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# Consensus on current management of endometriosis

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**STUDY QUESTION:** Is there a global consensus on the management of endometriosis that considers the views of women with endometriosis?

**SUMMARY ANSWER:** It was possible to produce an international consensus statement on the current management of endometriosis through engagement of representatives of national and international, medical and non-medical societies with an interest in endometriosis.

**WHAT IS KNOWN ALREADY:** Management of endometriosis anywhere in the world has been based partially on evidence-based practices and partially on unsubstantiated therapies and approaches. Several guidelines have been developed by a number of national and international bodies, yet areas of controversy and uncertainty remain, not least due to a paucity of firm evidence.

**STUDY DESIGN, SIZE, DURATION:** A consensus meeting, in conjunction with a pre- and post-meeting process, was undertaken.

**PARTICIPANTS/MATERIALS, SETTING, METHODS:** A consensus meeting was held on 8 September 2011, in conjunction with the 11th World Congress on Endometriosis in Montpellier, France. A rigorous pre- and post-meeting process, involving 56 representatives of 34 national and international, medical and non-medical organizations from a range of disciplines, led to this consensus statement.

**MAIN RESULTS AND THE ROLE OF CHANCE:** A total of 69 consensus statements were developed. Seven statements had unanimous consensus; however, none of the statements were made without expression of a caveat about the strength of the statement or the statement itself. Only two statements failed to achieve majority consensus. The statements covered global considerations, the role of endometriosis organizations, support groups, centres or networks of expertise, the impact of endometriosis throughout a woman's life course, and a full range of treatment options for pain, infertility and other symptoms related to endometriosis.

**LIMITATIONS, REASONS FOR CAUTION:** This consensus process differed from that of formal guideline development. A different group of international experts from those participating in this process would likely have yielded subtly different consensus statements.

**WIDER IMPLICATIONS OF THE FINDINGS:** This is the first time that a large, global, consortium, representing 34 major stakeholding organizations from five continents, has convened to systematically evaluate the best available current evidence on the management of endometriosis, and to reach consensus. In addition to 18 international medical organizations, representatives from 16 national endometriosis organizations were involved, including lay support groups, thus generating input from women who suffer from endometriosis.

**STUDY FUNDING/COMPETING INTEREST(S):** The World Endometriosis Society commissioned and hosted the consensus meeting. Financial support for participants to attend the meeting was provided by the organizations that they represented. There was no other specific funding for this consensus process. Full disclosures of all participants are presented herein.

**Key words:** endometriosis / evidence based / management / WES Montpellier Consortium / World Endometriosis Society

[†] The complete list of people representing The World Endometriosis Society Montpellier Consortium is given in Appendix.

# Introduction

Endometriosis is an inflammatory condition characterized by lesions of endometrial-like tissue outside of the uterus and is associated with pelvic pain and infertility (Giudice, 2010). It affects an estimated 176 million women of reproductive age worldwide (Adamson *et al.*, 2010). It is widely assumed that lesions arise through retrograde endometrial tissue loss during menstruation, coelomic metaplasia and lymphatic spread in immunologically and genetically susceptible individuals. While its underlying cause is uncertain, it is likely to be multifactorial including genetic factors with possible epigenetic influences, perhaps promoted through environmental exposures. Endometriosis has elements of a pain syndrome with central neurological sensitization (and some hallmarks of a neurological disorder) (Stratton and Berkley, 2011), and is a proliferative, estrogen-dependent disorder (with growing evidence of progesterone resistance) (Pabona *et al.*, 2012). There is overlap with other conditions characterized by pelvic–abdominal pain and infertility. Some symptomatic women with pelvic pain, who do not have diagnosed endometriosis or who are prior to diagnosis, may benefit from similar treatments.

Women with endometriosis typically have a range of pelvic–abdominal pain symptoms, including dysmenorrhoea, dyspareunia, heavy menstrual bleeding, non-menstrual pelvic pain, pain at ovulation, dyschezia and dysuria, as well as chronic fatigue (Kennedy *et al.*, 2005; Nnoaham *et al.*, 2011). Endometriosis lesions, particularly deep infiltrating lesions, are often innervated. The presence of endometriotic lesions, followed by denervation and re-innervation, may result in accompanying changes in the central nervous system (central sensitization), creating a chronic pain syndrome (Stratton and Berkley, 2011). Endometriosis is also associated with infertility, with a strong association between severity of disease and impact on fertility, probably due to impaired tubo-ovarian function, the presence of ovarian endometrioma, subclinical pelvic inflammation, possibly reduced oocyte quality and reduced endometrial receptivity to implantation (Lessey, 2011). Both endometriosis and adenomyosis (lesions occurring in the uterine intramural muscular layer) reduce the chance of success of assisted reproductive treatment (Barnhart *et al.*, 2002; Maubon *et al.*, 2010).

Symptoms of endometriosis contribute substantially to the burden of disease and add substantial cost to society through reduced economic and personal productivity (Simoens *et al.*, 2007; Nnoaham *et al.*, 2011; Simoens *et al.*, 2012).

While symptoms and examination findings may suggest endometriosis (Nnoaham *et al.*, 2011, 2012), the gold standard for making the diagnosis remains the laparoscopic visualization of lesions preferably with histologic confirmation (Kennedy *et al.*, 2005). In the absence of histological sampling, the false-positive rate with laparoscopic visualization alone may approach 50% especially in women with minimal or mild endometriosis (Wykes *et al.*, 2004). Laparoscopy also enables endometriosis to be staged by the revised American Society for Reproductive Medicine (r-ASRM, 1997) scoring system, the 'scoring' system most commonly in current use, objectively defining the disease as minimal (stage I), mild (stage II), moderate (stage III) or severe (stage IV) based on its laparoscopic appearance. It is recognized that the stage/extent of disease may not correlate with symptoms experienced, reproductive outcome or recurrence risk (Adamson, 2011). Much research has recently focused on serum biomarkers, including cancer antigen-125 (CA125), leptin, monocyte chemotactic protein-1 (MCP-1), regulated on activation normal T cell expressed and secreted (RANTES) and macrophage migration inhibitory factor (MIF), although these have not been useful diagnostic predictors owing to poor sensitivity or specificity, small sample size or inadequate validation of their accuracy (May *et al.*, 2010). Recent interest has focused on endometrial immunohistochemistry for nerve fibre density (Al-Jefout *et al.*, 2009; Bokor *et al.*, 2009) and on urinary markers (cytokeratin 19, urinary peptide 1.8 kDa) (May *et al.*, 2010). These less invasive diagnostic tests require future formal and robust evaluation of their accuracy.

Several guidelines have been developed by a number of national and international bodies: the European Society for Human Reproduction and Embryology (http://guidelines.endometriosis.org/), the American Society of Reproductive Medicine: (http://www.asrm.org/uploadedFiles/ASRM_Content/News_and_Publications/Practice_Guidelines/Educational_Bulletins/endometriosis_and_infertility(1).pdf and http://www.asrm.org/uploadedFiles/ASRM_Content/News_and_Publications/Practice_Guidelines/Educational_Bulletins/Treatment_of_pelvic_pain(1).pdf), the Royal College of Obstetricians and Gynaecologists (http://www.rcog.org.uk/files/rcog-corp/GTG24100 22011.pdf), the Society of Obstetrics and Gynecology of Canada (http://www.sogc.org/guidelines/documents/gui244CPG1007E.pdf) and the Cochrane Database of Systematic Reviews (http://thecochranelibrary.com), yet areas of controversy and uncertainty remain, not least due to a paucity of firm evidence.

The World Endometriosis Society (WES) has therefore developed a process to bring together representatives of national and international, medical and non-medical societies with an interest in endometriosis, aiming to derive a consensus on the management of endometriosis from a global perspective, in which the views of women with endometriosis were represented.

# Methods

We developed a consensus process supported by a specific methodology (Supplementary data, Information 1). This differed from a formal guideline methodology, which typically involves a more lengthy and proscriptive process.

There were 51 national and international societies invited to participate in the WES Consensus on the Management of Endometriosis and to nominate a representative for their organization in the consensus process and at the meeting in Montpellier on 8 September 2011. From these nominees, along with members of the WES Board, a group of participants in the WES Montpellier Consortium was established and this ultimately comprised 56 representatives from 34 organizations (18 medical organizations, 16 non-medical endometriosis organizations). Pharmaceutical companies with an interest in developing products for treating endometriosis were invited to send a representative to the Montpellier meeting as an observer and two companies participated. All participants and their roles are summarized in Table I.

The participants were involved in an on-going email discussion group for 4 months and a teleconference in advance of the meeting, with the following goals:

(i) to have all participants conversant with the evidence;
(ii) to define topics for presentation;
(iii) to determine reviewers to present these topics;

**Table I The World Endometriosis Society Montpellier Consortium.**

| Name | Pre-meeting email consultations | 3 August 2011 phone meeting | Presenter | Attended 8 September 2011 meeting | Voted | Manuscript revision |
|---|---|---|---|---|---|---|
| Mauricio Abrao | x | x | x | x | x | x |
| David Adamson | x | — | x | x | x | x |
| Catherine Allaire | — | — | — | x | x | x |
| Vibeke Amelung | — | — | — | — | x | x |
| Elisabet Andersson | x | — | — | x | x | x |
| Mary-Lou Ballweg | — | — | — | x | Resigned | |
| Christian Becker | — | — | — | x | x | x |
| Kolbrún Birna Árdal | x | — | — | x | — | x |
| Deborah Bush | x | x | x | x | x | x |
| Bianca de Bie | — | — | — | x | x | x |
| Kristof Chwalisz | — | — | — | x | — | x |
| Hilary Critchley | — | — | — | — | x | x |
| Thomas D'Hooghe | x | — | x | x | x | x |
| Gerard Dunselman | x | — | x | x | x | x |
| Johannes Evers | x | — | — | x | x | x |
| Cindy Farquhar | x | x | x | x | x | x |
| Thomas Faustmann | x | — | — | x | x | x |
| Axel Forman | — | — | — | — | — | x |
| Jessica Fourquet | — | — | — | x | x | x |
| Ian Fraser | — | — | — | x | x | x |
| Linda Giudice | x | x | x | x | — | x |
| Stephan Gordts | x | — | x | x | x | x |
| Heather Guidone | x | — | — | — | x | x |
| Sun-Wei Guo | — | — | — | — | x | x |
| David Healy | x | — | x | x | Deceased | |
| Bernard Hedon | — | — | — | x | x | x |
| Johanna Hulkkonen | x | — | — | x | x | x |
| Louise Hull | — | — | — | x | x | x |
| Lone Hummelshoj | x | x | x | x | x | x |
| Neil Johnson | x | x | x | x | x | x |
| Miriam Just | x | — | — | x | x | — |
| Ludwig Kiesel | — | — | — | — | x | x |
| Alan Lam | — | — | — | — | x | x |
| Clodagh Lynam | x | — | — | x | x | x |
| Liselotte Mettler | — | — | — | x | x | x |
| Charles Miller | x | — | x | x | — | — |
| Helen North | — | — | — | x | x | x |
| Rishma Pai | — | — | — | — | x | x |
| Carlos Petta | x | x | x | x | x | x |
| Lucy Prentice | — | — | — | x | — | x |
| Fernando Reis | — | — | — | x | x | x |
| Shelley Reilly | — | — | — | x | — | x |
| Edgardo Rolla | x | x | x | x | x | x |

