be considered/reasonable the usefulness is unknown/unclear/uncertain the usefulness/effectiveness is not well established
Non-analytic studies **case reports / case series**	3	High (++) / moderate (+)	**D**	
experts' opinions	4	/	**GPP**	the GDG recommends
All studies		Low (-)	**Excluded from the guideline**	

Adapted from the Scottish Intercollegiate Guidelines Network (SIGN)

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 with 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. Furthermore, we published an invitation for review in the ESHRE e-newsletter, ESHRE update, edition March 2013.

Furthermore, selected reviewers were invited personally through email. These selected reviewers included:

- The guideline development group members who wrote the guideline in 2005 and did not participate in the current guideline development.
- Non-expert gynaecologists: every GDG member suggested two gynaecologists as reviewers, resulting in a group of non-expert balanced over Europe.
- Contact persons of patient organisations across Europe.
- Contact persons of all related National Societies across Europe.

Guideline Implementation strategy

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

Each guideline will be published on the ESHRE Website, in Human Reproduction and on the National Guidelines Clearinghouse's Website and other guideline websites. The announcement procedure includes an announcement in "Focus on Reproduction", a newsflash on the ESHRE website's homepage and a news item in the monthly digital ESHRE newsletter. Moreover, 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 are separately informed about the guideline release but are also formally asked if they would like to endorse it. 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 - for instance, European policy makers, patients societies and industry representatives - will be separately informed.

Additionally, a patient version of the guideline will be developed by a subgroup of the guideline development group together with patient representatives. This version of the guideline will translate the recommendations in everyday language. 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 guideline development group, as experts in the field, will be asked to select 5 recommendations for which they believe implementation will be difficult. They will also be asked to elaborate on the barriers for implementation for each selected recommendation (variance in practice, costs, need for resources, contradictory evidence,..) and 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 query, 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 methodological expert. In case of important new findings, the methodological expert will contact the chair of the guideline development group and decide in consensus 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 on the website www.eshre.eu.

1. DIAGNOSIS OF ENDOMETRIOSIS

Introduction

Several studies have reported a large diagnostic delay 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 early onset of symptoms, normalization of pain by family doctors, intermittent use of contraceptives causing hormonal suppression of symptoms, the use of non-discriminatory examinations, misdiagnosis, and attitude towards menstruation (Ballard *et al.*, 2006; Nnoaham *et al.*, 2011; Hudelist *et al.*, 2012).

In this section, the symptoms and signs of endometriosis are listed and recommendations are written on how the diagnosis of endometriosis should be established, in an attempt to improve knowledge of gynaecologists and other clinicians, and to decrease the diagnostic delay and the 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 (Davis *et al.*, 1993, Lemaire, 2004, Luscombe *et al.*, 2009, Bellelis *et al.*, 2010). Dysmenorrhea was the chief complaint, reported by 62% 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 that of incapacitating dysmenorrhea was 28%.

The location of endometriosis has an effect on the symptomatology of endometriosis. Deep infiltrating endometriosis (DIE) of the posterior pelvis is associated with an increased severity of dyschezia (i.e. difficulty in defecating) in comparison to women with pelvic endometriosis without posterior DIE (Seracchioli *et al.*, 2008). DIE of the rectovaginal septum is associated with the most severe forms of dyschezia and dyspareunia (Thomassin *et al.*, 2004, Seracchioli *et al.*, 2008).

Intestinal complaints – periodic bloating, diarrhoea or constipation - are some of the unrecognized symptoms of endometriosis (Luscombe *et al.*, 2009; Bellelis *et al.*, 2010; Davis *et al.*, 2010). In a prospective, controlled study, cyclic bloating was seen in 96%, diarrhoea in 27% and constipation in 16% of the women with endometriosis (Luscombe *et al.*, 2009). The corresponding figures 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/diarrhoea 67%, and referred pain 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 difference in the rates of pelvic pain, dyspareunia or vaginal discharge were seen among women with endometriosis versus 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.

Based on the limited evidence, supplemented with the opinion and experience of the GDG, the following general practice points were written to make clinicians aware of some associated symptoms and consider further exploration of a diagnosis of endometriosis in women experiencing these symptoms.

Recommendations

Rec 1.1	The GDG recommends that clinicians should consider the diagnosis of endometriosis in women of reproductive age with cyclical symptoms.	GPP
Rec 1.2	The GDG recommends that clinicians should consider the diagnosis of endometriosis in the presence of symptoms such as dysmenorrhea, non-menstrual pelvic pain, deep dyspareunia, infertility and fatigue.	GPP

Key question

Are there symptoms that are predictive of the diagnosis of endometriosis?

Clinical evidence

Abdominopelvic pain, dysmenorrhea, menorrhagia, 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 three years before the diagnosis of endometriosis (n=5540) vs. four matched (year-of-birth and practice) controls, women with subsequent diagnosis of endometriosis had higher proportion of abdominopelvic pain, dysmenorrhagia or menorrhagia (73 vs. 20%) (Ballard *et al.*, 2008). When compared with controls, women with endometriosis had ORs (95% CI) for the following symptoms: abdominopelvic pain 5.2 (4.7-5.7), dysmenorrhea 8.1 (7.2-9.3), menorrhagia 4.0 (3.5-4.5), infertility 8.2 (6.9-9.9), dyspareunia/postcoital bleeding 6.8 (5.7-8.2), urinary tract symptoms 1.2 (1.0-1.3). In addition, history of being diagnosed with an ovarian cyst 7.3 (5.7-9.4), with irritable bowel syndrome 1.6 (1.3-1.8), with pelvic inflammatory disease 3.0 (2.5-3.6) or with 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 risk of having received the diagnosis of irritable bowel syndrome, namely the 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 risk of having received the diagnosis of pelvic inflammatory disease is increased among women with endometriosis. In the UK general practice research database study the OR (95%) 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

In women seeking help from general practitioners, the following symptoms were found to be predictive of endometriosis: abdominopelvic pain, dysmenorrhea, menorrhagia, infertility, dyspareunia and/or postcoital bleeding and/or a previous diagnosis of ovarian cyst, irritable

bowel syndrome or 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.

Although the included evidence is limited, exploring the diagnosis of endometriosis in women seeking help with these symptoms could result in an earlier diagnosis of endometriosis and in an improved quality of life for the patients.

Recommendations

Rec 1.3	Clinicians may consider the diagnosis of endometriosis in infertile women with severe dysmenorrhea (Ballard *et al.*, 2008).	C

Rec 1.4	Clinicians may consider the diagnosis of endometriosis in women with abdominopelvic pain, dysmenorrhea, menorrhagia, infertility, dyspareunia, postcoital bleeding, and/or previous diagnosis of ovarian cyst, irritable bowel syndrome or pelvic inflammatory disease (Forman *et al.*, 1993; Ballard *et al.*, 2008).	C

References

Introduction

Ballard K, Lowton K, Wright J. What's the delay? A qualitative study of women's experiences of reaching a diagnosis of endometriosis. Fertil Steril. 2006 Nov;86(5):1296-301.

Hudelist G, Fritzer N, Thomas A, Niehues C, Oppelt P, Haas D, Tammaa A, Salzer H. Diagnostic delay for endometriosis in Austria and Germany: causes and possible consequences. Hum Reprod. 2012 Sep 17.

Nnoaham KE, Hummelshoj L, Webster P, d'Hooghe T, de Cicco Nardone F, de Cicco Nardone C, Jenkinson C, Kennedy SH, Zondervan KT; World Endometriosis Research Foundation Global Study of Women's Health consortium. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril. 2011 Aug;96(2):366-373.e8.

Clinical evidence

Ballard KD, Seaman HE, de Vries CS, Wright JT. Can symptomatology help in the diagnosis of endometriosis? Findings from a national case-control study--Part 1. BJOG. 2008 Oct;115(11):1382-91.

Bellelis P, Dias JA Jr, Podgaec S, Gonzales M, Baracat EC, Abrão MS. Epidemiological and clinical aspects of pelvic endometriosis–a case series. Rev Assoc Med Bras. 2010 Jul-Aug;56(4):467-71.

Davis GD, Thillet E, Lindemann J. Clinical characteristics of adolescent endometriosis. J Adolesc Health. 1993 Jul;14(5):362-8.

Eskenazi B, Warner M, Bonsignore L, Olive D, Samuels S, Vercellini P. Validation study of nonsurgical diagnosis of endometriosis. Fertil Steril. 2001 Nov;76(5):929-35.

Forman RG, Robinson JN, Mehta Z, Barlow DH. Patient history as a simple predictor of pelvic pathology in subfertile women. Hum Reprod. 1993 Jan;8(1):53-5.

Hsu AL, Sinaii N, Segars J, Nieman LK, Stratton P. Relating pelvic pain location to surgical findings of endometriosis. Obstet Gynecol. 2011 Aug;118(2 Pt 1):223-30.

Lemaire GS. More than just menstrual cramps: symptoms and uncertainty among women with endometriosis. J Obstet Gynecol Neonatal Nurs. 2004 Jan-Feb;33(1):71-9.

Luscombe GM, Markham R, Judio M, Grigoriu A, Fraser IS. Abdominal bloating: an under-recognized endometriosis symptom. J Obstet Gynaecol Can. 2009 Dec;31(12):1159-71.

Seracchioli R, Mabrouk M, Guerrini M, Manuzzi L, Savelli L, Frascà C, Venturoli S. Dyschezia and posterior deep infiltrating endometriosis: analysis of 360 cases. J Minim Invasive Gynecol. 2008 Nov-Dec;15(6):695-9.

Thomassin I, Bazot M, Detchev R, Barranger E, Cortez A, Darai E. Symptoms before and after surgical removal of colorectal endometriosis that are assessed by magnetic resonance imaging and rectal endoscopic sonography. Am J Obstet Gynecol. 2004 May;190(5):1264-71.

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 (Chapron *et al.*, 2002; Bazot *et al.*, 2009,). 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 (Ripps and Martin, 1992; Koninckx *et al.*, 1996; Bazot *et al.*, 2009). Visualization of deep infiltrating endometriosis on the vagina can be performed using 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 (Ripps and Martin, 1992; Koninckx *et al.*, 1996; Eskenazi *et al.*, 2001; Condous *et al.*, 2007; Bazot *et al.*, 2009).

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 infiltrating 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 has been investigated. The prevalence of endometriosis on the uterosacral ligaments, pouch of Douglas, vagina, bladder, rectovaginal space and rectosigmoid was 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 infiltrating endometriosis (Chapron *et al.*, 2002; Bazot *et al.*, 2009; Hudelist *et al.*, 2011).

Conclusion and considerations

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

For the general practice point, the GDG weight the benefits versus the burden for patients. Regarding the benefits, clinical examination is useful for a faster diagnosis of endometriosis or 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 limited since it can be performed at low costs.

From a patient perspective, it was noted that vaginal examination is inappropriate in adolescents and that it can be very painful in some women. In these women, with high burden/discomfort (adolescents, due to religion, painful examination) clinical examination should be omitted and other medical technologies, as described in the next section, should be used as a first step towards diagnosis.

Recommendations

Rec 1.5	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.	GPP
Rec 1.6	Clinicians may consider the diagnosis of deep infiltrating endometriosis in women with induration and/or nodules of the uterosacral ligaments found during clinical examination (Bazot *et al.*, 2009).	C
Rec 1.7	Clinicians may consider the diagnosis of ovarian endometrioma in women with adnexal masses detected during clinical examination (Ripps and Martin, 1992; Koninckx *et al.*, 1996; Eskenazi *et al.*, 2001; Condous *et al.*, 2007; Bazot *et al.*, 2009).	C

Rec 1.8	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

References

Bazot M, Lafont C, Rouzier R, Roseau G, Thomassin-Naggara I, Daraï E. Diagnostic accuracy of physical examination, transvaginal sonography, rectal endoscopic sonography, and magnetic resonance imaging to diagnose deep infiltrating endometriosis. Fertil Steril. 2009 Dec;92(6):1825-33.

Chapron C, Dubuisson JB, Pansini V, Vieira M, Fauconnier A, Barakat H, Dousset B. Routine clinical examination is not sufficient for diagnosing and locating deep infiltrating endometriosis. J Am Assoc Gynecol Laparosc. 2002 May;9(2):115-9.

Condous G, Van Calster B, Van Huffel S, Lam A. What is the value of preoperative bimanual pelvic examination in women undergoing laparoscopic total hysterectomy? J Minim Invasive Gynecol. 2007 May-Jun;14(3):334-8.

Eskenazi B, Warner M, Bonsignore L, Olive D, Samuels S, Vercellini P. Validation study of nonsurgical diagnosis of endometriosis. Fertil Steril. 2001 Nov;76(5):929-35.

Hudelist G, Ballard K, English J, Wright J, Banerjee S, Mastoroudes H, Thomas A, Singer CF, Keckstein J. Transvaginal sonography vs. clinical examination in the preoperative diagnosis of deep infiltrating endometriosis. Ultrasound Obstet Gynecol. 2011 Apr;37(4):480-7.

Koninckx PR, Meuleman C, Oosterlynck D, Cornillie FJ. Diagnosis of deep endometriosis by clinical examination during menstruation and plasma CA-125 concentration. Fertil Steril. 1996 Feb;65(2):280-7.

Ripps BA, Martin DC. Correlation of focal pelvic tenderness with implant dimension and stage of endometriosis. J Reprod Med. 1992 Jul;37(7):620-4.