*Continued*

**Table I** *Continued*

| Name | Pre-meeting email consultations | 3 August 2011 phone meeting | Presenter | Attended 8 September 2011 meeting | Voted | Manuscript revision |
|---|---|---|---|---|---|---|
| Luk Rombauts | x | x | x | x | x | x |
| Karl-Werner Schweppe | x | — | x | x | x | x |
| Tamer Seckin | x | — | — | x | x | — |
| Kathy Sharpe-Timms | — | — | — | — | x | x |
| Dian Shepperson Mills | x | — | — | x | x | x |
| Sony Singh | x | x | x | x | — | x |
| David Soriano | — | — | — | x | x | — |
| Martyn Stafford-Bell | x | — | — | x | x | x |
| Pamela Stratton | x | x | x | x | x | x |
| Robert Taylor | x | x | x | x | x | x |
| Jim Tsaltas | x | — | x | x | x | x |
| Jacqueline Veit | — | — | — | x | — | x |
| Paolo Vercellini | x | — | x | x | x | x |

Representing: AAGL, Abbott Laboratories, Associazione Italiana Endometriosis, AGES, ALMER, AOFOG, American Society for Reproductive Medicine, Bayer Pharma, Cochrane Collaboration, Endometrioseforeningen (Norway), Endometriose Stichting (NL), Endometriose Foreningen (Denmark), Endometriosföreningen Sweden, Endometriosis Association (USA), Endometriosis Association of Ireland, Endometriosis Foundation of America, Endometriosis New Zealand, Endometriosis Research Center (USA), Endometriosis SHE Trust UK, Endometriosis UK, Endometrioosiyhdistys (Finland), European Society of Gynaecologic Endoscopy, European Society of Human Reproduction and Embryology, European Endometriosis Liga, FIGO, Fundación Puertorriquena de Pacientes con Endometriosis, International Federation of Fertility Societies, International Society of Gynecologic Endoscopy, Israeli Endometriosis Society, RANZCOG, Samtök Kvenna med Endómetríósu (Iceland), Sociedade Brasileira de Endometriose, Society of Gynecologic Investigation, Society of Obstetrics and Gynaecology Canada, World Endometriosis Research Foundation, WES.

(iv) to refine the clinical questions addressed, including the patient populations, interventions and outcomes to be considered.

The consensus meeting took place on 8 September 2011 in Montpellier, in association with the 11th World Congress on Endometriosis. Topics were presented by each reviewer, who had been asked to prepare draft consensus statements, based on their extensive literature reviews (see Supplementary data, Information 2). After full discussion, the proposed consensus statements were modified if necessary by agreement.

The relevant evidence was appraised according to the GRADE system (Guyatt *et al.*, 2008) (see Supplementary data, Information 3), leading to a consensus statement, graded as either strong or weak, the abiding principle being that where, across the range of issues considered important by women with endometriosis, fully informed women were likely to make different choices, a weak statement was made (Guyatt *et al.*, 2008). Where evidence from studies was lacking, but where the group felt that we had sufficient expertise and anecdotal experience to make an important statement, the statement was ascribed a 'good practice point' (GPP) and, through discussion, determined as strong or weak. For GPPs the definition of a strong statement was one where the disease burden was high and the potential impact of an intervention was considerable with minimal down side. The level of consensus around each statement was also ascribed a consensus grade, using the consensus grading system developed by the Australasian CREI Consensus Expert Panel on Trial evidence Group of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) (Kroon *et al.*, 2011). For the consensus grades ascribed to each of our statements, α (unanimous or near-unanimous) was where more than 80% agreed without caveat and fewer than 5% disagreed, β (unanimous with caveat) was where fewer than 5% disagreed but fewer than 80% agreed without caveat (the major caveats have been highlighted in the text), γ (majority) was where 50–80% agreed and δ (no consensus) was where fewer than 50% agreed with or without caveat.

Evidence tables (Supplementary data, Information 4) were established for all the evidence considered at the consensus meeting. Where the evidence base was considered to be well established, for example with medical treatments for endometriosis (first and second line), the evidence was amalgamated into a single table. For treatments where the evidence base was less well established, particularly for emerging treatments or complementary therapies, each table represented evidence for individual treatments.

A consensus statement was drafted by the meeting conveners (N.J. and L.H.) with further reference to the Power Point presentations and an audiotape of the proceedings of the meeting. A post-meeting online survey was conducted to systematically define the consensus around each of the statements made by a formal voting procedure. Of the WES Montpellier Consortium, 57% ($n = 32$) contributed to the pre-meeting debates, 84% ($n = 47$) attended the meeting in Montpellier and 80% ($n = 45$) completed the post-meeting online survey. One participant was deceased and one participant resigned from the Consortium after the meeting. Those contributing to this consensus, who did not attend the meeting in Montpellier, acted as first-level external reviewers ($n = 9$). Following three rounds of modification by circulation to and feedback from the WES Montpellier Consortium, the consensus statement was finalized. A more detailed version of the methodology may be found in Supplementary data, Information 1. Consortium members' contributions at each step of the process are outlined in Table I.

# Results

## The WES consensus statements

The evidence tables (Supplementary data, Information 4) provide the evidence that was considered to reach the consensus statements. The consensus statements, categorized as either strong or weak, are summarized in Table II, along with the level of consensus that applied to each statement.

### *General principles*

It was suggested that a philosophical shift to consideration of 'endometriosis and pelvic pain' as a spectrum or continuum of disease will avoid excluding women who lack laparoscopic confirmation of a diagnosis of endometriosis.

### *Endometriosis in low-resource settings*

From a global perspective, there was strong consensus that diagnosis and management of endometriosis should be incorporated into the primary health care of women worldwide. In low-resource settings, diagnosis may commence with two simple questions about pelvic-abdominal pain and infertility (accepting that a negative response does not exclude endometriosis). Management, including prevention, should be integrated with other women's healthcare strategies in low-resource settings, and may include education, progestin-based contraceptives, family planning and lactation.

### *Centres/networks of expertise*

Women with endometriosis often require individualized care over a long-term period, where priorities may change depending upon the type and severity of symptoms, impact of these symptoms, current or future fertility goals and lifestyle factors. However, not all women with endometriosis require a large number of experts and some women are treated effectively for the rest of their lives by a single laparoscopic surgical procedure. Individualized care benefits from a multidisciplinary network of experts sufficiently skilled in providing advice on and treatment of endometriosis and its associated symptoms, based on the best available evidence, their extensive experience and their transparent record of success rates. Previously the term 'centre of excellence' has been used (D'Hooghe and Hummelshoj, 2006) but we now agree that 'centre (or network) of expertise' is more appropriate. It was accepted that a centre/network of expertise would take differing forms in different settings, although consensus over precisely what form this would take (involving either a team, a network or a physical unit or centre where expertise is concentrated and coordinated) was not reached. However, it was agreed that such centres/networks should ideally comprise a multi-disciplinary team approach with specialists who have undergone specific training in endometriosis, advanced surgeons with a high caseload of managing deep endometriosis (also known as deep infiltrating endometriosis, DIE), ready access to an endometriosis organization with substantial input on behalf of women and a track record of commitment to collaborative management and research. As laparoscopic surgery will likely continue to be pivotal in the management of women with endometriosis, accreditation should be focused on the training and expertise of laparoscopic surgeons. The centre/network should have a transparent record of outcome-based success rates. There was no consensus on the accreditation or longevity of such an accreditation. Whilst it is impractical that all women with endometriosis are currently managed in a centre/network of expertise, those with higher stage of disease and/or more intractable clinical problems should receive care from such a centre or network.

### *Endometriosis support groups and endometriosis organizations*

National endometriosis support groups and endometriosis organizations exist around the world. Feedback from women and endorsement from health professionals and other stakeholders substantiate the value of effective support groups and endometriosis organizations to individuals (Kennedy *et al.*, 2005; Bush, 2009), although not all women need these services. Endometriosis support groups provide a valuable forum for women with endometriosis, having the potential to assist women to improve their quality of life by teaching coping mechanisms and sharing experiences. Engagement of experienced and skilled medical practitioners, accredited educators and other stakeholders brings strength to an endometriosis organization.

### *Life journey of women with endometriosis*

The stage of a woman's life is an important determinant of her requirement for treatment options, particularly according to her current symptoms, including present or future fertility wishes. Most of the consensus statements that follow relate to women within the reproductive age group; however it is acknowledged, as follows, that endometriosis may persist after natural or surgical menopause and must be managed accordingly.

### *Adolescents with endometriosis*

Endometriosis should be considered as a possible diagnosis in adolescents with suggestive symptoms—most women diagnosed with endometriosis date the onset of their symptoms to their teens (Nnoaham *et al.*, 2011). Most adolescents have stage I or II disease (Laufer *et al.*, 1997), although endometriosis of any stage may present in adolescence (Roman, 2010). Currently, there is insufficient evidence to make strong recommendations for management amongst adolescents who may have endometriosis (Dovey and Sanfilippo, 2010; Yeung *et al.*, 2011). Treatment (both medical and surgical) for this age group may improve the quality of life, reduce symptoms, prevent more severe disease developing later and reduce the likelihood of compromised future fertility, but further research to clarify these issues is essential. An appropriate balance of discussion of endometriosis as a possible diagnosis, then appropriate treatment (either empirical medical or surgical), without an over-interventional approach, must be sought. There is a pressing need for research into and guidelines for the management of symptomatic endometriosis and possible endometriosis amongst adolescents.

### *Obstetric outcomes for women with endometriosis*

Evidence is emerging that women with endometriosis have a higher risk of obstetric complications, including preterm delivery, antepartum haemorrhage, possibly pre-eclampsia and Caesarean section (Fernando *et al.*, 2009; Stephansson *et al.*, 2009; Brosens *et al.*, 2012), in addition to rare life-threatening situations where intra-abdominal bleeding from endometriotic lesions can lead to the need for urgent

**Table II World Endometriosis Society Montpellier Endometriosis Consensus Statements.**

| | Consensus grading |
|---|---|
| Endometriosis in low-resource settings | α |
| (1) Endometriosis diagnosis and management should be incorporated into the primary health care of women worldwide (strong GPP). | |
| (2) In low-resource settings, diagnosis may commence with two simple questions about pelvic–abdominal pain and infertility (strong GPP). | β |
| (3) Management, including prevention, should be integrated with other women's healthcare strategies in low-resource settings, and may include education, progestin-based contraceptives, family planning and lactation (strong GPP). | α |
| Networks of expertise | |
| (4) Women with endometriosis require individualised care over a long-term period, where priorities may change owing to the type and severity of symptoms, impact of these symptoms, current or future fertility wish and lifestyle factors (strong GPP). | α |
| (5) Individualised care benefits from a multi-disciplinary network of experts sufficiently skilled in providing advice on and treatment of endometriosis and its associated symptoms, based on the best available knowledge, their extensive experience and their transparent record of success rates (strong GPP). | β |
| Endometriosis organizations and support groups | |
| (6) Endometriosis support groups provide a valuable forum for women with endometriosis having the potential to assist women to improve their quality of life by teaching coping mechanisms and sharing experiences (strong GPP). | γ |
| (7) Engagement of experienced and skilled medical practitioners, accredited educators and other stakeholders brings strength to an endometriosis organization (strong GPP). | α |
| (8) A philosophical shift to consideration of 'endometriosis and pelvic pain' as a spectrum or continuum of disease will avoid excluding women who lack laparoscopic confirmation of a diagnosis of endometriosis (weak GPP). | γ |
| Endometriosis and adolescence | |
| (9) Endometriosis should be considered as a possible diagnosis in adolescents with suggestive symptoms (strong). | α |
| (10) Currently, there is insufficient evidence to make strong recommendations for management amongst adolescents who may have endometriosis (weak). | γ |
| Endometriosis and obstetric outcomes | |
| (11) Endometriosis should be considered an obstetric risk factor and pregnancies managed accordingly (strong). | γ |
| Endometriosis and menopause | |
| (12) Although endometriosis may occasionally recur, there is no strong evidence to deprive women of HRT if they suffer severe menopausal symptoms but have a history of endometriosis, although combined estrogen-progestin hormone therapy is advisable (weak). | γ |
| Endometriosis and cancer | |
| (13) The relative risk and absolute risk of ovarian cancer amongst women with endometriosis is so low as not to justify routine ovarian cancer screening (strong). | γ |
| Lifestyle/dietary interventions | |
| (14) Dietary intervention following endometriosis surgery in the form of vitamins, minerals, salts, lactic ferments and fish oil appears to be a suitable alternative to hormonal treatment, that is associated with similar pelvic pain reduction and quality of life improvement (weak). | δ |
| Empirical medical treatment | |
| (15) Well-tolerated, low-cost, easily accessible options such as non-steroidal anti-inflammatory drugs (NSAIDs), other analgesics, combined OCP and progestins should be considered for use as first-line empirical medical treatment (strong). | γ |
| (16) In some circumstances, second-line medical treatment with gonadotrophin-releasing hormone agonists (GnRH-a) with add-back HRT, or the LNG-IUS may be considered for use as empirical medical treatment for women who are not optimally treated with first-line empirical therapy prior to surgical diagnosis and treatment, whilst awaiting laparoscopic surgery (weak). | γ |
| Surgery for women with symptomatic endometriosis | |
| (17) Laparoscopic surgical removal of endometriosis is an effective first-line approach for treating pain related to endometriosis (strong). | α |
| (18) Although current RCTs have failed to demonstrate benefit of excision over ablation, it is recommended to excise lesions where possible, especially deep endometriotic lesions (weak). | α |
| (19) Laparoscopic surgery for endometriosis should always be undertaken in preference to laparotomy, where possible (strong GPP). | γ |
| (20) The addition of LUNA to laparoscopic removal of endometriosis does not improve pain relief (strong). | β |
| (21) Although PSN might benefit a small number of women, the benefits are likely to be outweighed by the potential for harmful effects (strong). | γ |
| (22) Laparoscopic excision (cystectomy) for ovarian endometriomas is preferred where possible to minimise symptom recurrence and endometrioma recurrence (strong). | γ |
| (23) The best surgical approach to deep endometriosis is unclear (weak). | γ |

*Continued*

**Table II** *Continued*

| | Consensus grading |
|---|---|
| (24) Highly specialised surgical expertise is required by surgeons, who undertake surgery for deep endometriosis, and it should be undertaken only within centres of expertise (strong GPP). | α |
| Medical therapy for women with symptomatic endometriosis | |
| (25) Well-tolerated, low-cost, easily accessible options such as non-steroidal anti-inflammatory drugs (NSAIDs), other analgesics, combined OCP and progestins should be considered for first-line medical treatment of laparoscopically diagnosed endometriosis (strong). | γ |
| (26) The combined OCP is an effective medical treatment to minimise the endometrioma recurrence rate after surgical removal of the cyst (strong). | α |
| (27) Second-line medical treatments could include gonadotrophin-releasing hormone agonists (GnRH-a, which should be used with add-back HRT, routinely), the LNG-IUS and depot progestins (weak). | γ |
| (28) Danazol and gestrinone should not be used other than for women, established on these treatments in the absence of side effects, for whom other treatments have proven ineffective (strong). | α |
| Emerging medical therapies for women with symptomatic endometriosis | |
| (29) Aromatase inhibitors might be reasonable as a second-line medical treatment, but more research is required (weak). | γ |
| (30) SPRMs might be a reasonable second-line medical treatment, but more research is required (weak). | γ |
| (31) Gonadotrophin-releasing hormone (GnRH) antagonists might be reasonable as second-line medical treatment, but more research is required (weak). | γ |
| (32) There is no evidence of a benefit of pentoxifylline on the reduction of pain (strong). | α |
| (33) There is no evidence of a benefit of anti-TNFα (anti tumour necrosis factor alpha) on the reduction of pain (weak). | γ |
| (34) There is no benefit from raloxifene on prevention of recurrence of pain (strong). | α |
| (35) There is insufficient evidence of a benefit of rosiglitazone on the reduction of pain (weak). | γ |
| (36) There is insufficient evidence of benefit of valproic acid on the reduction of pain (weak). | γ |
| (37) Anti-angiogenesis agents are at research level only (strong). | α |
| Complementary therapies for women with symptomatic endometriosis | |
| (38) There is some evidence of effectiveness of acupuncture, but it requires repeated treatments and effects are unlikely to be long lasting (weak). | γ |
| (39) There is evidence of effectiveness of TENS for short-term pain management for women with dysmenorrhoea (weak). | γ |
| (40) There is insufficient evidence of effectiveness of traditional Chinese medicine (TCM) and applicability is uncertain outside of TCM settings (weak). | α |
| (41) Vitamin B1 and B6 can be used to relieve pain for women with dysmenorrhoea but there is limited evidence of effectiveness and there are safety concerns with vitamin B6 at higher doses (weak). | γ |
| (42) There is some evidence of effectiveness of magnesium in reduction of pain for women with dysmenorrhoea (weak). | γ |
| (43) There is no evidence of effectiveness for topical heat (weak). | γ |
| (44) There is no evidence to support spinal manipulation (weak). | γ |
| (45) There is insufficient evidence to support behavioural interventions (weak). | γ |
| Surgery for infertility in women with endometriosis | |
| (46) Laparoscopic surgical removal of endometriosis improves fertility in stage I and II endometriosis (strong). | γ |
| (47) Although RCTs have failed to demonstrate benefit of excision over ablation, it is recommended to excise lesions where possible, especially where pain is present (weak). | γ |
| (48) Laparoscopic excision (cystectomy) where possible for endometriomas is preferred to laparoscopic ablation (drainage and coagulation) to enhance fertility (strong). | α |
| (49) The best surgical approach to deep endometriosis in women with infertility is unclear (weak). | γ |
| (50) Medical adjunct therapy in conjunction with laparoscopic surgery has not been shown to have fertility benefit (strong). | α |
| Assisted conception for infertility in women with endometriosis | |
| (51) There is no evidence to support the use of controlled OS alone and insufficient evidence to recommend one agent over another (weak). | γ |
| (52) Intrauterine insemination (IUI) with controlled OS (COS) is effective in improving fertility in minimal and mild endometriosis, but the role of unstimulated IUI is uncertain (strong). | γ |
| (53) Double insemination should be considered for intrauterine insemination (IUI) (weak). | δ |

*Continued*

**Table II** *Continued*

| | Consensus grading |
|---|---|
| (54) Although IVF may be less effective for endometriosis than for other causes of infertility, it should be considered for use to improve the success rate above expectant management (strong). | γ |
| Adjuncts to assisted conception for infertility in women with endometriosis | |
| (55) There is insufficient evidence of benefit of gonadotrophin-releasing hormone (GnRH-a) treatment before intrauterine insemination (IUI) (weak). | α |
| (56) There is insufficient evidence of benefit of laparoscopic surgery prior to IUI/COS (weak). | γ |
| (57) GnRH analogue administered for 3–6 months prior to IVF/ICSI in women with endometriosis increases the clinical pregnancy rate (strong). | γ |
| (58) There is insufficient evidence to support the use of the combined OCP prior to IVF/ICSI (weak). | γ |
| (59) There are no data to compare the approach of pretreatment with the combined OCP versus gonadotrophin-releasing hormone agonists (GnRH-a) (weak). | γ |
| (60) There is no evidence that surgical removal of endometriosis or surgical treatment of endometriomas (by aspiration or cystectomy) improves success rates through IVF (weak). | γ |
| (61) Ovarian response might be reduced in some women who have undergone surgery for endometriomas (weak). | α |
| (62) Since endometriomas may damage the ovary, and since complications can arise in women with endometriomas undergoing ART, laparoscopic ovarian cystectomy may sometimes be recommended for women with endometriomas larger than 3 cm diameter (weak). | α |
| Medical therapy for infertility in women with endometriosis | |
| (63) There is no evidence of fertility benefit from medical treatment—ovulation suppression may delay pregnancy and this is not recommended (strong). | α |
| Emerging therapies for infertility in women with endometriosis | |
| (64) Lipiodol hysterosalpingogram improves live birth rates in women with endometriosis, but otherwise unexplained infertility, who are attempting natural conception (weak). | γ |
| (65) There is no evidence of fertility benefit from pentoxifylline for women with mild-to-moderate endometriosis (strong). | α |
| (66) There is no evidence of fertility benefit of TCM over gestrinone or Danazol (weak). | γ |
| (67) There is insufficient evidence of increased pregnancy rates from the use of vitamins (weak). | α |
| (68) There is insufficient reliable evidence of improved fertility with mifepristone (weak). | α |
| (69) There is no evidence of impact of rosiglitazone on fertility (weak). | α |

The above represent the consensus statements from the WES Montpellier Consensus.
GPP, good practice point; α, unanimous or near-unanimous (more than 80% agreed without caveat and fewer than 5% disagreed); β, unanimous with caveat (fewer than 5% disagreed but fewer than 80% agreed without caveat); γ, majority (50–80% agreed); δ, no consensus (fewer than 50% agreed with or without caveat).

surgery (Mutihir and Nyango, 2010). It was agreed that a history of endometriosis should be considered an obstetric risk factor and pregnancies managed accordingly.