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 suspected based on the history, the symptoms and signs, is corroborated by physical examination and imaging techniques and is finally 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 proof or rule out the presence of endometriosis.

1.3a Laparoscopy in the diagnosis of endometriosis

Clinical evidence

A systematic review on the accuracy of laparoscopy to diagnose endometriosis, with biopsy and histology as gold standard, showed that only limited reports of good quality exist (N=4) assessing the value of visual diagnosis of endometriosis at laparoscopy. Overall, the accuracy of a diagnostic laparoscopy was evaluated in 433 patients to diagnose endometriosis. A negative diagnostic laparoscopy (i.e. a laparoscopy during which no endometriosis is identified) seems to be highly accurate for excluding endometriosis and thereby of usefulness 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 [positive likelihood ratio (LR+) 4.30, 95% CI 2.45-7.55; negative likelihood ratio (LR–) 0.06, 95% CI 0.01-0.47]. With a prevalence of 20% the post-test probability is 51.8 (95% CI 38.0– 65.4) if the test is positive and 1.5 (95% CI 0.2–10.5) if the test is negative (Wykes *et al.*, 2004).

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

The LR for a positive test on laparoscopy (4.30, 95% CI 2.45–7.45) is unlikely to raise the pre-test probability of endometriosis over any threshold for advanced management in most clinicians' practice, unless disease prevalence is very high (Wykes *et al.*, 2004).

Conclusion and considerations

Laparoscopy with or without histological verification is widely used as the gold standard 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 equally limited, and one could expect a reporting bias. However, from the current available data, laparoscopy (with histology) can be described as both a successful and safe diagnostic intervention.

Recommendations

Rec 1.9	The GDG recommends to perform a laparoscopy to diagnose endometriosis, although evidence is lacking that a positive laparoscopy truly proves the presence of disease.	GPP
Rec 1.10	A negative diagnostic laparoscopy in women with symptoms and signs of the disease is highly accurate for the exclusion of the diagnosis of endometriosis (Wykes *et al.*, 2004).	A
Rec 1.11	The GDG recommends that clinicians confirm a positive laparoscopy by histology, since positive histology confirms the diagnosis of endometriosis although negative histology does not exclude it.	GPP
Rec 1.12	The GDG recommends that clinicians obtain tissue for histology in women undergoing surgery for ovarian endometrioma (>3cm in diameter), and/or deep infiltrating disease, to exclude rare instances of malignancy.	GPP

References

Wykes CB, Clark TJ, Khan KS. Accuracy of laparoscopy in the diagnosis of endometriosis: a systematic quantitative review. BJOG. 2004 Nov;111(11):1204-12.

1.3b Ultrasound in the diagnosis of rectal endometriosis

Clinical evidence

In women with a strong suspicion of endometriosis, especially in deep infiltrating disease, studies have been performed to evaluate the accuracy of ultrasound to diagnose rectal endometriosis.

In a systematic review the diagnostic value of transvaginal sonography (TVS) for non-invasive, pre-surgical detection of bowel endometriosis in 1105 women was evaluated. The gold standard was histological verification in all but 32 women, in whom the diagnosis was made by laparoscopic visualisation. In the studies evaluated, the prevalence of bowel endometriosis was 47 % (95% CI 36.7–57.3). In these studies the following characteristics of transvaginal sonography to diagnose bowel endometriosis were found: 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

From this review it can be concluded that transvaginal sonography is useful for 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) not in all women bowel surgery was performed, so it is difficult to confirm the presence/absence of disease, (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 they cannot recommend TVS to be used for diagnosis of rectal endometriosis, except if performed by clinicians highly experienced in TVS.

Recommendation

Rec 1.13	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, Keckstein J. Diagnostic accuracy of transvaginal ultrasound for non-invasive diagnosis of bowel endometriosis systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2011 Mar;37(3):257-63.

1.3c Ultrasound in the diagnosis of ovarian endometriosis

Clinical evidence

In women with an adnexal mass and the suspicion of endometriosis, several studies were performed to evaluate the accuracy of ultrasound to diagnose ovarian endometriosis.

In a systematic review, transvaginal and transabdominal ultrasound scanning, with or without Doppler, was evaluated as a diagnostic test for the accurate diagnosis of pelvic endometriosis. A total of 1257 adnexal masses were evaluated, histology being the gold standard except in eight cases where only cytology was performed. The prevalence of endometriosis was 13 to 38%. Diagnostic characteristics were: Sensitivity ranged from 64 to 89%; Specificity ranged from 89 to 100%; LR+ ranged from 7.6 to 29.8; LR- ranged from 0.1 to 0.4 (Moore *et al.*, 2002).

Conclusion and considerations

From the included evidence, it can be concluded that ovarian endometrioma can be diagnosed and excluded by transvaginal sonography. For the diagnosis of ovarian endometriosis, TVS is less operator dependent and can be applied more widely. The GDG recommends that clinicians base the diagnosis of ovarian endometrioma on ultrasound characteristics of ovarian endometrioma published recently (Van Holsbeke *et al.*,2010).

Recommendations

Rec 1.14	Clinicians are recommended to perform transvaginal sonography to diagnose or to exclude an ovarian endometrioma (Moore *et al.*, 2002).	A

Rec 1.15	The GDG recommends that clinicians base the diagnosis of ovarian endometrioma in premenopausal women on the following criteria: 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, Kennedy S. A systematic review of the accuracy of ultrasound in the diagnosis of endometriosis. Ultrasound Obstet Gynecol. 2002 Dec;20(6):630-4.

Van Holsbeke C, Van Calster B, Guerriero S, Savelli L, Paladini D, Lissoni AA, Czekierdowski A, Fischerova D, Zhang J, Mestdagh G, Testa AC, Bourne T, Valentin L, Timmerman D. Endometriomas: their ultrasound characteristics. Ultrasound Obstet Gynecol. 2010 Jun;35(6):730-40.

1.3d 3D ultrasound in the diagnosis of rectovaginal endometriosis

Clinical evidence

In women with the suspicion of rectovaginal endometriosis, the value of 3D ultrasound was evaluated to diagnose rectovaginal disease.

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

With a prevalence of rectovaginal endometriosis of 50%, there was a sensitivity of 89.5% (95% CI 73.3-94.5), a specificity of 94.7% (95% CI 78,6-99,7), a LR+ of 17.2 (95% CI 2.51-115) and a LR– of 0.11 (95% CI 0.03-0.41). Given the pre-test probability of 50, this becomes 94 with a positive test and 10 with a negative test.

Conclusion and considerations

Since this is only a small case series and since 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 clinicians.

Recommendation

Rec 1.16	The usefulness of 3D ultrasound to diagnose rectovaginal endometriosis is not well established (Pascual *et al.*, 2010).	D

References

Pascual MA, Guerriero S, Hereter L, Barri-Soldevila P, Ajossa S, Graupera B,Rodriguez I. Diagnosis of endometriosis of the rectovaginal septum using introital three-dimensional ultrasonography. Fertil Steril. 2010 Dec;94(7):2761-5.

1.3e Magnetic resonance imaging in the diagnosis of endometriosis

Clinical evidence

In women with the suspicion of endometriosis, the value of MRI was evaluated to diagnose the disease.

In a case series of 44 women with a clinical suspicion of endometriosis the value of MRI in predicting the presence of peritoneal endometriosis was evaluated by Stratton and co-workers (2003). The gold standard was laparoscopy, and the macroscopic and microscopic presence of endometriosis. With a prevalence of endometriosis of 86%, there was a sensitivity of 69% and a specificity of 75%, LR+ 2.76, LR– 0.41. These LRs are too low to use the MRI to diagnose or exclude peritoneal disease. Overall, compared with biopsy results for each lesion, MRI had a diagnostic sensitivity of 38% and a 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 magnetic resonance is not a cost-effective diagnostic tool.

Recommendation

Rec 1.17	Clinicians should be aware that the usefulness of 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, Nieman LK. Diagnostic accuracy of laparoscopy, magnetic resonance imaging, and histopathologic examination for the detection of endometriosis. Fertil Steril. 2003 May;79(5):1078-85.

1.3f Biomarkers in the diagnosis of endometriosis

Clinical evidence

May and co-workers (2011) performed a systematic review to assess critically the clinical value of markers retrieved from endometrial tissue, menstrual or uterine fluid to diagnose endometriosis in a non-invasive way. They included 182 studies. In all studies visual and/or histological confirmation of endometriosis after laparoscopy or laparotomy, defined as the presence of peritoneal endometriotic lesions, endometriomata and/or rectovaginal endometriotic nodules, was described (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) most promising markers related to nerve fibres and cell cycle and (4) whilst no marker has conclusively been shown to diagnose endometriosis, several high-quality studies that identified endometrial nerve fibres and molecules involved in cell cycle control (apoptotic pathway), cell adhesion and angiogenesis were promising candidates for future biomarker research.

Serum CA-125 in the diagnosis of endometriosis

Clinical evidence

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 to diagnose endometriosis in a non-invasive way (Mol *et al.*, 1998).

They included 2131 patients who all underwent a laparoscopy because of pain and/or infertility. With a prevalence of endometriosis varying between 0.19 and 0.86, the following characteristics were found: Sensitivity ranged from 0.04 to 1.0; Specificity ranged from 0.38 to 1.0; Positive likelihood ratio was 2.8. A summary ROC curve showed a low diagnostic performance.

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

Despite its limited diagnostic performance, the authors believe that the 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

Clinical evidence

May and co-workers (2010) performed a systematic review to assess critically the clinical value of all proposed immunological biomarkers for endometriosis in serum, plasma and urine. They included 161 studies. In all studies visual and/or histological confirmation of endometriosis after laparoscopy or laparotomy, defined as the presence of peritoneal endometriotic lesions, endometriomata and/or rectovaginal endometriotic nodules was described. The total number of involved patients, the prevalence of the disease nor the sensitivity and specificity of the tests of the individual studies evaluated were not mentioned (May *et al.*, 2010).

Conclusion and considerations

The overall conclusion of the authors was (1) lack of high-quality studies investigating large numbers of well-phenotyped patients (2) the search identified over 100 possible immunological biomarkers that have been investigated; however, none of these have been clearly shown to be of clinical use.

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

Recommendations

Rec 1.18	Clinicians are recommended not to use biomarkers in endometrial tissue, menstrual or uterine fluids to diagnose endometriosis (May *et al.*, 2011).	A

Rec 1.19	Clinicians are recommended not to use immunological biomarkers in plasma, urine or serum, including CA-125, to diagnose endometriosis (Mol *et al.*, 1998; May *et al.*, 2010).	A

References

May KE, Conduit-Hulbert SA, Villar J, Kirtley S, Kennedy SH, Becker CM. Peripheral biomarkers of endometriosis: a systematic review. Hum Reprod Update. 2010 Nov-Dec;16(6):651-74.

May KE, Villar J, Kirtley S, Kennedy SH, Becker CM. Endometrial alterations in endometriosis: a systematic review of putative biomarkers. Hum Reprod Update. 2011 Sep-Oct;17(5):637-53.

Mol BW, Bayram N, Lijmer JG, Wiegerinck MA, Bongers MY, van der Veen F, Bossuyt PM. The performance of CA-125 measurement in the detection of endometriosis: a meta-analysis. Fertil Steril. 1998 Dec;70(6):1101-8

Key question

Can the extent of deep infiltrating endometriosis be established by application of specific medical technologies?

In women with the clinical suspicion of deep infiltrating endometriosis, it is deemed beneficial to establish the extent of the disease. The key issue is whether it is possible to predict in which patients there is involvement of the bowel wall preoperatively.

1.3i Barium enema, transvaginal sonography, transrectal sonography and MRI to establish the extent of disease in deep infiltrating endometriosis

Clinical evidence

In six cohort studies, 575 patients with a high suspicion of deep infiltrating 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) (Landi *et al.*, 2004; Faccioli *et al.*, 2008; Ribeiro *et al.*, 2008; Anaf *et al.*, 2009; Bergamini *et al.*, 2010; Savelli *et al.*, 2011).

The gold standard in these studies was laparoscopy and histology of the resected endometriosis from the bowel wall. Since not all patients had a bowel resection, there was no histology was not available in all cases, thereby reducing the quality of the studies. The prevalence of bowel wall involvement was between 48 and 100%. The sensitivity, specificity, positive predictive value and negative predictive value stated in the different studies were less reliable because of this lack of a histological gold standard.

From the results of these studies it is hardly possible to draw firm conclusions to what extent a preoperative barium enema, transvaginal or transrectal sonography are accurate to diagnose bowel wall involvement in women with deep infiltrating endometriosis

Studies reporting on the value of MRI in predicting the extent of disease in DIE are either prospectively (Abrao *et al.*, 2007) or retrospectively conducted (Chapron *et al.*, 2004. Bazot *et al.*, 2007). Only one study included women with surgically proven endometriosis (Chapron *et al.*, 2004). Positive LR ranged from 12.0 to 41.7. This indicates that MRI is a good test to predict whether DIE actually infiltrates the bowel wall. The negative 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 (trans-rectal and/or transvaginal and/or renal), with or without barium enema studies depending upon the individual circumstances, to map the extent of disease present, which may be multi-focal.