### *Menopausal women with endometriosis*

It has been reported that after a diagnosis of endometriosis, 96.9% of women become free from pain after menopause (Fagervold *et al.*, 2009). However, post-menopausal endometriosis has seldom been investigated, though symptoms usually disappear after a natural or a surgical menopause. The risk of recurrence with hormone therapy is probably increased in women with residual disease after surgery and the consequent management is best monitored by responding to specific symptoms (Moen *et al.*, 2010). Although endometriosis may recur, there is no strong evidence to deprive women of hormone replacement treatment (HRT) if they suffer severe menopausal symptoms but have a history of endometriosis, although combined estrogen-progestin hormone therapy is advisable (Al Kadri *et al.*, 2009; Moen *et al.*, 2010).

### *Ovarian cancer*

There is a recognized association between endometriosis and clear cell, low-grade serous and endometrioid ovarian cancer (Pearce *et al.*, 2012), but the overall risk of ovarian cancer amongst women with endometriosis remains low, with a relative risk ranging from 1.3 to 1.9 (Sayasneh *et al.*, 2011) which means that at worst the lifetime risk of ovarian cancer is increased from ~1 in 100 to 2 in 100. Yet so far there is no unequivocal evidence of causality in this association. Thus, there is no evidence in favour of routine ovarian cancer screening for women with endometriosis, but the question remains as to whether there is a higher risk group amongst women with endometriosis in whom screening may be justified (such as those with recurrent ovarian cysts or suspected but unremoved endometrioma in the menopause). It is recommended that future studies must endeavour to clearly establish or exclude causality rather than mere association due to shared risk factors. Establishing a genetic basis of subgroups of women with endometriosis may lead to the identification of any pre-disposition of certain cancers, and thus a possible identification of high-risk subgroups. Only then can specific clinical guidelines be recommended.

### *Lifestyle and dietary interventions*

Whilst the overwhelming response from women managing their endometriosis is that these interventions do help to improve the quality of life, few well-designed studies have examined lifestyle factors. Examples of lifestyle interventions described as helpful but not so far exposed to randomized controlled trial (RCT) scrutiny include simply 'talking to someone', cognitive behavioural therapy and different types of exercise including yoga. No well-designed studies have examined exercise, but a small observational retrospective study suggests that exercise might be effective in reducing dysmenorrhoea (Koppan *et al.*, 2010). There is no evidence to support weight reduction having a beneficial impact on symptomatic endometriosis. No consensus could be established regarding dietary interventions, although evidence from two RCTs showed that dietary intervention following endometriosis surgery in the form of vitamins, minerals, salts, lactic ferments and fish oil appears to be an effective alternative to hormonal treatment, that is associated with similar pelvic pain reduction and quality of life improvement (Sesti *et al.*, 2007, 2009). Observations that certain diets (especially a gluten-free diet) improve symptoms for some women with endometriosis remain unconfirmed in RCTs. For dysmenorrhoea in the absence of proven endometriosis, one small trial showed fish oil (omega-3 fatty acids) to be more effective than placebo for pain relief (Proctor and Murphy, 2001).

### *Empirical medical treatment for symptoms of endometriosis*

Many clinicians support empirical medical treatment of endometriosis either prior to or without laparoscopic confirmation of endometriosis. Time to surgery may delay appropriate treatment, there is a false-negative rate in laparoscopic diagnosis, and surgery is invasive and expensive compared with empirical therapies, and carries a risk of morbidity. Nonetheless, a full evaluation that includes consideration of other causes of the symptoms and assessment of the disease impact for the woman is required prior to empirical treatment. Management of pelvic pain should not be delayed in order to obtain surgical confirmation of endometriosis, even though most of the RCT evidence is from women with surgically confirmed endometriosis. Although the definition of medical treatments as first line versus second line is arbitrary, we adopted as first line those treatments that most clinicians would consider using empirically and second line those treatments that most would reserve for treatment following laparoscopic diagnosis. Well-tolerated, low-cost, easily accessible options such as non-steroidal anti-inflammatory drugs (NSAIDs) (Allen *et al.*, 2009), other analgesics (paracetamol and opioids, although most clinicians would reserve opioid analgesics for second-line treatment), the combined oral contraceptive pill (OCP) (Davis *et al.*, 2007; Harada *et al.*, 2008; Guzick *et al.*, 2011; Vercellini *et al.*, 2011) and traditional progestins such as medroxyprogesterone acetate (Crosignani *et al.*, 2006; Schlaff *et al.*, 2006) and norethisterone (Vercellini *et al.*, 2011; Brown *et al.*, 2012) or newer progestins such as dienogest (Cosson *et al.*, 2002; Harada *et al.*, 2009; Momoeda *et al.*, 2009; Köhler *et al.*, 2010; Strowitzki *et al.*, 2010a, b, 2012; Petraglia *et al.*, 2012), should be considered for use as first-line empirical medical treatment. Some clinicians would, in certain circumstances, consider second-line medical treatment with gonadotrophin-releasing hormone agonists (GnRH-a) with add-back HRT (Brown *et al.*, 2010), the levonorgestrel-releasing intrauterine system (LNG-IUS) (Abou-Setta *et al.*, 2006) or opioid analgesics as empirical treatment for women who are not optimally treated with first-line empirical therapy prior to surgical diagnosis and treatment, whilst awaiting laparoscopic surgery (and some women successfully treated with second-line empirical medical treatment might not proceed to surgery). It is unclear whether medical treatment prior to laparoscopy might mask the diagnosis by reducing the appearance of endometriotic implants and hence may make endometriosis more difficult to treat surgically. It is important to highlight that NSAIDs have important side effects, including peptic ulceration and an adverse impact on ovulation, and that analgesics, particularly opiates, if used inappropriately and without medical monitoring, carry a risk of abuse and/or addiction. All women receiving medical treatment should be carefully monitored with regular follow-up consultations.

### *Surgical management of endometriosis symptoms*

The issue of appropriate laparoscopic surgical training is considered vital and there are strong arguments for standardization of what constitutes the relevant experience and expertise for those undertaking complex laparoscopic surgery for endometriosis. Crucial aspects in planning laparoscopic surgery are that surgery should be carried out in the most appropriate setting which can ensure adequate preoperative counselling, appropriate surgical expertise (to ensure the most appropriate procedure is undertaken by the most experienced surgeon at the most appropriate time), adequate technical resources and postoperative support care. Whenever possible, laparoscopic surgery should always be undertaken in preference to laparotomy. It is also important, particularly in cases of more severe endometriosis, that surgeons consider the option of limiting surgical excision at an initial operation in order to refer to a surgeon better equipped to deal with endometriosis, as the first definitive surgical intervention has been shown to deliver the greatest benefit (Abbott *et al.*, 2004).

Laparoscopic surgical removal of endometriosis (through either excision or ablation of endometriosis or both) is an effective first-line approach for treating pain related to endometriosis (Jacobson *et al.*, 2009). Although RCTs have failed to demonstrate the benefit of excision over ablation (Wright *et al.*, 2005; Healey *et al.*, 2010), there is unanimous consensus over the recommendation to excise lesions where possible, especially deep endometriotic lesions, which is felt by most surgeons to give a more thorough removal of disease (Koninckx *et al.*, 2012). It is also acknowledged that, even after expert removal of endometriosis, there may be a recurrence rate of symptoms and endometriotic lesions that varies from 10 to 55% within 12 months (Vercellini *et al.*, 2009), with recurrence affecting ~10% of the remaining women each additional year (Guo, 2009). The risk of requirement for repeat surgery is higher in women younger than 30 years at the time of surgery (Shakiba *et al.*, 2008). First operations tend to produce a better response than subsequent surgical procedures, with pain improvements at 6 months in the region of 83% for first excisional procedures versus 53% for second procedures (Abbott *et al.*, 2004). Excessive numbers of repeat laparoscopic procedures should therefore be avoided. The role of a purely diagnostic laparoscopy has been questioned and, ideally, there should always be the option of continuing to surgical removal of endometriosis, within the limitations of the surgeon's expertise.

There is insufficient evidence to necessitate the planning of surgery for a particular time of the cycle; however, surgery in the follicular

phase avoids the complicating factor of the presence of a haemorrhagic corpus luteum and one study suggested an increased recurrence rate for surgery undertaken in the luteal phase, hypothesized to be due to re-implantation through retrograde loss of endometrial tissue at subsequent menses whilst the sites of surgically removed lesions were still healing (Schweppe and Ring, 2002).

There is no place for adding laparoscopic uterine nerve ablation (LUNA) to laparoscopic removal of endometriosis (Proctor *et al*., 2005). Although presacral neurectomy (PSN) might provide benefit for a small number of women with central dysmenorrhoea, the benefits are likely to be outweighed by the potential for harmful effects (including presacral haematoma and dysfunction of bladder and/or bowel) and PSN is not usually recommended (Proctor *et al*., 2005). Laparoscopic PSN, if ever undertaken, should be performed only by expert surgeons.

Laparoscopic excision (cystectomy) for ovarian endometriomas is preferred to laparoscopic ablation (drainage and coagulation) where possible to minimize symptom recurrence and endometrioma recurrence, although care must be taken to minimize damage to surrounding normal ovarian tissue (Hart *et al*., 2008). Despite most endometriotic cysts being predominantly extra-ovarian in nature, systematic cystectomy performed by highly experienced surgeons has been shown to reduce ovarian volume (Biacchiardi *et al*., 2011). The value of a multiple-step procedure (interval surgery that utilizes intervening medical suppressive treatment) requires further evaluation, particularly for large ovarian endometriomas (Tsolakidis *et al*., 2010).

Although the OCP reduces the recurrence rate of endometriomas after ovarian cystectomy (Seracchioli *et al*., 2010), evidence does not otherwise support the use of short-term pre- or post-operative medical treatment, in association with laparoscopic removal of endometriosis, for improving pain outcomes or recurrence rates (Furness *et al*., 2009).

Different approaches have been taken to surgery for deep endometriosis. The dilemma is that incomplete resection may reduce symptomatic outcomes (Vercellini *et al*., 2006), but that radical interventions increase the risk of major complications such as ureteric and rectal injuries (Koninckx *et al*., 1996). Evidence is still lacking to guide the best surgical approach to deep endometriosis. If the disease includes bowel endometriosis, the surgical options for the bowel include shaving, disc excision or segmental excision and re-anastomosis. Rather than undertake bowel surgery initially, the optimal approach is to first consider medical treatment. Bowel surgery should only proceed on the basis of shared decision-making after thorough consideration of risks versus benefits, ideally following multi-disciplinary consultations that include provision of information for women on potential complications of surgery. Only then should bowel surgery be performed laparoscopically by experts, avoiding laparotomy whenever possible. What is clear is that highly specialized surgical expertise is required in surgery for deep endometriosis and it should be undertaken only in centres of expertise.

Debate continues over the role of hysterectomy and of concurrent oophorectomy, with little reliable evidence to inform practice, but if such surgery is undertaken, it should be performed laparoscopically where possible. Observational studies have suggested improved pain outcomes for women who undergo hysterectomy for r-ASRM Stage IV endometriosis (Ford *et al*., 2004), but this may be related to associated pathology such as adenomyosis.

### *Medical management of endometriosis symptoms*

We again arbitrarily defined as first line those medical treatments that most clinicians would consider using empirically and second line those treatments that most would reserve for treatment following laparoscopic diagnosis. Medical treatment may be given routinely as an adjunct to surgery either pre- or post-operatively (see above under surgical management), as a defined course of treatment remote from surgery or as a longer term medical treatment strategy designed to prevent recurrence of endometriosis or endometriomas (Vercellini *et al*., 2013).

Well-tolerated, low-cost, easily accessible options such as NSAIDs (Allen *et al*., 2009), other analgesics (that include paracetamol, with an aim of effective pain relief) and OCPs can be considered for use as first-line medical treatment of laparoscopically proven endometriosis (Davis *et al*., 2007; Harada *et al*., 2008; Guzick *et al*., 2011; Vercellini *et al*., 2011); OCPs are particularly effective in minimizing endometrioma recurrence rates after surgical removal of the cyst (Seracchioli *et al*., 2010). Progestins with a proven effect in RCTs and with a specific indication for the treatment of endometriosis such as medroxyprogesterone acetate (Crosignani *et al*., 2006; Schlaff *et al*., 2006), norethisterone (Vercellini *et al*., 2011; Brown *et al*., 2012) and dienogest (Cosson *et al*., 2002; Harada *et al*., 2009; Momoeda *et al*., 2009; Köhler *et al*., 2010; Strowitzki *et al*., 2010a, b, 2012; Petraglia *et al*., 2012) can also be considered as first-line treatments taking into consideration their different side-effect profiles. It is important to discuss potential side effects with the woman before treatment commences, and careful monitoring through regular follow-up appointments is recommended.

Second-line medical treatments could include GnRH-a (Brown *et al*., 2010), which should be used with add-back HRT routinely (Farmer *et al*., 2009), LNG-IUS, despite more research into effectiveness and relative effectiveness being required (Abou-Setta *et al*., 2006), depot progestins, although the side-effect profile and thus treatment burden is high (Bayoglu *et al*., 2011), and opioid analgesics. Other possible second-line medical treatments include non-oral combined hormonal contraceptives, such as transdermal patches and vaginal rings (Vercellini *et al*., 2010). Danazol and gestrinone should not be used owing to the high-treatment burden of androgenic side effects (Selak *et al*., 2007), other than for women, established on these treatments in the absence of side effects, for whom other treatments have proven ineffective. Again, acceptable side effects need to be discussed carefully with the woman.

Hypothetically, medical maintenance therapy might be an effective treatment option that could, in some cases, control the denervation and re-innervation changes that are believed to precede central sensitization and the development of a chronic pain syndrome. Whilst the use of medical treatments such as OCP may be long term, specific studies are needed to investigate whether medical intervention may prevent the development of a chronic pain syndrome. However, most medical agents are only effective for the duration of their use and symptoms often recur on treatment cessation.

### *Emerging medical treatments for management of endometriosis symptoms*

For the emerging medical treatments, data are insufficient to recommend these treatments for routine clinical use. Aromatase inhibitors

(anastrazole, fadrozole, formestane, exemestane, letrozole) (Ferrero *et al.*, 2011), selective progesterone receptor modulator (mifepristone, ulipristal) (Guo *et al.*, 2011) and orally active GnRH antagonists (elagolix) (Struthers *et al.*, 2009) have shown some promise and effectiveness in RCTs, but more clinical experience is required with these agents and more clinical trial research data are essential, especially with regard to their long-term efficacy and side effects. For the immunomodulator, pentoxifylline (Lu *et al.*, 2012), and the anti-TNF-α agent, infliximab (Koninckx *et al.*, 2008), RCTs have not shown benefit to date. The selective estrogen receptor modulator (SERM), raloxifene, has been shown not to provide benefit (Stratton *et al.*, 2008). Possible future treatments yet to be exposed to RCT scrutiny, but where observational studies and case series have suggested promise, include the selective progesterone receptor modulators (SPRMs) asoprisnil and megestrol (Spitz, 2009), the thiazolidinedione, rosiglitazone (Moravek *et al.*, 2009) and valproic acid (Liu and Guo, 2008). As angiogenesis is a crucial activity for the normal processes of the reproductive tract and other organ systems, it is dubious whether agents used for their anti-angiogenic properties (including cabergoline, endostatin, sirolimus, thalidomide and vascular endothelial growth factor inhibitors) will be useful clinically and these have been used only in animal research to date (Laschke and Menger, 2012).

### *Complementary therapies for endometriosis symptoms*

Complementary therapies may help women to cope better with their endometriosis and its treatment and are supported by some evidence from RCTs.

*Endometriosis specific*. Acupuncture appears to be moderately effective and safe but requires repeated treatments (Zhu *et al.*, 2011). High-frequency transcutaneous electrical nerve stimulation (TENS) has some effectiveness for short-term pain management (Proctor *et al.*, 2002). There is limited evidence in favour of Chinese herbal medicine that may be difficult to apply outside of the Traditional Chinese Medicine setting (Zhu *et al.*, 2008; Flower *et al.*, 2012). While a voluminous literature exists in almost exclusively Chinese medical journals, various problems in study design, execution, statistical analysis and reporting among papers published in Chinese journals make it extremely difficult to judge the efficacy of the evaluated herbal medicine (Guo *et al.*, 2010).

*Dysmenorrhoea only*. There is limited evidence of benefit for vitamins B1 and B6, with safety concerns associated with higher doses of vitamin B6 (Proctor and Murphy, 2001). Moderate quality evidence supports the use of magnesium (Proctor and Murphy, 2001). Topical heat may be effective for low back pain, but there are no studies specifically examining dysmenorrhea (French *et al.*, 2006). Spinal manipulation (Proctor *et al.*, 2006) and behavioural interventions (Proctor *et al.*, 2007) are not recommended currently, with more research required for these types of interventions. Cannabis has been shown to be moderately effective for relieving chronic pain (Lucas, 2012), but its benefits are far outweighed by potentially serious side effects and there are no studies in women with endometriosis.

### *Surgery for endometriosis-associated infertility*

The principles of laparoscopic surgery for subfertility are similar to those for other endometriosis symptoms. Appropriate surgical training is again the key to the best outcomes. It is very important to consider ovarian reserve prior to laparoscopic surgery in the woman experiencing infertility (Pellicano *et al.*, 2008) in particular because evidence is growing that surgical treatment of endometriomas contributes to reduced ovarian reserve (Somigliana *et al.*, 2012; Streuli *et al.*, 2012). The co-existence of pain will be an important factor to consider that will impact on the decision whether to proceed with surgery, although surgery and ART should be considered as complementary strategies.

Laparoscopic surgical removal of endometriosis is recognized as being effective in improving fertility in stage I and II endometriosis (Jacobson *et al.*, 2010). Although RCTs have failed to demonstrate the benefit of excision over ablation, it is recommended to excise lesions where possible, especially deep endometriosis where pain is present (Koninckx *et al.*, 2012). No RCTs have to date assessed whether surgery improves fertility in stage III and IV endometriosis and in deep endometriosis. The functional appearance of the fallopian tubes and ovaries at the end of the laparoscopic procedure appears to contribute to the chance of natural conception post-operatively (Adamson and Pasta, 2010).

Laparoscopic excision (cystectomy) whenever possible for endometriomas $>4$ cm in diameter improves fertility more than ablation (drainage and coagulation) (Hart *et al.*, 2008). However, much care needs to be taken in identification of tissue planes and careful dissection of the endometrioma to avoid removing normal ovarian tissue and thus impacting on ovarian reserve. There is also the possibility that suturing for haemostasis might maintain ovarian reserve more effectively than electrosurgical haemostasis (Pellicano *et al.*, 2008) and, at the very least, minimization of the use of energy modalities in haemostasis is imperative. Young women, for whom fertility is a consideration, might benefit from discussion of the option of oocyte freezing prior to undergoing ovarian endometrioma surgery, especially if bilateral.

The best surgical approach for deep endometriosis in the context of endometriosis-related infertility remains unclear, even though observational studies suggest good fertility results in women who undergo laparoscopic excision (Chapron *et al.*, 1999; Vercellini *et al.*, 2006; Barri *et al.*, 2010) or laparoscopic shaving (Donnez and Squifflet, 2010). Similarly, colorectal excision is suggested to be beneficial in observational studies (Ferrero *et al.*, 2009; Stepniewska *et al.*, 2010). So far these surgical approaches have not been assessed in RCTs and carry a high risk of complications. Laparoscopic surgery for deep endometriosis, including colorectal endometriosis, should be considered a second-line treatment after failed IVF (unless IVF is not feasible or the patient has severe pain symptoms) and its place in the absence of on-going pain symptoms needs further evaluation.

The pregnancy rate after repeat surgery is lower, approximately half that after first surgery (Vercellini *et al.*, 2009), and two cycles of IVF might be more effective, but surgery should be considered for women with endometriosis-related infertility who continue to be symptomatic or have enlarging endometriomas, and women for whom IVF is declined or repeatedly unsuccessful.

Medical adjunct therapy in conjunction with laparoscopic surgery has not been shown to benefit fertility and is not recommended (Furness *et al.*, 2009); post-operative medical adjunct therapy may delay pregnancy at a time when fertility has been improved by surgery.

*Assisted conception for endometriosis-associated infertility*

In terms of medically assisted reproduction (MAR), IUI combined with ovarian stimulation (OS) is an effective option for women with minimal-to-mild endometriosis, if the fallopian tubes are normal (Tummon *et al*., 1997; Costello, 2004). IUI/COS is more effective than unstimulated IUI, with gonadotrophin stimulation appearing to be more effective than that with clomiphene, and the role of unstimulated IUI is uncertain for women with endometriosis (Costello, 2004). However, multiple pregnancy is a key hazard of OS and all reasonable steps should be employed to avoid multiple pregnancy. No consensus could be established over double insemination for IUI (Subit *et al*., 2011). However, IVF is commonly offered first line in preference to IUI when endometriosis is more severe and tubal function is impaired, or in the context of advanced female age and/or reduced sperm quality.

It is unclear whether controlled OS alone provides fertility benefit for women with endometriosis and whether gonadotrophins provide benefit over, for example, letrozole (Aygen *et al*., 2010).

Endometriosis may have a negative impact on IVF success rates compared with other causes of infertility (Barnhart *et al*., 2002). Nonetheless, IVF is recommended as a fertility treatment for women with endometriosis, especially if fallopian tube function is compromised or if there are other infertility factors such as male factor (Soliman *et al*., 1993). The chance of success is similar for GnRH antagonist versus GnRH agonist protocols (Benschop *et al*., 2010). IVF does not appear to increase the risk of recurrence of endometriosis (D'Hooghe *et al*., 2006).

*Adjunct therapy to assisted conception for endometriosis-associated infertility*

Medical treatment (including GnRH agonist) (Rickes *et al*., 2002) and laparoscopic surgical treatment (Tanahatoe *et al*., 2005) prior to IUI/COS is not recommended, since there are insufficient data demonstrating benefit.