Conclusion and considerations

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

Recommendation

Rec 1.20	The GDG recommends that clinicians should assess ureter, bladder, and bowel involvement by additional imaging if there is clinical suspicion of deep infiltrating endometriosis, in preparation for further management.	GPP

References

Abrao MS, Gonçalves MO, Dias JA Jr, Podgaec S, Chamie LP, Blasbalg R. Comparison between clinical examination, transvaginal sonography and magnetic resonance imaging for the diagnosis of deep endometriosis. Hum Reprod. 2007 Dec;22(12):3092-7.

Anaf V, El Nakadi I, De Moor V, Coppens E, Zalcman M, Noel JC. Anatomic significance of a positive barium enema in deep infiltrating endometriosis of the large bowel. World J Surg. 2009 Apr;33(4):822-7.

Bazot M, Bornier C, Dubernard G, Roseau G, Cortez A, Daraï E. Accuracy of magnetic resonance imaging and rectal endoscopic sonography for the prediction of location of deep pelvic endometriosis. Hum Reprod. 2007 May;22(5):1457-63.

Bergamini V, Ghezzi F, Scarperi S, Raffaelli R, Cromi A, 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 Dec;35(6):732-6.

Chapron C, Vieira M, Chopin N, Balleyguier C, Barakat H, Dumontier I, Roseau G, Fauconnier A, Foulot H, Dousset B. Accuracy of rectal endoscopic ultrasonography and magnetic resonance imaging in the diagnosis of rectal involvement for patients presenting with deeply infiltrating endometriosis. Ultrasound Obstet Gynecol. 2004 Aug;24(2):175-9.

Faccioli N, Manfredi R, Mainardi P, Dalla Chiara E, Spoto E, Minelli L, Mucelli RP. Barium enema evaluation of colonic involvement in endometriosis. AJR Am J Roentgenol. 2008 Apr;190(4):1050-4.

Landi S, Barbieri F, Fiaccavento A, Mainardi P, Ruffo G, Selvaggi L, Syed R, Minelli L. Preoperative double-contrast barium enema in patients with suspected intestinal endometriosis. J Am Assoc Gynecol Laparosc. 2004 May;11(2):223-8.

Ribeiro HS, Ribeiro PA, Rossini L, Rodrigues FC, Donadio N, Aoki T. Double-contrast barium enema and transrectal endoscopic ultrasonography in the diagnosis of intestinal deeply infiltrating endometriosis. J Minim Invasive Gynecol. 2008 May-Jun;15(3):315-20.

Savelli L, Manuzzi L, Coe M, Mabrouk M, Di Donato N, Venturoli S, Seracchioli R. Comparison of transvaginal sonography and double-contrast barium enema for diagnosing deep infiltrating endometriosis of the posterior compartment. Ultrasound Obstet Gynecol. 2011 Oct;38(4):466-71.

2. TREATMENT OF ENDOMETRIOSIS-ASSOCIATED PAIN

Introduction

Women with endometriosis are confronted with two major problems being endometriosis-associated pain and infertility, or both. For the reason of clarity, this section deals with treatments for pain, while chapter 3 deals with treatments for infertility.

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

In the section on medical treatment, we focussed 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 pain medication without a prior definitive diagnosis by laparoscopy. This is partially due to the invasiveness of the laparoscopic procedure, but also due to the ease of prescribing oral 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 much as possible. It is common practice that if women do not react favourably to the prescribed medical or hormonal pain treatment a laparoscopy is performed to exclude or diagnose and possibly treat endometriosis at the same time. However, the response to hormonal therapy does not always predict the presence or absence of endometriosis (Ling, 1999; Jenkins *et al.*, 2008). It has to be emphasized as well that prescribing oral contraceptives in adolescents with pelvic pain without a definitive diagnosis of endometriosis might be partly responsible for the well known delay in diagnosing the disease. It has been argued that starting oral contraceptives in young girls because of primary dysmenorrhoea could be indicative of the diagnosis of deep infiltrating endometriosis in later life (Chapron *et al.*, 2011).

Recommendation

Rec 2.1	Empirical treatment for painful symptoms presumed to be due to endometriosis without a definitive diagnosis includes counselling, adequate analgesia, progestagens, combined oral contraceptives (OCP) and nutritional therapy. It is unclear whether the OCP should be taken conventionally, continuously or in a tricycle regimen.	GPP

This chapter on treatment of endometriosis-associated pain is subdivided in 5 sections: medical treatment, surgical treatment, pre- or postoperative medical treatment, 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.

References

Chapron C, Souza C, Borghese B, Lafay-Pillet MC, Santulli P, Bijaoui G, Goffinet F, 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 Aug;26(8):2028-35.

Jenkins TR, Liu CY, White J. Does response to hormonal therapy predict presence or absence of endometriosis? J Minim Invasive Gynecol. 2008 Jan-Feb;15(1):82-6.

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 Jan;93(1):51-8.

2.1 Medical therapies for treatment of endometriosis-associated pain

Key question

Are medical therapies effective for painful symptoms associated with endometriosis?

Endometriosis is considered an estrogen dependent disease. Thus, hormonal suppression might be an attractive medical approach to treat the disease and symptoms.

Many studies have compared various hormonal treatments with each other. Early studies often failed to compare these drugs with 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 drugs are free of side effects, but the severity and tolerability can differ quite significantly. In addition, significant cost differences exist between treatment groups. In conclusion, all these factors should be taken into consideration when prescribing hormones to women suffering from endometriosis-associated pain.

Currently, contraceptives, progestagens and anti-progestagens, GnRH agonists and antagonists, and aromatase inhibitors are in clinical use. These compounds are discussed in detail below.

With no overwhelming medical evidence to support particular treatments over others, it is important to recognise that the decisions involved in any treatment plan are individual, and that a woman is able to make these based on an informed choice and a good understanding of what is happening to her body.

Recommendations

Rec 2.2	Clinicians are recommended to prescibe hormonal treatment (combined oral contraceptives, progestagens, gestrinone, danazol, or GnRH agonists) as one of the options, as it reduces endometriosis-associated pain.	A
Rec 2.3	The GDG recommends that clinicians take patient preferences, side effects, costs and availability into consideration when choosing medical treatment for endometriosis-associated pain.	GPP

2.1a Contraceptives

Clinical evidence

A systematic review investigated the effects 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); 4. Combined OCP versus conservative surgical treatment (Davis *et al.*, 2007).

Only one study could be included comparing the GnRHa goserelin with a low dose combined OCP (20 µg ethinylestradiol, 150 µg 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 in reducing pain. For non-menstrual pain, there was no difference between the OCP and goserelin. During treatment with goserelin, amenorrhoea occurred, so dysmenorrhea could not be compared between both groups at the end of a 6-month treatment period.

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 this low dose combined OCP or 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).

Conclusion and considerations

In the Cochrane review, only one study was found and included discussing the use of contraceptives in treatment of pain in endometriosis. The authors of the study conclude that the use of this low dose cyclic OCP is effective in reducing pain symptoms in patients with endometriosis but mention that the sample size for their study is limited and that data are limited to a 6-month period. They also state that their study was underpowered to detect minor differences that might exist between OCP and goserelin. No data were found on the use of continuous versus cyclical OCP.

The guideline development group noted that although the evidence is limited, OCP is widely used as treatment for either endometriosis-associated pain, or pain in women suspected of endometriosis.

Recommendations

Rec 2.4	Clinicians can consider prescribing a low dose combined oral contraceptive, as it reduces endometriosis-associated dyspareunia, dysmenorrhea, and non-menstrual pain (Vercellini *et al.*, 1993).	B

References

Davis L, Kennedy SS, Moore J, Prentice A. Modern combined oral contraceptives for pain associated with endometriosis. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD001019.

Vercellini P, Trespidi L, Colombo A, Vendola N, Marchini M, Crosignani PG. A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. Fertil Steril. 1993 Jul;60(1):75-9.

2.1b Progestagens and anti-progestagens

Clinical evidence

A recent systematic Cochrane review investigated the effectiveness of progestagens or anti-progestagens in the treatment of endometriosis-associated pain (Brown *et al.*, 2012). Although published after finishing the literature searches, this Cochrane review replaces the initially included review by Kives, last edited in 2010 (Kives *et al.*, 2000).

The review included two RCTs comparing progestagens with placebo and eight studies comparing progestagens with other treatments (2 discussed depot progestagens, 6 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, 100 mg) or danazol (200 mg three times daily), for six months), as compared to patients receiving placebo. The second study showed no significant effect on pain. In this study, 12 days of 40 or 60 mg of dydrogesterone was compared with placebo during the luteal phase in women with endometriosis who were trying to conceive.

Eight RCTs compared pragestagens with other treatments. Two studies were included comparing depot progestagens to a cyclic monophasic OCP combined with danazol, and leuprolide acetate. Six studies discussed oral progestagens compared to danazol, intranasal nafarelin, a combined oral contraceptive pill (2 studies), buserelin acetate or three-monthly leuprolide acetate. Based on the 8 included studies comparing progestagens with other medical treatments, the reviewers concluded that there was no evidence to suggest a benefit of progestagens, as compared to the other treatments

The anti-progestagen gestrinone was tested in four RCTs. Hornstein *et al.* showed in a total of twelve patients that twice-weekly oral intake of either 1.25 mg or 2.5 mg gestrinone were equally effective, but side effects were less common in the lower dose group. An Italian and a

British-lead study each compared gestrinone with danazol. Pelvic pain and deep dyspareunia in the first study and pelvic pain and dysmenorrhea in the 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 multicenter study compared the effect of oral gestrinone with intra-muscular leuprolide acetate for six months in patients with endometriosis-associated pelvic pain. Both treatments were effective in reducing dysmenorrhea, deep dyspareunia and non-menstrual pain during treatment and 6 months of follow-up.

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

Another Cochrane review summarized studies comparing oral danazol with placebo or no treatment and danazol vs. oral MPA vs. placebo (Farquhar *et al.*, 2010). Five studies met the inclusion criteria but in three trials, treatment was used in addition to surgery. The two remaining studies might have some patient overlap. In these latter trials, patients were treated for 6 months. Endometriosis-associated pain, back pain and dyschezia scores were reduced at six 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 taken off the market in some countries due to its side-effect profile, but recently vaginal applications may be more tolerable.

Three studies investigated the potential use of a levonorgestrel-releasing intrauterine system (LNG-IUS) for endometriosis-associated symptoms. The first randomised controlled multicentre study by Petta and colleagues randomised 83 patients to either the LNG-IUS or monthly leuprolide acetate (Petta *et al.*, 2005). After six months of treatment both groups had significantly reduced visual analogue pain scores, but no difference was found between the groups. A second study primarily assessed the effect of an LNG-IUS on ASRM stage using a similar regimen as described above (Gomes *et al.*, 2007). However, they also found a significant decrease in pelvic pain scores after six 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). Similar 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 their better side-effect profile.

Conclusion and considerations

There is sufficient evidence on the effectiveness of progestagens and anti-progestagens (gestrinone) in reducing pain in women with endometriosis, including the levonorgestrel-releasing intrauterine system. The GDG and specifically the patient-representative, 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

Rec 2.5	Clinicians are recommended to use progestagens (oral or depot medroxyprogesterone acetate, dienogest, cyproterone acetate or danazol) or anti-progestagens (gestrinone) as one of the options, as they reduce endometriosis-associated pain (Brown *et al.*, 2012).	A
Rec 2.6	Clinicians should take the different side effect profiles of progestagens and anti-progestagens into account when prescribing these drugs.	GPP
Rec 2.7	Clinicians should consider prescribing a levonorgestrel-releasing intrauterine system as one of the options to reduce endometriosis-associated pain (Petta *et al.*, 2005; Gomes *et al.*, 2007; Ferreira *et al.*, 2010).	A

References

Brown J, Kives S, AkhtarM. Progestagens and anti-progestagens for pain associated with endometriosis. Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD002122. DOI: 10.1002/14651858.CD002122.pub2.

Farquhar C, Prentice A, Singla AA, Selak V. Danazol for pelvic pain associated with endometriosis. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD000068.

Ferreira RA, Vieira CS, Rosa-E-Silva JC, Rosa-e-Silva AC, Nogueira AA, Ferriani RA. Effects of the levonorgestrel-releasing intrauterine system on cardiovascular risk markers in patients with endometriosis: a comparative study with the GnRH analogue. Contraception. 2010 Feb;81(2):117-22.

Gomes MK, Ferriani RA, Rosa e Silva JC, Japur de Sá Rosa e Silva AC, Vieira CS, Cândido dos Reis FJ. The levonorgestrel-releasing intrauterine system and endometriosis staging. Fertil Steril. 2007 May;87(5):1231-4.

Kives S, Brown J, Prentice A,Deary A, Bland ES. Progestagens and anti-progestagens for pain associated with endometriosis. Cochrane Database of Systematic Reviews 2000, Issue 2. Art. No.: CD002122.

Petta CA, Ferriani RA, Abrao MS, Hassan D, Rosa E Silva JC, Podgaec S, 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 Jul;20(7):1993-8.

2.1c GnRH agonists

Clinical evidence

A Cochrane review compared GnRH analogues (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). Results suggest that GnRHa are more effective than placebo, but not compared to levonorgestrel-releasing intrauterine system or oral danazol. The review found a worse side effect profile for GnRHa in all studies. According to one study, it appears that no difference exists for dysmenorrhea, pelvic pain, tenderness and induration if women are treated for 3 or 6 months with GnRHa (leuprolide), but dyspareunia is decreased in the shorter protocol (Hornstein *et al.*, 1995). No difference in effectiveness exists when GnRHa are 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 and 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 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 as well as avoiding/minimising menopausal symptoms such as hot flushes, sleep disturbances, 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 (Mäkäräinen *et al.*, 1996), nafarelin plus norethisterone acetate (1,2 mg; NEA) 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 Premarin® 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 without add-back therapy).