Treatment with GnRH agonist for 3–6 months prior to IVF is effective at improving the chance of IVF success (Sallam *et al*., 2006). There are insufficient data to recommend the use of OCP prior to IVF/ICSI (de Ziegler *et al*., 2010) and no data to compare the approach of pretreatment with OCP versus GnRH agonist. There is concern that the presence of an endometrioma may damage the ovary, yet on the other hand, ovarian response to stimulation in IVF might be reduced in some women who have had an endometrioma removed (Yu *et al*., 2010). The benefit of laparoscopic removal of endometriosis and/or endometriomas prior to IVF is unclear with respect to IVF outcome (Bianchi *et al*., 2009; Benschop *et al*., 2010), although it may improve access to the ovaries and even reduce the chance of infection related to the oocyte collection procedure. Whilst laparoscopic surgery following repeat failure of IVF treatment may improve the chance of natural conception, its role as an adjunct to IVF is unclear. Any decisions to perform surgery for endometriomas or deep endometriosis before ART should be made only after fully informed consent by surgeons with appropriate expertise.

*Medical therapy for endometriosis-associated infertility*

There is no evidence of fertility benefit from medical treatment; ovulation suppression may delay pregnancy and this is not recommended (Hughes *et al*., 2007).

*Emerging therapies for endometriosis-associated infertility*

In one RCT, uterine bathing and tubal flushing with the oil-soluble contrast medium lipiodol has been reported to improve live birth rates in women, with endometriosis with otherwise unexplained infertility, who are attempting natural conception (Johnson *et al*., 2004). The role of lipiodol hysterosalpingography as an adjunct to IVF remains unclear (Reilly *et al*., 2011).

There is insufficient evidence to recommend the use of the following for fertility benefit: pentoxifylline (Lu *et al*., 2012), traditional Chinese medicine (Guo *et al*., 2010; Flower *et al*., 2012), vitamins C or E (Mier-Cabrera *et al*., 2008), mifepristone (Guo *et al*., 2011), rosiglitazone (Moravek *et al*., 2009) or valproic acid (Liu and Guo, 2008).

# Discussion

We have developed a first international consensus statement on the management of endometriosis through rigorous methodology. An obvious finding in the quest for a consensus statement is that unanimity from a range of experts in any statement is difficult to attain. In our survey that followed the consensus meeting, none of the statements made achieved 100% agreement without the expression of a caveat about either the statement or the strength of the statement, and only 7 of our 69 consensus statements were associated with a 0% disagreement rate from the survey respondents. However, in the case of only two statements, we were unable to achieve a majority consensus.

The strength of this consensus statement is that it is truly international, with a breadth of representation from six continents across medical, surgical and fertility organizations, including a voice for the women themselves via 16 involved endometriosis organizations. There are potential weaknesses in a consensus process such as this. Some of our statements are not strongly based on research evidence and were termed GPPs; however, such statements could still be associated with a strong consensus amongst the group of experts. We will inevitably have overlooked some interventions that could be relevant, in spite of the methodology and feedback from all participants. It is therefore intended that this consensus will be updated regularly in response to feedback and, hopefully, increasing evidence in our field.

Unsurprisingly, there are similarities in our consensus statements with existing guidelines for managing endometriosis, but also the kind of differences that might be expected from the coalescence of an eclectic group of experts from many different standpoints. One of the real values to the participants in such an exercise is the opportunity to recognize a completely new perspective and interpretation of existing evidence; this can be applied in any multidisciplinary setting, where specialists in medical, surgical and fertility treatment join forces with women affected by endometriosis. In some cases, the strength of our statements (and in some cases, even the GRADE score) or the content of statements themselves conflict with those in other guidelines. We endeavoured to make strong statements (i) where the evidence was moderate or strong, in other words derived from reliable and reproducible RCTs (and even in some cases where the evidence was insufficient or negative where such evidence was deemed strong) or (ii) where the risk or expense of an intervention strongly justifies its non-use in the context of marginal or insufficient evidence or (iii) where there was enormous potential for benefit from a simple, low-invasive, low-cost intervention, to overcome a substantial burden of suffering, even in the face of only weak or absent research evidence (as in the case of our GPPs).

It must be emphasized that our process differed from that of guideline development. There is no general consensus on the most appropriate methodology for consensus statements and so we have adopted the methodology for the GRADE system of grading the quality of evidence (Guyatt *et al*., 2008) (now felt to be the most relevant method of grading evidence and recommendations in guidelines) and adapted this to our consensus process. The turbulence that is present in the normal clinical environment is reflected by the fact that there is much lack of consensus amongst experts surrounding all aspects of the management of endometriosis. This also reflects the fact that the reality of the clinical situation at an individual level is far more complex than the idealized situation in an RCT. It must also be acknowledged that a consensus statement from international experts would almost certainly be subtly different with a different group of experts, although it is hoped that our broad sample of individuals was representative of the spectrum of viewpoints of all the members of all the organizations and societies represented.

Key issues that we have few answers for are management of the adolescent who has, or might have, endometriosis (more research is required and focus needs to be applied to management algorithms for young women and adolescents) as well as intervention strategies in the younger age group designed to prevent endometriosis; lifestyle and dietary interventions (where research evidence is largely absent); standardization of long-term strategies for prevention of recurrent endometriosis; clarification of management strategies, both surgical and medical, for women with deep endometriosis; development of standards of experience and expertise required for surgeons undertaking advanced laparoscopic endometriosis surgery; standardization of centres/networks of expertise with regard to definition, accreditation and longevity; development of models of care in low-resource settings and understanding endometriosis and its potential treatment after menopause. We have not addressed the important issue of diagnosis and classification of endometriosis, which would benefit from a similar international consensus approach. Individualization of every woman's care is an important factor in long-term management. Furthermore, it is possible that a subpopulation of women with endometriosis (depending on age, impact of symptoms, severity of disease, current or future fertility wishes, lifestyle factors, previous treatments and possibly disease markers) will benefit from some form of medical treatment to alter the course of this condition longer term (Vercellini *et al*., 2011); the challenge is to identify these subpopulations and long-term management strategies. Further assessment of emerging therapies is also a key factor and this has been much neglected in recent times. It is of concern that, although many pre-clinical studies have shown positive results, very few have progressed to become phase II/III clinical trials, let alone proved to be effective (Guo *et al*., 2009). In 2009, of 15 registered clinical trials in endometriosis, listed as completed, only three had been published, whilst the remaining 12 (80%) were unpublished (Guo *et al*., 2009). More systematic and coordinated research effort and funding is required at an international level, so that any breakthrough treatment does not remain elusive, nor any research effort is ignored in order for others to continue to build upon results, be these positive or negative.

# Conclusion

This consensus initiative, undertaken on a global scale through global collaboration by the WES, kept uppermost the goal of improving the quality of life for women with endometriosis. This paper is the outcome of the first ever attempt to bring a global collaborative consensus to the management of endometriosis, reflecting the best scientific evidence available.

# Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

# Acknowledgements

This consensus statement is dedicated to our friend and colleague Professor David Healy who contributed to and presented at the consensus meeting in Montpellier, but whose untimely passing in May 2012 has meant the loss of a visionary leader in our field.

# Authors' roles

N.P.J. and L.H. accept full authorship responsibility on behalf of the WES Montpellier Consortium.

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# Conflict of interest

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# Appendix

The complete list of people representing The World Endometriosis Society Montpellier Consortium is as follows: M.S. Abrao, G.D. Adamson, C. Allaire, V. Amelung, E. Andersson, C. Becker, K.B. Birna Árdal, D. Bush, B. de Bie, K. Chwalisz, H. Critchley, T. D'Hooghe, G. Dunselman, J.L.H. Evers, C. Farquhar, T. Faustmann, A. Forman, J. Fourquet, I. Fraser, L. Giudice, S. Gordts, H. Guidone, S.W. Guo, D. Healy, B. Hedon, J. Hulkkonen, L. Hull, L. Hummelshoj, N.P. Johnson, M. Just, L. Kiesel, A. Lam, C. Lynam, L. Mettler, C. Miller, H. North, R. Pai, C. Petta, L. Prentice, S. Reilly, F. Reis, E. Rolla, L. Rombauts, K.W. Schweppe, T. Seckin, K. Sharpe-Timms, D. Shepperson Mills, S. Singh, D. Soriano, M. Stafford-Bell, P. Stratton, R. Taylor, J. Tsaltas, J. Veit and P. Vercellini.

**Supplementary Information 1: Methodology**

| | |
|---|---|
| March 2011 | Invitations sent to 51 national and international medical and non-medical organisations to participate in this consensus process and to nominate their society's representative; 36 accepted, seven declined, and there was no response from nine societies |
| April 2011 | Participants confirmed, and invited to provide feedback to the process |
| May 2011 | Process finalised and topics raised with potential speakers |
| June 2011 | Draft agenda with topics and speakers circulated for feedback |
| July 2011 | Email discussion on topics and content |
| July – August 2011 | Extensive literature search |
| 3 August 2011 | Telephone meeting to finalise agenda |
| 20 August 2011 | Submission of PowerPoint presentations |
| 8 September 2011 | Consensus meeting |
| Sep-Nov 2011 | Draft consensus statements |
| Dec 2011 – Jan 2012 | First round of manuscript feedback |
| Feb-March 2012 | Online vote on each of the 69 consensus statements |
| April-August 2012 | Manuscript revision |
| September-November 2012 | Final manuscript review |

**Supplementary Information 2: Detailed instructions to presenters at the WES Montpellier Consensus Meeting on the Current Management of Endometriosis**

Feedback was given from the participants on the various topics and the suggested scope of speakers. Speakers were then asked to volunteer their proposed scope, which was considered, refined and finalised. Speakers were reminded to cover the material in 10 minutes and thereby requested to leave time for discussion.

The brief to speakers was:

- To prepare a presentation to last no more than half the allotted time, ie. max 10 minutes for a 20-minute timeslot.
- To present the evidence, working from an 'evidence hierarchy'
    1) First systematic review (if possible, a Cochrane review) if available, then any other RCTs published since the systematic review search was conducted; if not available then:
    2) Individual RCT evidence in the absence of a systematic review of RCTs; if not available then:
    3) Controlled study; if not available then:
    4) Observational study; if not available then:
    5) Other evidence or expert advice.
- To consider benefits – but also risks, burden and costs.
- To consider where there are gaps in the evidence necessitating further research.
- To consider the GRADE system in assessing evidence and to come up with a suggested GRADE of quality of evidence for each of the statements (see Supplementary Information for GRADE System and attached document regarding GRADE System if further info is required)
- To prepare a concluding slide (or slides) with proposals for the consensus statements in their particular topic for comments/voting by meeting participants in Montpellier.
- To complete the presentation by 3 August 2011.
- To outline any problems encountered at the audio conference on 3 August 2011.
- To then finalise the presentation on PowerPoint and send this to Lone Hummelshoj and Neil Johnson before 20 August 2011.
- To deliver the presentation at the WES Montpellier Consensus Meeting on the Current Management of Endometriosis on 8 September 2011.

The finalised topic lists with their revised scope proposed (including suggestions for patients, interventions, comparisons and outcomes (PICO) where appropriate) for each speaker were as follows.

**Introduction, Concept, Expectations, AGREE Tool, sub-populations, GRADE and consensus process (Neil Johnson)**

**Causes/associations of endometriosis (Linda Giudice)**

Brief summary of the proposed main causes or associations of endometriosis, including mechanisms of endometriosis formation; genetic, environmental, molecular and immune associations.

**What evidence is there that endometriosis is associated with pain and other symptoms? (Pam Stratton)**

Evidence to describe the association or causation of pain and other (non-infertility) symptoms (such as menstrual bleeding problems and fatigue) by endometriosis.

Free rein to explore the evidence that pain and other non-infertility symptoms are associated with the pathophysiological aspects of endometriosis.

To extend this into other non-infertility symptoms in addition to pain, such as abnormal menstrual bleeding, fatigue etc.

**What evidence is there that endometriosis is associated with infertility? (Thomas D'Hooghe)**

Evidence to describe the association or causation of infertility by endometriosis.

Again free rein, as above.

**How is endometriosis diagnosed clinically, including potential bio-markers? (Robert Taylor)**

Brief mention of gold standard diagnosis and how the other 'diagnostic tests' perform in comparison to the gold standard

P: Women who may have endometriosis

I: Diagnostic tests, including:

Symptoms

Signs

Biomarkers

Combinations of the above

Non-invasive diagnostic tests (including nerve fibre density in endometrial biopsies and other endometrial changes)

Blood tests incl CA125 levels

Urine tests

Imaging, including ultrasound, transvaginal and transrectal sonography, MRI

Others

Laparoscopy +/- Biopsy

C: Diagnostic accuracy in comparison to gold standard test (laparoscopy +/- biopsy)

O: Likelihood ratios

Diagnostic odds ratios

Sensitivity

Specificity

Positive predictive value

Negative predictive value

Any others?

**What evidence supports centres of expertise in the management of endometriosis? (Lone Hummelshoj)**

P: Women with endometriosis

Women with histologic confirmation and those without histology sampling

Those previously surgically treated, those not previously surgically treated and both

Women with endometriomas

Deep endometriosis

Bowel endometriosis

I: Management in a centre of expertise

What are the important elements of a centre of expertise?

C: Management outside a centre of expertise

O: Quality of life

Pain symptoms (dysmenorrhoea, dyspareunia, dyschezia, general chronic pelvic pain)

Other symptoms – menstrual bleeding anomalies, fatigue, bowel symptoms etc

Fertility outcomes

Risks, burden and costs

**What evidence supports patient support organisations in the management of endometriosis? (Deborah Bush)**

P: Women in whom a diagnosis of endometriosis has been suspected or made but who have not had laparoscopic confirmation (empirical emerging therapy interventions)

Women with endometriosis diagnosed at laparoscopy

Women with histologic confirmation and those without histology sampling

Those previously surgically treated, those not previously surgically treated and both

Women with endometriomas

Deep infiltrating endometriosis

Bowel endometriosis

Adolescents

Menopausal women

I: Management involving patient support organisation

C: Management without involving patient support organisation

O: Quality of life

Pain symptoms (dysmenorrhoea, dyspareunia, dyschezia, general chronic pelvic pain)

Other symptoms – menstrual bleeding anomalies, fatigue, bowel symptoms etc

Fertility outcomes

Risks, burden and costs

**Life Journey of Women with Endometriosis (10 minutes each topic, ie. 3 slides from each presenter and max 3 minutes presentation, followed by 7 minutes discussion):**

**Adolescence (Mauricio Abrao)**

Brief presentation of key proposed consensus statements for discussion relating to adolescence and endometriosis

**Obstetric Issues (Liselotte Mettler)**

Brief presentation of key proposed consensus statements for discussion relating to obstetric issues for women with endometriosis

**Menopause (Stephan Gordts)**

Brief presentation of key proposed consensus statements for discussion relating to menopause and endometriosis

**Ovarian cancer (David Healy)**

Brief presentation of key proposed consensus statements for discussion relating to cancer and endometriosis

**Low Resource Settings Including Developing countries (David Adamson)**

To propose a small number of consensus statements that could be considered priorities for developing countries in the management of endometriosis

**Interventions for pain and other symptoms:**

**What evidence supports lifestyle interventions (including dietary & exercise) in the management of endometriosis? (Carlos Petta)**

P: Women in whom a diagnosis of endometriosis has been suspected or made but who have not had laparoscopic confirmation (empirical lifestyle interventions)

Women with endometriosis diagnosed at laparoscopy

Women with histologic confirmation and those without histology sampling

Those previously surgically treated, those not previously surgically treated and both

Women with endometriomas

Deep infiltrating endometriosis

Bowel endometriosis

I: Dietary intervention

Exercise intervention

Other lifestyle intervention

C: Placebo or no intervention

Medical treatment incl. OCP or progestins used continuously

O: Quality of life

Pain symptoms (dysmenorrhoea, dyspareunia, dyschezia, general chronic pelvic pain)

Other symptoms – menstrual bleeding anomalies, fatigue, bowel symptoms etc.

Risks, burden and costs

**What evidence supports empirical medical treatment in the management of endometriosis? (Sony Singh)**

P: Women in whom a diagnosis of endometriosis has been suspected or made but who have not had laparoscopic confirmation

I: Oral contraceptive pill

Progestins

GnRH analogues

Other empirical medical treatments

C: No treatment

Other medical treatment (incl. OCP or progestins used continuously)

Surgical intervention

O: Quality of life

Pain symptoms (dysmenorrhoea, dyspareunia, dyschezia, general chronic pelvic pain)

Other symptoms – menstrual bleeding anomalies, fatigue, bowel symptoms etc.

Risks, burden and costs

**What evidence supports surgery in the management of endometriosis? (Charles Miller)**

P: Women with endometriosis (diagnosed at laparoscopy)

Women with histologic confirmation and those without histology sampling

Those previously surgically treated, those not previously surgically treated and both

Women with endometriomas

Deep endometriosis

Bowel endometriosis

I: Laparoscopic removal

Excision (and the important modalities or techniques of excision), Ablation (electrosurgical diathermy, $CO_2$ laser, Helica, other modalities) or Both

Stripping versus drainage/coagulation of endometrioma

Adhesiolysis

Radical surgery – hysterectomy and/or oophorectomy

Nerve interruption – presacral neurectomy and LUNA

Adhesion barriers

Pre- and/or post-op medical adjunct therapy (Cochrane review updated January 2011)

C: No intervention

Diagnostic laparoscopy

Medical treatment incl. OCP or progestins used continuously

O: Quality of life

Pain symptoms (dysmenorrhoea, dyspareunia, dyschezia, general chronic pelvic pain)

Other symptoms – menstrual bleeding anomalies, fatigue, bowel symptoms etc.

Risks, burden and costs

**What evidence supports medical therapies (analgesics and hormonal) in the management of endometriosis? (Karl-Werner Schweppe)**

P: Women with endometriosis diagnosed at laparoscopy

Women with histologic confirmation and those without histology sampling (so not just restricted to women with a histologic diagnosis, but could be sub-grouped by this)

Those previously surgically treated, those not previously surgically treated and both

Women with endometriomas

Deep infiltrating endometriosis

Bowel endometriosis

I: Analgesics

NSAIDs

Other analgesics

Hormonal

OCP (and cyclic versus continuous)

Progestins – oral, injectable depot preparations, levonorgestrel-releasing intrauterine system (LNG-IUS)

Gestrinone

Danazol

GnRH-a (with/without add back HRT)

Others – anti-progestins, SERMs, aromatase inhibitors

C: Placebo or no intervention

Medical treatment incl. OCP or progestins used continuously

Surgical treatment

O: Quality of life

Pain symptoms (dysmenorrhoea, dyspareunia, dyschezia, general chronic pelvic pain)

Other symptoms – menstrual bleeding anomalies, fatigue, bowel symptoms etc.

Risks, burden and costs

**What evidence supports complementary therapies in the management of endometriosis? (Cindy Farquhar)**

P: Women in whom a diagnosis of endometriosis has been suspected or made but who have not had laparoscopic confirmation (empirical complementary therapy interventions)

Women with endometriosis diagnosed at laparoscopy

Women with histologic confirmation and those without histology sampling

Those previously surgically treated, those not previously surgically treated and both

Women with endometriomas

Deep infiltrating endometriosis

Bowel endometriosis

I: Behavioural interventions

Chinese herbal medicine

Acupuncture

Other complementary interventions purported as treatments

Any inferences from the primary dysmenorrhoea review incl. interventions such as thiamine, Vit E, high frequency TENS, topical heat, Japanese herbal remedy toku-shakuyaku-san, Vit B12, fish oil, magnesium, acupuncture, other herbal remedies, behavioural interventions, spinal manipulation?

C: Placebo

Medical treatment incl. OCP or progestins used continuously

O: Quality of life

Pain symptoms (dysmenorrhoea, dyspareunia, dyschezia, general chronic pelvic pain)

Other symptoms – menstrual bleeding anomalies, fatigue, bowel symptoms etc.

Risks, burden and costs

**What evidence supports emerging therapies in the management of endometriosis? (Gerard Dunselman)**

P: Women in whom a diagnosis of endometriosis has been suspected or made but who have not had laparoscopic confirmation (empirical emerging therapy interventions)

Women with endometriosis diagnosed at laparoscopy

Women with histologic confirmation and those without histology sampling

Those previously surgically treated, those not previously surgically treated and both

Women with endometriomas

Deep infiltrating endometriosis

Bowel endometriosis

I: SERMs

SPRMs including antiprogestins (eg. mifepristone)

Aromatase inhibitors

Statins

TGF modulators incl. infliximab

Pentoxifylline

Anti-angiogenic therapies

Others

C: Placebo

Medical treatment incl. OCP or progestins used continuously

O: Quality of life

Pain symptoms (dysmenorrhoea, dyspareunia, dyschezia, general chronic pelvic pain)

Other symptoms – menstrual bleeding anomalies, fatigue, bowel symptoms etc.