A multicentre RCT compared a combined oral contraceptive pill containing 750 µg gestroden and 30 µg ethinylestradiol for 12 months with 4 months of triptorelin (3.75 mg 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 statistics were presented. No significant difference between groups was seen.

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

Conclusion and considerations

From the evidence, 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 GnRH agonist can be recommended over another in relieving endometriosis associated pain.

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

Both the evidence and the patient representative suggest severe side effects of GnRH agonists, which should be discussed with the woman when offering this treatment.

Recommendations

Rec 2.8	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
Rec 2.9	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 (Mäkäräinen *et al.*, 1996;; Bergqvist *et al.*, 1997; Taskin *et al.*, 1997; Moghissi *et al.*, 1998).	A
Rec 2.10	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 their maximum bone density.	GPP

References

Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. Am J Obstet Gynecol. 1992 Feb;166(2):740-5.

Bergqvist A, Jacobson J, Harris S. A double-blind randomized study of the treatment of endometriosis with nafarelin or nafarelin plus norethisterone. Gynecol Endocrinol. 1997 Jun;11(3):187-94.

Brown J, Pan A, Hart RJ. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. Cochrane Database Syst Rev. 2010 Dec 8;12:CD008475.

Hornstein MD, Yuzpe AA, Burry KA, Heinrichs LR, Buttram VL Jr, Orwoll ES. Prospective randomized double-blind trial of 3 versus 6 months of nafarelin therapy for endometriosis associated pelvic pain. Fertil Steril. 1995 May;63(5):955-62.

Mäkäräinen L, Rönnberg L, Kauppila A. Medroxyprogesterone acetate supplementation diminishes the hypoestrogenic side effects of gonadotropin-releasing hormone agonist without changing its efficacy in endometriosis. Fertil Steril. 1996 Jan;65(1):29-34.

Moghissi KS, Schlaff WD, Olive DL, Skinner MA, Yin H. Goserelin acetate (Zoladex) with or without hormone replacement therapy for the treatment of endometriosis. Fertil Steril. 1998 Jun;69(6):1056-62

Parazzini F, Di Cintio E, Chatenoud L, Moroni S, Ardovino I, Struzziero E, Falsetti L, Bianchi A, Bracco G, Pellegrini A, Bertulessi C, Romanini C, Zupi E, Massobrio M, Guidetti D, Troiano L,

Beretta P, Franchi M. Estroprogestin vs. gonadotrophin agonists plus estroprogestin in the treatment of endometriosis-related pelvic pain: a randomized trial. Eur J Obstet Gynecol Reprod Biol. 2000 Jan;88(1):11-4.

Taskin O, Yalcinoglu AI, Kucuk S, Uryan I, Buhur A, Burak F. Effectiveness of tibolone on hypoestrogenic symptoms induced by goserelin treatment in patients with endometriosis. Fertil Steril. 1997 Jan;67(1):40-5.

Zhao SZ, Kellerman LA, Francisco CA, Wong JM. Impact of nafarelin and leuprolide for endometriosis on quality of life and subjective clinical measures. J Reprod Med. 1999 Dec;44(12):1000-6.

2.1d Aromatase inhibitors

Clinical evidence

Two systematic reviews looked at the potential usefulness of aromatase inhibitors for the treatment of endometriosis-associated pain (Patwardhan *et al.*, 2008; Ferrero *et al.*, 2011). Patwardhan *et al*. identified five studies of which all but one 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 *et al*. performed another systematic review including seven studies, two of which from the author's 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 (250 µg daily) or orally (1 mg 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 conclude 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 the 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 that both evaluated mostly non-randomised 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 the evidence on the long-term effect 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

Rec 2.11	In women with pain from rectovaginal endometriosis, refractory to other medical or surgical treatment, clinicians can consider prescribing aromatase inhibitors in combination with progestagens, the oral contraceptive pill or GnRH analogues, as they reduce endometriosis-associated pain (Patwardhan *et al.*, 2008; Ferrero *et al.*, 2011).	B

References

Ferrero S, Gillott DJ, Venturini PL, Remorgida V. Use of aromatase inhibitors to treat endometriosis-related pain symptoms: a systematic review. Reprod Biol Endocrinol. 2011 Jun 21;9:89.

Patwardhan S, Nawathe A, Yates D, Harrison GR, Khan KS. Systematic review of the effects of aromatase inhibitors on pain associated with endometriosis. BJOG. 2008 Jun;115(7):818-22.

2.2 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 one 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 (275 mg, four times per day) with placebo (four times per day) in 24 women with stage II-IV endometriosis (for a total of 4 months) (Kauppila *et al.*, 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 show whether non-steroidal anti-inflammatory drugs (NSAIDs) (naproxen sodium) are effective for the treatment of pain caused by endometriosis (Allen *et al.*, 2009).

A study that was not included in the systematic review used an oral COX-2 inhibitor (rofecoxib) versus control for 6 months in 28 patients (Cobelis *et al.*, 2004). The authors reported that dysmenorrhea, dyspareunia and chronic pelvic pain were significantly reduced in the rofecoxib group 6 months after the end of treatment ($P<0.001$) versus placebo. No side effects were found.

No further trials for any analgesics were available.

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 from one study published in 1985. A more recent study discussed the COX2 inhibitor rofecoxib, but this has been withdrawn from the market in some European countries due to severe side effects. However, there exists 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.

In conclusion, the effectiveness of NSAIDs (naproxen) in treating endometriosis-associated dysmenorrhea is not well established owing to a lack of studies (Kauppila *et al.*, 1985). Nevertheless, the GDG came to the following recommendation due to the known benefit of NSAIDs in primary dysmenorrhea.

Recommendation

Rec 2.12	The GDG recommends that clinicians should consider NSAIDs or other analgesics to reduce endometriosis-associated pain.	GPP

References

Allen C, Hopewell S, Prentice A, Gregory D. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD004753.

Cobellis L, Razzi S, De Simone S, Sartini A, Fava A, Danero S, Gioffrè W, Mazzini M, 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 Sep 10;116(1):100-2.

Kauppila A, Ronnberg L. Naproxen sodium in dysmenorrhoea secondary to endometriosis. Obstetrics and Gynaecology 1985;65(3): 379–83.

Marjoribanks J, Proctor M, Farquhar C, Derks RS. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD001751. DOI: 10.1002/14651858.CD001751.pub2.

2.3 Surgery for treatment of endometriosis-associated pain

Introduction

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

Key question

Is surgery effective for painful symptoms associated with endometriosis?

2.3a Laparotomy - laparoscopy for treatment of endometriosis-associated pain

Clinical evidence

A non-randomised report showed that both 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 by Jacobson analysed five RCTs, which

compared surgical treatment of endometriosis with diagnostic laparoscopy or medical treatment (Jacobson *et al.*, 2009). This Cochrane review showed significant benefit of laparoscopic surgery 6 and 12 months after the operation, whilst there was no significant difference compared to diagnostic laparoscopy at 3 months. In these five trials the method of treatment was either excision, coagulation or laser vaporisation of endometriotic lesions. The 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. There were no major complications in the studies included in this review.

Conclusion and considerations

Laparotomy and laparoscopy are equally effective in the treatment of endometriosis-associated pain. Operative laparoscopy (excision/ablation of endometriosis) is more effective for the treatment of pelvic pain associated with all stages of endometriosis compared to diagnostic laparoscopy only. Laparoscopic surgery is usually associated with less pain, shorter hospital stay and quicker recovery as well as better cosmesis, hence it is usually preferred to open surgery. However, if the relevant experience with laparosopcic surgery is not available, laparotomy may be performed or referral to a centre where this experience is available.

Recommendation

Rec 2.13	When endometriosis is identified at laparoscopy, clinicians should consider surgical treatment as it 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, Imparato E. Laparoscopy versus laparotomy in conservative surgical treatment for severe endometriosis. Fertil Steril. 1996 Nov;66(5):706-11.

Jacobson TZ, Duffy JMN, Barlow D, Koninckx PR, Garry R. Laparoscopic surgery for pelvic pain associated with endometriosis. Cochrane Database of Systematic Reviews 2009, Issue 4. Art.No.: CD001300.

Sutton CJ, Ewen SP, Whitelaw N, 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 Oct;62(4):696-700.

2.3b Ablation versus excision of endometriosis

Clinical evidence

A small RCT showed that both 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 and how ovarian cysts were treated. Furthermore, the excision group had higher scores according to the American Fertility Society (AFS).

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 and another larger study with suboptimal design, hence their conclusions should be interpreted with caution. Ablative techniques are unlikely to be suitable for advanced forms of endometriosis with DIE component.

Recommendation

Rec 2.14	Clinicians may consider both ablation and excision of peritoneal endometriotic spots to reduce endometriosis-associated pain. (Wright *et al.*, 2005; Healey *et al.*, 2010)	C

References

Healey M, Ang WC, Cheng C. Surgical treatment of endometriosis: a prospective randomized double-blinded trial comparing excision and ablation. Fertil Steril. 2010 Dec;94(7):2536-40.

Wright J, Lotfallah H, Jones K, Lovell D. A randomized trial of excision versus ablation for mild endometriosis. Fertil Steril. 2005 Jun;83(6):1830-6.

2.3c Surgical interruption of pelvic nerve pathways

Clinical evidence

Proctor *et al.* analysed the effectiveness of surgical interruption of pelvic nerve pathways in primary and secondary dysmenorrhea within a Cochrane review that included six RCTs on women with endometriosis (Proctor *et al.*, 2010). Three of these RCTs evaluated the effect of laparoscopic uterosacral nerve ablation (LUNA) together with conservative laparoscopic surgery for endometriosis and the other three studied the effect of presacral neurectomy (PSN) (two at laparotomy, one at laparoscopy) in addition to conservative surgery for endometriosis. The RCTs on LUNA showed that LUNA did not offer any additional benefit as an adjunct to conservative surgery one year after surgery. The 6 months assessment did not show any benefit either, but this included one additional trial including patients who had fibroids. There was significant benefit 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.*, 2010). Data suggested that the effect of PSN may be specific to midline pain only.

Conclusion and considerations

From the evidence, it can be concluded that laparoscopic uterosacral nerve ablation (LUNA) is not recommended as an additional procedure to conservative surgery for endometriosis, as this offers no additional benefit as compared to surgery alone (Proctor *et al.*, 2010).

There is a benefit of presacral neurectomy (PSN) for treatment of endometriosis related 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

Rec 2.15	Clinicians should not perform laparoscopic uterosacral nerve ablation (LUNA) as an additional procedure to conservative surgery to reduce endometriosis-associated pain (Proctor *et al.*, 2010).	A

Rec 2.16	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.*, 2010).	A

References

Proctor M, Latthe P, Farquhar C, Khan K, Johnson N. Surgical interruption of pelvic nerve pathways for primary and secondary dysmenorrhoea. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD001896.

2.3d Surgery for treatment of pain associated with ovarian endometrioma

Clinical evidence

A Cochrane review by Hart *et al.* reviewed two RCTs comparing laparoscopic excision of ovarian endometriotic cysts of 3 cm or larger, compared to drainage and coagulation by bipolar diathermy (Hart *et al.*, 2008, last updated 2011). Both studies demonstrated lower recurrence of dysmenorrhea and dyspareunia after cystectomy compared to drainage and coagulation only. There were fewer cyst recurrences after 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 and 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 as opposed 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 method was quicker, had shorter haemostasis times and it 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

It can be concluded that 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. Furthermore, cystectomy is probably more effective than CO_2 laser vaporization in women with ovarian endometrioma (≥3cm) with regard to recurrence of endometrioma.

Recommendations

Rec 2.17	Clinicians should perform cystectomy in women with ovarian endometrioma (> 3cm) instead of drainage and coagulation, as it reduces endometriosis-associated pain (Hart *et al.*, 2008, last updated 2011).	A

Rec 2.18	Clinicians can consider performing cystectomy rather than CO_2 laser vaporization in women with ovarian endometrioma (> 3cm), because of a lower recurrence rate (Carmona *et al.*, 2011).	B

References

Busacca M, Riparini J, Somigliana E, Oggioni G, Izzo S, Vignali M, Candiani M. Postsurgical ovarian failure after laparoscopic excision of bilateral endometriomas. Am J Obstet Gynecol. 2006 Aug;195(2):421-5.

Carmona F, Martínez-Zamora MA, Rabanal A, Martínez-Román S, Balasch J. Ovarian cystectomy versus laser vaporization in the treatment of ovarian endometriomas: a randomized clinical trial with a five-year follow-up. Fertil Steril. 2011 Jul;96(1):251-4.

Hart RJ, Hickey M, Maouris P, Buckett W. Excisional surgery versus ablative surgery for ovarian endometriomata. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD004992. *(Publication status and date: Edited (no change to conclusions), published in Issue 5, 2011.)*

Mossa B, Ebano V, Tucci S, Rega C, Dolce E, Frega A, Marziani R. Laparoscopic surgery for the management of ovarian endometriomas. Med Sci Monit. 2010 Apr;16(4):MT45-50.

2.3e Surgery for treatment of pain associated with deep infiltrating endometriosis

Clinical evidence

Deep infiltrating endometriosis (DIE) extends more than 5 mm beneath the peritoneum and may affect the uterosacral ligaments, pelvic side walls, rectovaginal septum, vagina, bowel, bladder or ureters. Excision of these nodules is usually performed when surgical treatment is chosen. Colorectal involvement is not rare with DIE and the treatment approaches to this condition includes superficial shaving, discoid resection or segmental resection of the bowel to remove the DIE nodules. There have been a large number of case series published in the literature with these methods since late 1980s. A systematic review by Meuleman *et al*. looked at 49 articles published on this subject, including laparoscopic, laparotomic, transvaginal or combined approaches. They found that a pain and quality of life (QoL) 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 as a proposal to standardize the reports of surgical trials for deep infiltrative endometriosis (Meuleman *et al*., 2011a).

Another systematic review by De Cicco *et al*. 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 DIE 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, the journals should adopt a standard way of reporting of indications, surgery, outcome, size and localisation of nodule. Common use of bowel resection may be due to presence of bowel surgeons who are used to resections for cancer treatment (De Cicco *et al*., 2011).

Surgery for DIE appears possible and effective but is associated with significant complication rates, particularly when rectal surgery is required. The reported total intra-operative complication rate is 2.1% and total postoperative complication rate 13.9% (9.5% minor, 4.6% major complications) (Kondo *et al*., 2011). There is an ongoing debate about the indication for shaving nodules as opposed to segmental resection (Donnez *et al*., 2010; Meuleman *et al*., 2011b).

Conclusion and considerations

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

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

Recommendations

Rec 2.19	Clinicians can consider performing surgical removal of deep infiltrating endometriosis, as it reduces endometriosis-associated pain and improves quality of life (Meuleman *et al.*, 2011a; De Cicco *et al.*, 2011).	B

Rec 2.20	The GDG recommends that clinicians refer women with suspected or diagnosed deep infiltrating endometriosis to an expert centre that offers all available treatments in a multidisciplinary context, including advanced operative laparoscopy or laparotomy.	GPP

References

De Cicco C, Corona R, Schonman R, Mailova K, Ussia A, Koninckx P. Bowel resection for deep endometriosis: a systematic review. BJOG. 2011 Feb;118(3):285-91.

Donnez J, Squifflet J. Complications, pregnancy and recurrence in a prospective series of 500 patients operated on by the shaving technique for deep rectovaginal endometriotic nodules. Hum Reprod. 2010 Aug;25(8):1949-58.

Kondo W, Bourdel N, Tamburro S, Cavoli D, Jardon K, Rabischong B, Botchorishvili R, Pouly J, Mage G, Canis M. Complications after surgery for deeply infiltrating pelvic endometriosis. BJOG. 2011 Feb;118(3):292-8. doi: 10.1111/j.1471-0528.2010.02774.x.

Meuleman C, Tomassetti C, D'Hoore A, Van Cleynenbreugel B, Penninckx F, Vergote I, D'Hooghe T. Surgical treatment of deeply infiltrating endometriosis with colorectal involvement. Hum Reprod Update. 2011a May-Jun;17(3):311-26.

Meuleman C, D'Hoore A, Van Cleynenbreugel B, Tomassetti C, D'Hooghe T. Why we need international agreement on terms and definitions to assess clinical outcome after endometriosis surgery. Hum Reprod. 2011b;26:1598-1599.

2.3f Surgery for treatment of extragenital endometriosis

Clinical evidence

Endometriosis has been found in almost any tissue in the body. Symptoms will 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 again 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 same principles of medical treatment for pelvic endometriosis will 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 is usually in the form of 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. Abdominal wall and perineal endometriosis is usually treated by complete excision of the nodule (Liang *et al.*, 1996; Marinis *et al.*, 2006; Nissotakis *et al.*, 2010; Nezhat *et al.*, 2011; 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 the 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 different tissues and body parts outside the genital tract. Pain is the most common presenting symptom, although a wide range of symptoms can manifest, by extragenital endometriotic lesions. Most of the rare cases of extrapelvic manifestations of endometriosis are published as case reports, or not even documented at all. The same accounts for the treatment, either medical or surgical, of pain related to extrapelvic endometriosis.

Recommendation

Rec 2.21	Clinicians may consider surgical removal of symptomatic extragenital/extrapelvic endometriosis to relieve symptoms (Marinis *et al.*, 2006; Liang *et al.*, 1996; Nisolle *et al.*, 2007; Nissotakis *et al.*, 2010; Nezhat *et al.*, 2011; Song *et al.*, 2011).	D

References

Bergqvist A. Extragenital endometriosis. A review. Eur J Surg. 1992 Jan;158(1):7-12.

Joseph J, Sahn SA. Thoracic endometriosis syndrome: new observations from an analysis of 110 cases. Am J Med. 1996 Feb;100(2):164-70.

Jubanyik KJ, Comite F. Extrapelvic endometriosis. Obstet Gynecol Clin North Am. 1997 Jun;24(2):411-40.

Liang CC, Tsai CC, Chen TC, Soong YK. Management of perineal endometriosis. Int J Gynaecol Obstet. 1996 Jun;53(3):261-5.

Marinis A, Vassiliou J, Kannas D, Theodosopoulos TK, Kondi-Pafiti A, Kairi E, Smyrniotis V. Endometriosis mimicking soft tissue tumors: diagnosis and treatment. Eur J Gynaecol Oncol. 2006;27(2):168-70.

Nezhat C, Hajhosseini B, King LP. Robotic-assisted laparoscopic treatment of bowel, bladder, and ureteral endometriosis. JSLS. 2011 Jul-Sep;15(3):387-92.

Nisolle M, Pasleau F, Foidart JM. [Extragenital endometriosis]. J Gynecol Obstet Biol Reprod (Paris). 2007 Apr;36(2):173-8.

Nissotakis C, Zouros E, Revelos K, Sakorafas GH. Abdominal wall endometrioma: a case report and review of the literature. AORN J. 2010 Jun;91(6):730-42; quiz 743-5.

Song JY, Borncamp E, Mehaffey P, Rotman C. Large abdominal wall endometrioma following laparoscopic hysterectomy. JSLS. 2011 Apr-Jun;15(2):261-3.

Veeraswamy A, Lewis M, Mann A, Kotikela S, Hajhosseini B, Nezhat C. Extragenital endometriosis. Clin Obstet Gynecol. 2010 Jun;53(2):449-66.

Victory R, Diamond MP, Johns DA. Villar's nodule: a case report and systematic literature review of endometriosis externa of the umbilicus. J Minim Invasive Gynecol. 2007 Jan-Feb;14(1):23-32.

2.3g Adhesion prevention after endometriosis surgery

Clinical evidence

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 (Interceed®) after laparoscopic surgery for endometriosis compared with endometriosis surgery only (Ahmad *et al.*, 2008). Although both studies included relatively small numbers of patients, they both showed significant reduction in adhesion formation rate at second look laparoscopy.

A multicentre RCT on 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 defined as the percentage of patients in whom the number of sites with adhesions is decreased by at least three or 30% of the number of sites lysed reached significance only for patients with more than 6 sites treated endometriosis (39% vs. 15%). For patients with primary diagnosis of infertility and endometriosis the AFS scores were reduced in 54% of the patients in the Icodextrin group as opposed to 24% in the LRS group. However, clinical success and AFS category did not significantly differ in 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 which 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 is based on a small number of studies, with limited patients per study.

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. The more recent trial did not show any benefit of Icodextrin (Trew *et al.*, 2011). Furthermore, the studies were sponsored by the manufacturer. Hence the guideline development group has decided not to recommend icodextrin for adhesion prevention.

Recommendations

Rec 2.22	Clinicians can use oxidised regenerated cellulose during operative laparoscopy for endometriosis, as it prevents adhesion formation (Ahmad *et al.*, 2008).	B
Rec 2.23	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

References

Ahmad G, Duffy JMN, Farquhar C, Vail A, Vanderkerchove P, Watson A, Wiseman D. Barrier agents for adhesion prevention after gynaecological surgery. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD000475.

Brown CB, Luciano AA, Martin D, Peers E, Scrimgeour A, diZerega GS; Adept Adhesion Reduction Study Group. Adept (icodextrin 4% solution) reduces adhesions after laparoscopic surgery for adhesiolysis: a double-blind, randomized, controlled study. Fertil Steril. 2007 Nov;88(5):1413-26.

Trew G, Pistofidis G, Pados G, Lower A, Mettler L, Wallwiener D, Korell M, Pouly JL, Coccia ME, Audebert A, Nappi C, Schmidt E, McVeigh E, Landi S, Degueldre M, Koninckx P, Rimbach S, Chapron C, Dallay D, Röemer T, McConnachie A, Ford I, Crowe A, Knight A, Dizerega G, Dewilde R. Gynaecological endoscopic evaluation of 4% icodextrin solution: a European, multicentre, double-blind, randomized study of the efficacy and safety in the reduction of de novo adhesions after laparoscopic gynaecological surgery. Hum Reprod. 2011 Aug;26(8):2015-27.

2.3 Medical therapies adjunct to surgery for treatment of endometriosis-associated pain

Key question

Are medical therapies effective as an adjunct to surgical therapy 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, last updated in 2011).

With regard to preoperative treatment, the available literature was limited with only two studies, both studying women of reproductive age (women < 35 and women between 18 and 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 six months. Both these studies also 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 rAFS 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 which was no different (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 additional benefit of preoperative treatment but they did note both trials were considered to be at high risk of bias and this may be reflected in their cautious conclusions (Furness *et al.*, 2004, last updated in 2011).

In the same Cochrane review, twelve studies were considered in the assessment of postoperative treatment in patients undergoing surgery for pain. These comprised of 5 studies with a postoperative placebo arm and 7 with a postoperative no treatment arm. The consensus from the included trials was that there was some reduction in pain at twelve 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 analysis demonstrated no benefit during either time period (1st year RR 0.76 95% CI 0.52 – 1.1, 2nd year RR 0.70 95% CI 0.47 -1.03). Disease recurrence assessed either laparoscopically (1 study) or on clinical examination or by scan (2 studies) also demonstrated no benefit in postoperative medical treatment. One study documented increased patient satisfaction in both of its treatment arms compared with placebo (Furness *et al.*, 2004, last updated in 2011).

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 pre- or postoperative medical therapy in women undergoing surgery for endometriosis-associated pain.

Conclusion and considerations

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

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 surgery, not to reduce pain after surgery.

Recommendations

Rec 2.24	Clinicians should not prescribe preoperative hormonal treatment to improve the outcome of surgery for pain in women with endometriosis (Furness *et al.*, 2004, last updated in 2011).	A
Rec 2.25	Clinicians should not prescribe adjunctive hormonal treatment in women with endometriosis, after surgery for endometriosis-associated pain, as it does not improve the outcome of surgery for pain (Furness *et al.*, 2004, last updated in 2011).	A
Rec 2.26	The GDG recommends that clinicians clearly distinguish between relatively short-term adjunctive hormonal treatment within six months after surgery as opposed to longer-term hormonal treatment aimed at secondary prevention.	GPP

References

Furness S, Yap C, Farquhar C, Cheong YC. Pre and post-operative medical therapy for endometriosis surgery. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD003678. DOI: 10.1002/14651858.CD003678.pub2 *(New search for studies and content updated (no change to conclusions), published in Issue1, 2011)*

2.4 Secondary prevention of endometriosis

Introduction

Secondary prevention is defined as interventions aimed at stopping or slowing down the progress of the disease after the diagnosis has been established. In the context of this guideline, secondary prevention was defined as interventions to prevent 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 endometriomata or by laparoscopy for all endometriosis lesions) in the long term, defined as more than 6 months after surgery, as opposed to 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 an operative laparoscopy for endometriosis, recurrence of dysmenorrhea was lower in the group receiving levonorgestrel-releasing intrauterine system (LNG-IUS) postoperatively than in the control group receiving expectant management (Abou-Setta *et al.*, 2006).

In women operated 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, last updated in 2011); Lu *et al.*, 2009).

In women operated for an endometrioma of 3 cm or more, when compared to drainage and electrocoagulation, ovarian cystectomy is associated with a reduced recurrence of dysmenorrhea, dyspareunia and non-menstrual pelvic pain (Hart *et al.*, 2008, last updated 2011).

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

In women with surgically treated endometriosis, including ovarian cystectomy if an endometrioma was present, postoperative oral contraceptive use during more than 6 months up 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 during 6 months only, when used 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 modulated according to patient preferences. The protective effect seems to be related to the duration of treatment (Serrachioli *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 and 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, they can use regularly oral contraceptives for the secondary prevention of ultrasound-diagnosed endometrioma.

In a general population of women operated 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, but without 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

Rec 2.27	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 preferences, costs, availability and side effects. For many interventions that might be considered here, there are limited data.	GPP
Rec 2.28	In women operated for an endometrioma of 3 cm or more, 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, last updated 2011).	A
Rec 2.29	After cystectomy for ovarian endometrioma in women not immediately seeking conception, clinicians should consider prescribing oral contraceptives, for the secondary prevention of ultrasound-diagnosed endometrioma (Vercellini *et al.*, 2010).	A

Rec 2.30	In women operated for endometriosis, including cystectomy for ovarian endometrioma, clinicians should consider prescribing postoperative use of a levonorgestrel-releasing intrauterine system or combined oral 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

References

Abou-Setta AM, Al-Inany HG, Farquhar C. Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery. Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD005072.

Furness S, Yap C, Farquhar C, Cheong YC. Pre and post-operative medical therapy for endometriosis surgery. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD003678. DOI: 10.1002/14651858.CD003678.pub2 *(New search for studies and content updated (no change to conclusions), published in Issue1, 2011)*

Hart RJ, Hickey M,Maouris P, BuckettW. Excisional surgery versus ablative surgery for ovarian endometriomata. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD004992. DOI: 10.1002/14651858.CD004992.pub3. *(Publication status and date: Edited (no change to conclusions), published in Issue 5, 2011.)*

Lu D, Song H, Li Y, Clarke J, Shi G. Pentoxifylline versus medical therapies for subfertile women with endometriosis. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD007677. DOI: 10.1002/14651858.CD007677.pub2.

Seracchioli R, Mabrouk M, Manuzzi L, Vicenzi C, Frascà C, Elmakky A, Venturoli S. Post-operative use of oral contraceptive pills for prevention of anatomical relapse or symptom-recurrence after conservative surgery for endometriosis. Hum Reprod. 2009 Nov;24(11):2729-35.

Vercellini P, Somigliana E, Viganò P, De Matteis S, Barbara G, Fedele L. Post-operative endometriosis recurrence: a plea for prevention based on pathogenetic, epidemiological and clinical evidence. Reprod Biomed Online. 2010 Aug;21(2):259-65.

2.5 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, last updated in 2010). Similarly, there are no data to indicate that dietary supplements are useful in controlling the pain symptom of endometriosis, although one low quality RCT suggested that a combination diet was of 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 the pain after surgical treatment of endometriosis. Another Cochrane review looked at the place of acupuncture in the treatment of pain in endometriosis. Only one small RCT was included and 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.*, 2009). Hence, this review concluded that evidence to support use of acupuncture for pain in endometriosis was limited.

There are no data to support the use of neuromodulators, anaesthesia, behavioural therapy, expert patient programmes, recreational drugs, reflexology, homeopathy, psychological therapy and 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, nutrition (including dietary supplements, vitamins, and minerals), expert patient programmes, recreational drugs, reflexology, homeopathy, psychological therapy, Traditional Chinese Medicine, 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 can conclude that the effectiveness of high- frequency transcutaneous electrical nerve stimulation, dietary supplements, acupuncture and traditional Chinese medicine are not well established for pain management in endometriosis. However, the guideline development group acknowledges that alternative and complementary therapies are often used, additional to traditional Western therapies, by women with endometriosis in an attempt to increase their quality of life.

Taken these considerations into account, the GDG reached the following good practice point on the use of complementary and alternative medicine in the treatment of endometriosis-associated pain:

Recommendations

Rec 2.31	The GDG does not recommend the use of nutrition, complementary and alternative medicine in the treatment of endometriosis-associated pain, because potential benefits and/or harms are unclear. However, the GDG acknowledges that some women who seek complementary and alternative medicine may benefit from this.	GPP

References

Astin JA, Marie A, Pelletier KR, Hansen E, Haskell WL. A review of the incorporation of complementary and alternative medicine by mainstream physicians. Arch Intern Med. 1998 Nov 23;158(21):2303-10.

Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, Kessler RC. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. JAMA. 1998 Nov 11;280(18):1569-75.

Flower A, Liu JP, Chen S, Lewith G, Little P. Chinese herbal medicine for endometriosis. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD006568.

Proctor M, Farquhar C, Stones W, He L, Zhu X, Brown J. Transcutaneous electrical nerve stimulation for primary dysmenorrhoea. Cochrane Database of Systematic Reviews 2002, Issue 1. Art. No.: CD002123. DOI: 10.1002/14651858.CD002123. *(Stable (no update expected for reasons given in 'What's new'), published in Issue 1, 2010))*

919 Sesti F, Pietropolli A, Capozzolo T, Broccoli P, Pierangeli S, Bollea MR, Piccione E. Hormonal
920 suppression treatment or dietary therapy versus placebo in the control of painful symptoms
921 after conservative surgery for endometriosis stage III-IV. A randomized comparative trial. Fertil
922 Steril. 2007 Dec;88(6):1541-7.

923 Zhu X, Hamilton KD, McNicol ED. Acupuncture for pain in endometriosis (Protocol). Cochrane
924 Database of Systematic Reviews 2009, Issue 3. Art. No.: CD007864.

925

3. TREATMENT OF ENDOMETRIOSIS-ASSOCIATED INFERTILITY

Introduction

Women with endometriosis are confronted with two major problems being endometriosis-associated pain, infertility, or both. For the reason of clarity the guideline development group decided to separately discuss the evidence focussing on pain as the outcome (chapter 2) and infertility as an outcome in this chapter.

For the literature searches, the outcomes included were live birth rate, pregnancy, multiple pregnancy rates, miscarriage rates, ectopic pregnancy, teratogeneity and side effects of treatment. It should be noted that although live birth rate is the most relevant outcome to be assessed, most studies only report on (biochemical or clinical) pregnancy rates.

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

3.1 Medical therapies for treatment of endometriosis-associated infertility

Key question

Are medical therapies effective for infertility associated with endometriosis?

Clinical evidence

The question of whether medical therapy has a role in the treatment of endometriosis-associated infertility has been thoroughly evaluated in a systematic Cochrane Review (Hughes *et al.*,2007, last updated in 2010). This statement however should be qualified in as much that the review does not evaluate individual medical treatments that are used in the treatment of pain associated with endometriosis but considers as a group all therapies that result in ovarian suppression and thus the assessment, strictly speaking, is of the role of ovarian suppression as a therapeutic modality to improve fertility.

Eighteen studies were included in the Cochrane review, most of which reported conception, pregnancy or clinical pregnancy as surrogate markers for the now accepted relevant end point of live birth rate. Therefore, there is limited reported 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 1.15, 95% CI 0.57 - 2.32). In another comparison gonadotrophin releasing hormone analogues were compared to the combined oral contraceptive pill (n=86, OR 0.69, 95% CI 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 the comparisons where pregnancy is used as the clinical endpoint. These comparisons however do not directly assess whether ovarian suppression per se is an effective intervention but merely reflect that there is no difference between different drugs in their effect on live birth rates (Hughes *et al.*, 2007, last updated in 2010).

Hughes and his colleagues have reported two comparisons of active drug against placebo or no treatment. The first of these includes all drugs and the second includes all drugs with the exception of Danazol. In both comparisons there was no significant difference in pregnancy rates (OR 1.02, 95% CI 0.69 - 1.52 and OR 1.10, 95% CI 0.70 - 1.73 respectively). Thus, it is clear that as a sole treatment for infertility recognized medical therapies for endometriosis that suppress ovulation are an ineffective therapy and should not be used.

Conclusion and considerations

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

The best quality evidence for this section is a Cochrane review (Hughes *et al.*, 2007, last updated in 2010) of high quality but limited by the underlying quality of the included trials of which most (14/18 trials) 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 the paucity of data relating to live births and thus the majority of conclusions are based on conception, pregnancy or clinical pregnancy as surrogate markers. Equally, there is a significant lack of reported data on adverse pregnancy outcomes such as miscarriage and ectopic pregnancy.

Recommendation

Rec 3.1	In infertile women with endometriosis, clinicians should not prescribe medical treatment for suppression of ovarian function to improve fertility (Hughes *et al.*,2007, last updated in 2010).	A

References

Hughes E, Brown J, Collins JJ, Farquhar C, Fedorkow DM, Vanderkerchove P. Ovulation suppression for endometriosis for women with subfertility. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD000155. DOI: 10.1002/14651858.CD000155.pub2. *(Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 1, 2010.)*

3.2 Surgery for treatment of endometriosis-associated infertility

Key question

Is surgery effective for infertility associated with endometriosis?

Clinical evidence

In patients with minimal to mild endometriosis (rAFS classification), operative laparoscopy including adhesiolysis is effective in increasing the live birth rate when compared to diagnostic laparoscopy (Jacobson *et al.*, 2010). These data are supported by the data from another well-designed RCT (Nowroozi *et al.*, 1987), not included in the Cochrane review by Jacobson and colleagues, only 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, although there is limited evidence in women with endometriosis as their major cause of infertility that the postoperative cumulative pregnancy rate after 36 months is higher after treatment with CO_2 laser vaporization with or without resection of endometriosis (87%) than after treatment with monopolar electrocoagulation (71%), by diagnostic laparoscopy (65%), or by diagnostic laparoscopy followed by 3 months treatment with danazol 800 mg/day (63%) (Chang *et al.*, 1997, pseudo RCT to be considered as prospective controlled cohort study).

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 limited to 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 is reported to be 48% in a review paper (Candiani *et al.*, 1991). According to 2 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 is 57-69% (moderate endometriosis) and 52-68% (severe endometriosis) (Nezhat *et al.*, 1989; Vercellini *et al.*, 2006). 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.*, 2006). Overall, these data suggest that laparoscopic surgery is effective for the treatment of infertility associated with moderate-severe endometriosis.

In patients with ovarian endometrioma receiving surgery for infertility or pain, excision of endometrioma capsule increases the spontaneous postoperative pregnancy rate when compared to drainage and electrocoagulation of the endometrioma wall (Hart *et al.*, 2008, last updated in 2011).

In women with infertility and severe pelvic pain, resistant to medical treatment or associated with 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), but this difference was not significant (P=0.57 for all

pregnancies; P=0.17 for spontaneous pregnancies only) (Stepniewska *et al.*, 2009 and 2010, both retrospective controlled cohort studies).

Conclusion and considerations

In women with minimal to mild endometriosis, the evidence, summarized in a Cochrane review, shows that operative laparoscopy is more effective than diagnostic laparoscopy in improving live birth rate. 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 2 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 a much lower crude pregnancy rate of 33% (moderate endometriosis) and 0% (severe endometriosis) after expectant management.

Recommendations

Rec 3.2	In infertile women with AFS/ASRM stage I/II endometriosis, clinicians should perform operative laparoscopy (excision or ablation of the endometriotic lesions) including adhesiolysis, rather than performing diagnostic laparoscopy only, to increase the live birth rate (Nowroozi *et al.*, 1987; Jacobson *et al.*, 2010).	A
Rec 3.3	In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may consider CO_2 laser vaporization of endometriosis, instead of monopolar electrocoagulation, since this is associated with higher cumulative spontaneous pregnancy rates (Chang *et al.*, 1997).	C
Rec 3.4	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 the spontaneous pregnancy rate (Hart *et al.*, 2008, last updated in 2011).	A
Rec 3.5	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.*, 2006).	B

References

Candiani GB, Vercellini P, Fedele L, Bianchi S, Vendola N, Candiani M. Conservative surgical treatment for severe endometriosis in infertile women: are we making progress? Obstet Gynecol Surv. 1991 Jul;46(7):490-8.

Chang FH, Chou HH, Soong YK, Chang MY, Lee CL, Lai YM. Efficacy of isotopic $13CO_2$ laser laparoscopic evaporation in the treatment of infertile patients with minimal and mild endometriosis: a life table cumulative pregnancy rates study. J Am Assoc Gynecol Laparosc. 1997 Feb;4(2):219-23.

Hart RJ, Hickey M, Maouris P, Buckett W. Excisional surgery versus ablative surgery for ovarian endometriomata. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD004992. DOI: 10.1002/14651858.CD004992.pub3. *(Publication status and date: Edited (no change to conclusions), published in Issue 5, 2011.)*

Jacobson TZ, Duffy JMN, Barlow D, Farquhar C, Koninckx PR, Olive D. Laparoscopic surgery for subfertility associated with endometriosis. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD001398.

Nezhat C, Crowgey S, Nezhat F. Videolaseroscopy for the treatment of endometriosis associated with infertility. Fertil Steril. 1989 Feb;51(2):237-40.

Nowroozi K, Chase JS, Check JH, Wu CH. The importance of laparoscopic coagulation of mild endometriosis in infertile women. Int J Fertil. 1987 Nov-Dec;32(6):442-4.

Olive DL, Stohs GF, Metzger DA, Franklin RR. Expectant management and hydrotubations in the treatment of endometriosis-associated infertility. Fertil Steril 1985;44:35-42.

Stepniewska A, Pomini P, Bruni F, Mereu L, Ruffo G, Ceccaroni M, Scioscia M, Guerriero M, Minelli L. Laparoscopic treatment of bowel endometriosis in infertile women. Hum Reprod. 2009 Jul;24(7):1619-25.

Stepniewska A, Pomini P, Guerriero M, Scioscia M, Ruffo G, Minelli L. Colorectal endometriosis: benefits of long-term follow-up in patients who underwent laparoscopic surgery. Fertil Steril. 2010 May 1;93(7):2444-6.

Vercellini P, Pietropaolo G, De Giorgi O, Daguati R, Pasin R, Crosignani PG. Reproductive performance in infertile women with rectovaginal endometriosis: is surgery worthwhile? Am J Obstet Gynecol. 2006 Nov;195(5):1303-10.

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

Key question

Are medical therapies effective as an adjunct to surgical therapy for treatment of infertility?

Clinical evidence

The role of pre- and postoperative medical therapy in relation to the management of cyst, pain and infertility has been assessed in a Cochrane review by Furness and colleagues (Furness *et al.*, 2004, last updated in 2011). Two studies on preoperative medical therapy were included in the review, but these two studies did not evaluate any outcomes regarding infertility.

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

Conclusion and considerations

For postoperative medical treatment, the existing evidence, which mostly results from low quality studies, is summarized in a Cochrane review. In the same review, no studies were found reporting on the effect of preoperative hormonal treatment on infertility after surgery. Furthermore, preoperative hormonal treatment was not shown to facilitate surgery for endometriosis. Considering that hormonal treatments were found not to be effective for improving infertility without surgery and that they have severe side effects, pre- or postoperative hormonal treatments are not recommended for improving infertility.

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 postoperative medical therapy in women undergoing surgery for endometriosis-associated infertility.

Recommendations

Rec 3.6	In infertile women with endometriosis, the GDG recommends clinicians not to prescribe adjunctive hormonal treatment before surgery, as suitable evidence is lacking.	GPP
Rec 3.7	In infertile women with endometriosis, clinicians should not prescribe adjunctive hormonal treatment after surgery to improve spontaneous pregnancy rates (Furness *et al.*, 2004, last updated in 2011).	A

References

Furness S, Yap C, Farquhar C, Cheong YC. Pre and post-operative medical therapy for endometriosis surgery. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD003678. DOI: 10.1002/14651858.CD003678.pub2 *(New search for studies and content updated (no change to conclusions), published in Issue1, 2011)*

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

In spite of conventional medicine, complementary and alternative medicine is used in pursuit of health and well being more often (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 within the field of endometriosis (Chan, 2008). Furthermore, reports on a possible role for recreational drugs, physical exercise and behavioural or psychological treatment as management strategy for endometriosis-associated infertility are also lacking.

Therefore, randomised 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 literature search, the following interventions can be considered for future study: antioxidant therapy (Agarwal *et al.*, 2005), Chinese herbal medicine (Xu *et al.*, 2003; Zhou and Qu, 2009; Burks-Wicks *et al.*, 2007), 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, nutrition (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 nutrition, 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 their quality of life and their coping with the disease and the traditional treatments. Furthermore, there is no evidence on a harmful effect of these therapies.

Recommendation

Rec 3.8	The GDG does not recommend the use of nutrition, complementary and alternative medicine in the treatment of endometriosis-associated infertility, because potential benefits and/or harms are unclear. However, the GDG acknowledges that some women who seek complementary and alternative medicine may benefit from this.	GPP

References

Agarwal A, Gupta S, Sharma RK. Role of oxidative stress in female reproduction. Reprod Biol Endocrinol. 2005 Jul 14;3:28.

Burks-Wicks C, Cohen M, Fallbacher J, N Taylor R, Wieser F. A Western primer of Chinese herbal therapy in endometriosis and infertility. Womens Health (Lond Engl). 2005 Nov;1(3):447-63.

Chan E. Quality of efficacy research in complementary and alternative medicine. JAMA. 2008 Jun 11;299(22):2685-6.

Gerhard I, Postneek F. Auricular acupuncture in the treatment of female infertility. Gynecol Endocrinol. 1992 Sep;6(3):171-81.

Harris P, Rees R. The prevalence of complementary and alternative medicine use among the general population: a systematic review of the literature. Complement Ther Med. 2000 Jun;8(2):88-96.

Wurn BF, Wurn LJ, King CR, Heuer MA, Roscow AS, Hornberger K, Scharf ES. Treating fallopian tube occlusion with a manual pelvic physical therapy. Altern Ther Health Med. 2008 Jan-Feb;14(1):18-23.

Xu X, Yin H, Tang D, Zhang L, Gosden RG. Application of traditional Chinese medicine in the treatment of infertility. Hum Fertil (Camb). 2003 Nov;6(4):161-8.

Zhou J, Qu F. Treating gynaecological disorders with traditional Chinese medicine: a review. Afr J Tradit Complement Altern Med. 2009 Jul 3;6(4):494-517.

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 procedures, and intrauterine (IUI), intracervical, and intravaginal insemination with semen of husband/partner or donor. Therefore, MAR includes IUI and ART.

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 have been 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 that deserve an updated assessment of the literature.

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

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 Technology; World Health Organization: The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology 2009.Hum Reprod 2009;24: 2683-2687.

Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, Sullivan E, Vanderpoel S; International Committee for Monitoring Assisted Reproductive Technology; World Health Organization: International Committee for Monitoring Assisted Reproductive Technology (ICMART)and the World Health Organization (WHO) revised glossary of ART terminology,2009.

4.1 Medically assisted reproduction in women with endometriosis

Key question

Is medically assisted reproduction effective for infertility associated with endometriosis?

4.1a Intrauterine insemination in women with endometriosis

Clinical evidence

The efficacy of controlled ovarian stimulation (COS) with gonadotrophins and intrauterine insemination (IUI) was assessed in a RCT including 103 couples with minimal/mild endometriosis, 53 of them having the treatment and 50 being 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 randomised and subsequently longitudinal study, Nulsen *et al.* 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 *et al.* compared one cycle of clomiphene citrate + HMG/FSH with HMG/FSH plus 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). The pregnancy rates (PR) were 33.6% and 16.3%, respectively ($p<0.05$) (Omland *et al.*, 1998). However, in a case control study the pregnancy rates following COS + homologous insemination were as high in women with minimal or mild endometriosis within 6 months of surgical treatment as in the control group with unexplained infertility (PR/cycle 20% vs. 20.5%) (Werbrouck *et al.*, 2006).

Kim *et al.*, in a RCT, compared the use of long (LP) and ultra long protocols (ULP) of GnRH agonist in the COS prior to IUI in 80 women with 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 19.0% (4/21) in the LP group (Kim *et al.*, 1996).

The influence of the presence 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, including 24 women with minimal endometriosis and 51 without endometriosis the pregnancy rate was 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, intrauterine insemination with controlled ovarian stimulation may be effective in increasing live birth rate when compared with expectant management. Furthermore, intrauterine insemination with gonadotrophins controlled ovarian stimulation may be more effective in increasing pregnancy rate than intrauterine insemination alone.

Intrauterine insemination with controlled ovarian stimulation may be as effective in women with minimal or mild endometriosis within 6 months of surgical treatment as in unexplained infertility.

Recommendations

Rec 4.1	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 rate (Tummon *et al.*, 1997).	C
Rec 4.2	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
Rec 4.3	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

References

Kim CH, Cho YK, Mok JE. Simplified ultralong protocol of gonadotrophin-releasing hormone agonist for ovulation induction with intrauterine insemination in patients with endometriosis. Hum Reprod. 1996 Feb;11(2):398-402.

Matorras R, Corcóstegui B, Esteban J, Ramón O, Prieto B, Expósito A, Pijoan JI. Fertility in women with minimal endometriosis compared with normal women was assessed by means of a donor insemination program in unstimulated cycles. Am J Obstet Gynecol. 2010; 203(4): 345.e1-6

Nulsen JC, Walsh S, Dumez S, Metzger DA. A randomized and longitudinal study of human menopausal gonadotropin with intrauterine insemination in the treatment of infertility. Obstet Gynecol. 1993 Nov;82(5):780-6.

Omland AK, Tanbo T, Dale PO, Abyholm T. Artificial insemination by husband in unexplained infertility compared with infertility associated with peritoneal endometriosis. Hum Reprod. 1998 Sep;13(9):2602-5.

Tummon IS, Asher LJ, Martin JS, Tulandi T. Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis. Fertil Steril. 1997 Jul;68(1):8-12.

Werbrouck E, Spiessens C, Meuleman C, D'Hooghe T. No difference in cycle pregnancy rate and in cumulative live-birth rate between women with surgically treated minimal to mild endometriosis and women with unexplained infertility after controlled ovarian hyperstimulation and intrauterine insemination. Fertil Steril. 2006 Sep;86(3):566-71.

4.1b 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 PR per initiated cycle, per succesful oocyte retrieval and per embryo transfer were similar in endometriosis and tubal factor couples and significantly higher than those of 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 PR for women with stage I/II was not significantly different from that for tubal factor (OR 0.79; 95% CI 0.60-1.03). However, the PR for women with stage III/IV was significantly lower than for those with tubal factor (OR 0.46; 95% CI 0.28-0.74) (Barnhart *et al.*, 2002).

In spite of being the only systematic review in this area, some caution must be applied in the interpretation of the results since the search period was Jan 1980 - May 1999 (when different drugs were used and the technical conditions were much different), 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. Society for Assisted Reproductive Technology (SART) and Human Fertilisation and Embryology Authority (HFEA)).

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

No study was found about possible implications of deep infiltrating endometriosis on the efficacy of IVF/ICSI.

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 (D'Hooghe *et al.*, 2006, Coccia *et al.*,2010, Benaglia *et al.*, 2010 and 2011).

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 the success rate after IVF/ICSI. The pregnancy rates after IVF/ICSI were reported to be lower in patients with stage III and IV endometriosis as compared to those with tubal factor. GnRH antagonist protocol may be not inferior to GnRH agonist protocol in women with minimal/mild endometriosis and endometrioma. No evidence was found relating deep infiltrating 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

Rec 4.4	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
Rec 4.5	In infertile women with AFS/ASRM stage III/IV 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 (D'Hooghe *et al.*, 2006; Coccia *et al.*,2010; Benaglia *et al.*, 2010 and 2011).	C
Rec 4.6	In women with endometriomas, clinicians may use antibiotic prophylaxis at the time of oocyte retrieval, although the risk for ovarian abscess following follicle aspiration is low (Benaglia *et al.*, 2008).	D

References

Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. Fertil Steril. 2002 Jun;77(6):1148-55.

Benaglia L, Somigliana E, Iemmello R, Colpi E, Nicolosi AE, Ragni G. Endometrioma and oocyte retrieval-induced pelvic abscess: a clinical concern or an exceptional complication? Fertil Steril. 2008 May;89(5):1263-6.

Benaglia L, Somigliana E, Santi G, Scarduelli C, Ragni G, Fedele L. IVF and endometriosis-related symptom progression: insights from a prospective study. Hum Reprod 2011; 26 (9): 2368-72.

Benaglia L, Somigliana E, Vercellini P, Benedetti F, Iemmello R, Vighi V, Santi G, Ragni G. The impact of IVF procedures on endometriosis recurrence. Eur J Obstet Gynecol Reprod Biol. 2010 Jan;148(1):49-52.

Coccia ME, Rizzello F, Gianfranco S. Does controlled ovarian hyperstimulation in women with a history of endometriosis influence recurrence rate? J Womens Health (Larchmt). 2010 Nov;19(11):2063-9.

D'Hooghe TM, Denys B, Spiessens C, Meuleman C, Debrock S. Is the endometriosis recurrence rate increased after ovarian hyperstimulation? Fertil Steril. 2006 Aug;86(2):283-90.

Omland AK, Fedorcsák P, Storeng R, Dale PO, Abyholm T, Tanbo T. Natural cycle IVF in unexplained, endometriosis-associated and tubal factor infertility. Hum Reprod. 2001 Dec;16(12):2587-92.

Pabuccu R, Onalan G, 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 Oct;88(4):832-9.

4.2 Medical therapies as an adjunct to treatment with assisted reproductive technologies 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. Reduced pregnancy rates in patients with endometriosis (OR 0.56 95% CI 0.44-0.70) have been reported by Barnhart in a meta-analysis of 22 non-randomised studies (Barnhart *et al.*, 2002). It has been proposed, following numerous non-randomised studies, that medical treatment of endometriosis prior to MAR may result in improved outcome either by improving oocyte quality or endometrial receptivity. This specific question with regard to GnRHa treatment has been addressed by Sallam and colleagues in a Cochrane review (Sallam *et al.*, 2006, last updated 2010). 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 is poor and thus are potentially at risk of methodological bias. Consequently, they recommend in their conclusions that there remains a need for high quality randomised studies using up to date assisted conception techniques. Nevertheless, they conclude that clinically down regulation for 3-6 months with a GnRHa in women with endometriosis increases the odds of clinical pregnancy by more than four fold. The odds of live birth are also improved but magnitude of the effect is unreliable due to the poor quality of the single study that included this as an outcome. This study and its included studies fails to address potential adverse effects of the intervention and specifically does not consider miscarriage rates, multiple pregnancy rates or ectopic pregnancy rates.

Conclusion and considerations

The question 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 is low. However, the results of these studies point in the same direction, towards a beneficial effect of GnRH agonists on the outcome of ART in women with endometriosis. Hence, the following B-level recommendation was drafted.

Recommendation

Rec 4.7	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, last updated 2010).	B

References

Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. Fertility and Sterility 2002;77(6):1148–55.

Sallam HN, Garcia-Velasco JA, Dias S, Arici A, Abou-Setta AM. Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD004635. DOI: 10.1002/14651858.CD004635.pub2. (Publication status and date: Edited (no change to conclusions), published in Issue 11, 2010.)

4.3 Surgical therapies as an adjunct to treatment with assisted reproductive technologies in women with endometriosis

Key question

Should surgery be performed prior to treatment with ART to improve reproductive outcomes?

Since it was described in section 3.2 that surgery could have a beneficial effect on spontaneous pregnancy rates in women with endometriosis, one could speculate that surgical treatment of endometriosis prior to treatment with assisted reproductive technology (ART) could be effective to improve reproductive outcomes.

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

4.3a Surgery prior to treatment with assisted reproductive technologies in women with peritoneal endometriosis

Clinical evidence

With regard to the effect of surgical therapy on peritoneal endometriosis, a retrospective cohort study reports 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 of 262 women only a diagnostic laparoscopy was performed. In the group in which surgery had taken place prior to ART, a significant higher implantation rate, pregnancy rate and live birth rate was found. Moreover, the investigators report a shorter time to first pregnancy and a higher cumulative pregnancy rate after surgical removal of endometriosis prior to ART (Opoien *et al.*, 2011).

Conclusion and considerations

The evidence regarding surgery prior to treatment with ART in women with minimal to mild endometriosis is of moderate quality, but points in the same direction of a beneficial effect of surgery, leading to the following recommendation.

Recommendation

Rec 4.8	In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may consider complete surgical removal of endometriosis prior to treatment with assisted reproductive technologies to improve live birth rate (Opoien *et al.*, 2011).	C

References

Opoien HK, Fedorcsak P, Byholm T, Tanbo T. Complete surgical removal of minimal and mild endometriosis improves outcome of subsequent IVF/ICSI treatment. Reprod Biomed Online 2011 Sep;23(3):389-395.

4.3b Surgery prior to treatment with assisted reproductive technologies in women with ovarian endometrioma

Clinical evidence

With regard to the surgical therapy for cysts, a Cochrane review based on four randomised trials involving 312 women, concludes that laparoscopic aspiration or cystectomy of endometriomata 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, last updated 2011). Other smaller cohort studies show partly contradictory results. In one cohort study the conclusion is drawn that cyst wall vaporisation does not impair IVF outcome (Donnez *et al.*, 2001). There is a need for more randomised controlled trials in order to find an answer to the question whether small ovarian endometriotic cysts should be removed prior to ART, or not.

Conclusion and considerations

Laparoscopic ovarian cystectomy in women with unilateral endometriomas between 3 and 6 cm in diameter 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.

Recommendations

Rec 4.9	In infertile women with endometriomas, clinicians should not perform cystectomy prior to treatment with assisted reproductive technologies if the only aim is to improve pregnancy rates (Donnez *et al.*, 2001; Hart *et al.*, 2008, last updated 2011; Benschop *et al.*, 2010).	B

Rec 4.10	In women with an ovarian endometrioma, the GDG recommends clinicians to consider cystectomy prior to treatment with assisted reproductive technologies to confirm the diagnosis histologically, reduce the risk of infection after oocyte retrieval, improve accessibility of follicles or improve endometriosis-associated pain, although it does not improve pregnancy rates.	GPP

Rec 4.11	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, Heineman MJ. Interventions for women with endometrioma prior to assisted reproductive technology. Cochrane Database Syst Rev. 2010 Nov 10;(11):CD008571.

Donnez J, Wyns C, Nisolle M. Does ovarian surgery for endometriomas impair the ovarian response to gonadotropin? Fertil Steril. 2001 Oct;76(4):662-5.

Hart RJ, Hickey M, Maouris P, Buckett W. Excisional surgery versus ablative surgery for ovarian endometriomata. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD004992. (Publication status and date: Edited (no change to conclusions), published in Issue 5, 2011.)

4.3c Surgery prior to treatment with assisted reproductive technologies in women with deep infiltrating endometriosis

Clinical evidence

Surgical therapy for deep infiltrating endometriosis is predominantly performed because of pain rather than because of infertility. One cohort study in which women with deep infiltrating 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 infiltrating 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, requesting surgical treatment.

Recommendation

Rec 4.12	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, Serafini PC.Extensive excision of deep infiltrative endometriosis before in vitro fertilization significantly improves pregnancy rates. J Minim Invasive Gynecol.2009 Mar-Apr;16(2):174-80.

Papaleo E, Ottolina J, Viganò P, Brigante C, Marsiglio E, De Michele F, Candiani M. Deep pelvic endometriosis negatively affects ovarian reserve and the number of oocytes retrieved for in vitro fertilization. Acta Obstet Gynecol Scand. 2011 Aug;90(8):878-84.

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 of 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.

Key question

How should menopausal symptoms be treated in women with a history of endometriosis?

Clinical evidence

From the literature search, one systematic review came out that included two randomised controlled trials regarding recurrence of pain and endometriosis lesions in patients submitted to bilateral oophorectomy (Al Kadri *et al.*, 2009). In the first one, 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 group experienced moderate pelvic pain. In the second study, 115 patients received non-stop 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 patients treated and no case of recurrence in the control group. Those 2 patients had to be re-operated. All the differences found were not statistically significant. Authors referred to residual disease as risk factor to recurrence (Al Kadri *et al.*, 2009).

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

Regarding the regimen of hormone replacement therapy, there are no data available. 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. There are also very limited data suggesting that unopposed estrogens could be a risk factor for ovarian malignancy in endometriosis patients with high body mass index.

The ideal time delay to start hormonal therapy after surgical menopause is also not known and the decisions in this point are not supported by any available evidence.

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

Conclusion and considerations

We can 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 deprive severely symptomatic women from this treatment in order to relieve their menopausal symptoms.

We found no high quality evidence on the recurrence of disease in menopausal endometriosis patients treated with hormone replacement therapy. The larger part of the literature on this topic are case reports that all use different regimens.

Recommendations

Rec 5.1	In women with surgically induced menopause because of endometriosis, estrogen/progestagen therapy or tibolone can be effective for treatment of menopausal symptoms (Al Kadri *et al.*, 2009).	B
Rec 5.2	The GDG recommends that in postmenopausal hysterectomised women with a history of endometriosis, clinicians should consider avoiding 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
Rec 5.3	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, Hajeer A. Hormone therapy for endometriosis and surgical menopause. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD005997.

6. ASYMPTOMATIC ENDOMETRIOSIS

Introduction

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

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 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 and the fact that it is likely that there is little risk that asymptomatic minimal disease will become symptomatic (Moen and Stokstad, 2002). However, in view of the possible other negative effects of endometriosis e.g. 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 points. However, it should be noted that large differences exist in clinical practice and in clinical opinion among the guideline group members.

Recommendations

Rec 6.1	The GDG recommends that clinicians should not routinely perform surgical excision and ablation for an incidental finding of asymptomatic endometriosis, since the natural course of the disease is not clear.	GPP
Rec 6.2	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, Geirsson RT. Pelvic endometriosis diagnosed in an entire nation over 20 years Am J Epidemiol 2010 172:237–243.

Moen MH, Stokstad T. A long-term follow-up study of women with asymptomatic endometriosis diagnosed incidentally at sterilization. Fertil Steril 2002 78(4):773-6.

Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, Nagle CM, Doherty JA, Cushing-Haugen KL, Wicklund KG, Chang-Claude J, Hein R, Lurie G, Wilkens LR, Carney ME, Goodman MT, Moysich K, Kjaer SK, Hogdall E, Jensen A, Goode EL, Fridley BL, Larson MC, Schildkraut JM, Palmieri RT, Cramer DW, Terry KL, Vitonis AF, Titus LJ, Ziogas A, Brewster W, Anton-Culver H, Gentry-Maharaj A, Ramus SJ, Anderson AR, Brueggmann D, Fasching PA, Gayther SA, Huntsman DG, Menon U, Ness RB, Pike MC, Risch H, Wu AH, Berchuck A; Ovarian Cancer Association Consortium. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. Lancet Oncol. 2012 Apr;13(4):385-94.

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 oriented towards interventions that could influence the development of endometriosis, without specifying on 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 (>or=42 metabolic equivalent (MET) hours/week) compared to those with a low (<3 MET hours/week) (rate ratio = 0.89 [95% CI 0.77-1.03]). Forty-two metabolic equivalent hours corresponds to 6 hours jogging or 8 hours bicycling per week. The association was limited to participants with no past or concurrent 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, but also searched for factors associated with the occurrence, prevalence and development of endometriosis. We only found evidence on oral contraceptives and physical exercise that resulted in the following concluding statements:

Recommendations

Rec 7.1	The usefulness of oral contraceptives for the primary prevention of endometriosis is uncertain (Vercellini *et al.*, 2011).	C
Rec 7.2	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, Fedele L. Oral contraceptives and risk of endometriosis: a systematic review and meta-analysis. Hum Reprod Update. 2011 Mar-Apr;17(2):159-70.

Vitonis AF, Hankinson SE, Hornstein MD, Missmer SA. Adult physical activity and endometriosis risk. Epidemiology. 2010 Jan;21(1):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 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 approx. 3) (Sayasneh *et al.*, 2011, Munksgaard & Blaakaer, 2011).

Although the SIR is increased in endometriosis patients as compared to control populations, the incidence of ovarian cancer is low in both groups. The cohort study of Melin *et al.* 2006 for instance reported a SIR of 1.43 (ranging from 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).

The incidence of non-Hodgkin's lymphoma is increased in cohort studies (n=3) 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 of 8 cohort studies, not increased in the 5 of 8 cohort and in 4 of 5 case-control studies, and decreased in one case-control study (Munksgaard & Blaakaer, 2011).

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

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

Rec 8.1	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, (3) some cancers (ovarian cancer and non-Hodgkin's lymphoma) are slightly more common in women with endometriosis.	GPP
Rec 8.2	The GDG recommends that clinicians explain the incidence of some cancers in women with endometriosis in absolute numbers.	GPP
Rec 8.3	The GDG recommends no change in the current overall management of endometriosis in relation to malignancies, since there is 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, Bergqvist A. Endometriosis and the risk of cancer with special emphasis on ovarian cancer. Hum Reprod. 2006 May;21(5):1237-42.

Munksgaard PS, Blaakaer J. The association between endometriosis and gynecological cancers and breast cancer: A review of epidemiological data. Gynecol Oncol. 2011 Jul 8.

Sayasneh A, Tsivos D, 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, Vercellini P. Association between endometriosis and cancer: a comprehensive review and a critical analysis of clinical and epidemiological evidence. Gynecol Oncol. 2006 May;101(2):331-41.

APPENDIX 1: ABBREVIATIONS

AFS	American Fertility Society
ART	Assisted reproductive technology
ASRM	American Society for Reproductive Medicine
CAMS	Complementary and alternative medicines
CERR	Cumulative endometriosis recurrence rate
CI	Confidence interval
COS	Controlled ovarian stimulation
CPR	Clinical pregnancy rate
DIE	Deep infiltrating endometriosis
FSH	Follicle stimulating hormone
GnRHa	Gonadotropin releasing hormone analogue
GPP	Good practice point
HCG	Human chorionic gonadotrophin
hMG	Human menopausal gonadotropin
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
NMPP	Non-menstrual pelvic pain
NPV	Negative predictive value
NSAIDs	Nonsteroidal anti-inflammatory drugs
OCP	Oral contraceptive pill

OR	Odds ratio
PPV	Positive predictive value
PR	Pregnancy rate
PSN	Pre-sacral neurectomy
QoL	Quality of life
rAFS	Revised American Fertility Society (rAFS) classification system
RCT	Randomised 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
ULP	Ultralong protocol
UNA	Uterosacral nerve ablation

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.

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.

Dyschezia: Painful or difficult defecation.

Dysmenorrhagia: Painful menstruation that are abnormally long or heavy.

Dysmenorrhea: Painful menstruation.

Dyspareunia: Painful intercourse.

In vitro fertilization (IVF): An ART procedure that involves extracorporeal fertilization.

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.

Intracytoplasmic sperm injection (ICSI): A procedure in which a single spermatozoon is injected into the oocyte cytoplasm.

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.

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

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.

Reproductive surgery: Surgical procedures performed to diagnose, conserve, correct and/or improve reproductive function.

Reference

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 Technology; World Health Organization. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology, 2009. Hum Reprod. 2009 Nov;24(11):2683-7.

APPENDIX 3: GUIDELINE GROUP

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

Chair of the guideline development group

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

Guideline development group 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)

Methodological 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).

The interest that were declared are as follows:

Name	Conflict of interest declared
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 minimize the potential conflicts of interest, the synthesis of the evidence was performed by the expert GDG member and the methodological expert (with no conflicts of interest). The possible influence of conflicts of interest was taken into account in the division of key questions among the guideline group members. Conflicts of interest were further limited by the discussion of the evidence and draft recommendations in the GDG group, 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 guideline development groups recommends that future research in the field of endometriosis is focussed on these research gaps and that researchers attempt to perform high quality randomised controlled trials and/or cohort studies, to answer the following clinical key issues.

- The natural course of endometriosis
- Prospective cohort studies on the signs and symptoms of endometriosis
- The diagnostic value of laparoscopy with or without histological verification
- The use of biomarkers for disease monitoring in endometriosis
- The usefulness of oral contraceptives for treatment of endometriosis-associated pain and the best regimen (continuous versus cyclical OCP versus progestins).
- 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.
- Primary prevention of endometriosis.
- Secondary prevention of endometriosis
- Clinical management of endometriosis in adolescents
- The effectiveness of surgical excision of AFS/ASRM stage III-IV endometriosis in comparison to direct referral to ART.
- The effectiveness of surgical excision of deep nodular lesions in symptomatic endometriosis patients before assisted reproductive technologies with regard to reproductive outcome.
- 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 the following 3 groups: direct ART, 6 month GnRH agonist treatment before ART, and ovarian cystectomy before ART. Secondary outcomes should be: pain relief, quality of life, ART complications, and ART cancellation rates.
- In women with endometriosis and an indication for ART: compare direct ART with 6/12 GnRH agonist downregulation, as the current recommendation is based on a low number of RCTs in a low number of patients
- The use of hormone replacement therapy for treatment of menopausal symptoms in women with endometriosis, with regard to effectiveness, disease and pain recurrence, the regimen to be used.
- The benefit of surgery in case of incidental finding of asymptomatic endometriosis.