Risks, burden and costs

**Fertility Interventions:**

**What evidence supports surgical interventions in the management of endometriosis-related infertility? (Jim Tsaltas)**

P: Women with endometriosis and infertility

Different stages

Women with histologic confirmation and those without histology sampling

Those previously surgically treated, those not previously surgically treated and both

Women with endometriomas (but treatments for endometriomas prior to ART will be dealt with elsewhere)

Deep endometriosis

Bowel endometriosis

I: Laparoscopic removal

Excision, Ablation (electrosurgical diathermy, CO2 laser, Helica, other modalities) or Both

Stripping versus drainage/coagulation of endometrioma

Adhesion barriers

Pre- and/or post-op medical adjunct therapy (Cochrane review updated January 2011)

C: Versus no intervention or diagnostic laparoscopy alone

Excision versus Ablation

Laparoscopic surgery versus laparotomy

Surgery versus ART

Surgery versus medical treatment

O: Live birth primary outcome

Pregnancy

Egg quality

Endometrial receptivity

Risks, burden and costs

(Note that the use of surgery as an adjunct treatment to ART will be dealt with in another presentation)

**What evidence supports IUI (stimulated and unstimulated) and IVF in the management of endometriosis-related infertility? (Edgardo Rolla)**

P: Women with endometriosis and infertility

Different stages

Women with histologic confirmation and those without histology sampling

Those previously surgically treated, those not previously surgically treated and both

Women with endometriomas (but treatments for endometriomas prior to ART will be dealt with elsewhere)

Deep endometriosis

Bowel endometriosis

I: IUI (who to treat, when, why, how to treat – stimulated, unstimulated, and who and when not to treat)

IVF – who, when, why, how and treatment limits incl. how many cycles

Specially tailored protocols

C: Versus no intervention

Versus surgery

Versus other medical treatment

Role of egg donation and surrogacy

O: Live birth primary outcome

Pregnancy

Egg quality

Endometrial receptivity

Risks, burden and costs

(Note that previous use of GnRH analogues will be dealt with in another presentation)

**What evidence supports the use of medical or surgical interventions that can be added to ART to improve the chance of its success in endometriosis-related infertility? (David Adamson)**

P: Women with endometriosis and infertility due to undergo ART (IVF or IUI)

Different stages

Women with histologic confirmation and those without histology sampling

Those previously surgically treated, those not previously surgically treated and both

Women with endometriomas

Deep infiltrating endometriosis

Bowel endometriosis

I: Prior medical interventions

Prior surgical interventions

Prior GnRH analogue treatment

Lipiodol / oil soluble contrast media

Treatments for endometriomas

C: Adjunct treatment + ART versus ART alone

O: Live birth primary outcome

Pregnancy

Egg quality

Endometrial receptivity

Risks, burden and costs

**What evidence supports emerging therapies for endometriosis-related infertility? (Luk Rombauts)**

P: Women with endometriosis and infertility due to undergo ART (IVF or IUI)

Different stages

Women with histologic confirmation and those without histology sampling

Those previously surgically treated, those not previously surgically treated and both

Women with endometriomas

Deep infiltrating endometriosis

Bowel endometriosis

I: Pentoxifylline

TGF modulators

Lipiodol / oil soluble contrast media

? Others

C: No intervention

O: Live birth primary outcome

Pregnancy

Egg quality

Endometrial receptivity

Risks, burden and costs

**Any other important consensus statements required? (Neil Johnson)**

Participants will be invited to propose any other consensus statements that they consider important, other than those already discussed, for further discussion and voting by participants.

**Summary discussion of consensus/controversy, further plan and close (Neil Johnson)**

The meeting will be brought to a close as above.

**Supplementary Information 3: Summary information regarding the GRADE System for ascribing a 'quality grade' to evidence that was provided to Montpellier Consortium participants**

Criteria for assigning grade of evidence:

| | | |
|---|---|---|
| Randomised trial | = High quality | Implies further research is very unlikely to change our confidence in the estimate of the effect |
| Non-randomised controlled study | = Moderate quality | Implies further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate |
| Observational study | = Low quality | Implies further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate |
| Other evidence or expert opinion | = Very low quality | Implies any estimate of effect is very uncertain |

Essentially, the grade of evidence should reflect the trade-off between the benefits and the risks, burden and costs of the intervention. Consensus and guideline panels should offer weak recommendations when, across the range of patient values, fully informed patients are likely to make different choices.

However the grade should be decreased if there is:

- inconsistency between studies;
- high probability of reporting bias;
- serious limitations to study quality;
- some or major uncertainty about directness;
- imprecise or sparse data (ie, a small study at the borderline of statistical significance).

But the grade should be increased if there is:

- strong evidence of an association (RR >2 or <0.5 base on consistent evidence from 2+ studies (+1);
- very strong evidence of an association (RR >5 or <0.2) based on direct evidence with no major threats to validity (+2);

- evidence of a dose-response gradient (+1);
- a reduced the effect by all plausible confounders (+1).

**Supplementary Information 4: Evidence Tables in Establishing Consensus Statements**

**GENERAL PRINCIPLES**

**ENDOMETRIOSIS IN LOW RESOURCE SETTINGS**

| **1. Endometriosis in low resource settings** | | |
|---|---|---|
| Description | Endometriosis is a global disease affecting an estimated 176 million women. | |
| Mechanism of action | Symptoms of endometriosis contribute substantially to the burden of disease and add substantial cost to society through reduced economic and personal productivity. In low resource settings, endometriosis has a low profile and its consequences remain hidden. | |
| Volume of evidence | Observations. | |
| Consistency of evidence | Good. | |
| Applicability of evidence | Variable owing to varied resources. | |
| Effectiveness | Inclusion of endometriosis diagnosis and management in the primary health care of women worldwide.<br>Diagnosis may commence with two simple questions about pain and infertility.<br>Management, including prevention, is easily integrated with other women's healthcare treatments and may include education, progestin-based contraceptives, family planning and lactation. | |
| Adverse effects | Variable reports of incidence of major intra- and post-operative complications from the radical surgical approaches, ranging from 0-13%. | |
| GRADE – evidence quality | Moderate to high – although based largely on expert opinion, the impact of the disease is clear-cut and the likely impact of even simple low-cost interventions is enormous. Thus strong recommendations can be made. | |
| Consensus statement and grading | 1) Endometriosis diagnosis and management should be incorporated into the primary health care of women worldwide (strong good practice point [GPP]). | **α** |
| | 2) In low resource settings, diagnosis may commence with two simple questions about pelvic-abdominal pain and infertility (strong | **β** |

| | | |
|---|---|---|
| | GPP). | |
| | 3) Management, including prevention, should be integrated with other women's healthcare strategies in low resource settings, and may include education, progestin-based contraceptives, family planning, and lactation (strong GPP). | **α** |
| References | | |

**CENTRES OR NETWORKS OF EXPERTISE**

| **2. Centres or networks of expertise** | |
|---|---|
| Description | Either a centre or a network in which a multidisciplinary team of experts collaborate to optimise the management. |
| Mechanism of action | Precise definitions of a centre or network of expertise, along with its accreditation requirements, yet to be finalised. Most experts agree this should include specialists who have undergone specific training in endometriosis, advanced surgeons with a high caseload of managing deep endometriosis, ready access to an endometriosis organisation with substantial input on behalf of women, and a track record of commitment to collaborative research. The centre/network should have a transparent record of outcome-based success rates. |
| Volume of evidence | Observational studies only. |
| Consistency of evidence | Unclear. |
| Applicability of evidence | Probably applicable, but on-going evaluation important. |
| Effectiveness | Proving effectiveness of centres/networks of expertise is elusive, but logic suggests that, based on the sound principles/mechanisms of a centres/network of expertise, outcomes for women should be improved. |
| Adverse effects | Minimal. |
| GRADE – evidence quality | Moderate – observational studies and expert opinion only, but there appears to be no down side to the development of centres/networks of expertise. |

| | | |
|---|---|---|
| Consensus statement and grading | 4) Women with endometriosis require individualised care over a long term period, where priorities may change owing to the type and severity of symptoms, impact of these symptoms, current or future fertility wish, and lifestyle factors (strong GPP). | **α** |
| | 5) Individualised care benefits from a multi-disciplinary network of experts sufficiently skilled in providing advice on and treatment of endometriosis and its associated symptoms, based on the best available knowledge, their extensive experience, and their transparent record of success rates (strong GPP). | **β** |
| References | D'Hooghe and Hummelshoj, 2006. | |

**ENDOMETRIOSIS ORGANISATIONS**

| **3. Endometriosis organisations and support groups** | |
|---|---|
| Description | An endometriosis support group is a group of people whose members provide various types of help, typically non-professional, for their common burden of endometriosis. The help may take the form of evaluating and providing relevant information, relating personal experiences, listening to and accepting others' experiences, providing sympathetic understanding and establishing social networks. An endometriosis support group may also work to inform the public or engage in advocacy. |
| Mechanism of action | Endometriosis organisations and support groups address issues such as the need to reduce diagnostic delay, promotion of aetiological research, avoidance of 'hit-and-miss' treatments, human and financial costs and burdens, quality of life factors, the chronic nature of the disease, and seek to dispel taboos, myths and stigmas. The more successful organisations have engaged with professionals managing endometriosis through integrating women's experiences to enhance the experienced, skilled medical perspective, allowing women to place all the available information in the proper context. The educating and informing component of an endometriosis organisation leads to promotion of quality of life amongst women who have, or who might have, |

| | | |
|---|---|---|
| | endometriosis. | |
| Volume of evidence | Observational studies and expert opinion only. | |
| Consistency of evidence | Unclear. | |
| Applicability of evidence | Probably applicable, but on-going evaluation important. | |
| Effectiveness | Feedback from women and endorsement from health professionals and other stakeholders substantiate the value of effective support groups and endometriosis organisations to individuals. | |
| Adverse effects | Potential harms occur when unqualified enthusiasts perpetuate questionable recommendations; opportunists might mislead women desperate for hope with simple answers to complex problems through unfiltered non-vetted medical information, leading to perpetuation of the cycle of unwellness. | |
| GRADE – evidence quality | Moderate – the small volume of research substantiates the effectiveness of endometriosis support groups and organisations representing other chronic diseases, however expert opinion is that there appears to be little down side to the development of effective endometriosis organisations and support groups. | |
| Consensus statement and grading | 6) Endometriosis support groups provide a valuable forum for women with endometriosis, having the potential to assist women to improve their quality of life by teaching coping mechanisms and sharing experiences (strong GPP). | **γ** |
| | 7) Engagement of experienced and skilled medical practitioners, accredited educators, and other stakeholders brings strength to an endometriosis organisation (strong GPP). | **α** |
| | 8) A philosophical shift to consideration of 'endometriosis and pelvic pain' as a spectrum or continuum of disease will avoid excluding women who lack laparoscopic confirmation of a diagnosis of endometriosis (weak GPP). | **γ** |
| References | Bush, 2009 | |

## ENDOMETRIOSIS AND ADOLESCENCE

| **4. Endometriosis and adolescence** | | |
|---|---|---|
| Description | Two thirds of adult women with endometriosis had their symptom onset prior to age 20 years. Reports of adolescents undergoing laparoscopic surgery for possible endometriosis report high levels of laparoscopically confirmed endometriosis. Empirical medical treatment and laparoscopic surgical treatment are options. | |
| Mechanism of action | Stage III and IV disease is uncommon amongst adolescents with endometriosis. It has been unclear whether laparoscopic removal of all peritoneal disease or whether empirical medical treatment prevents later endometriosis progression. | |
| Volume of evidence | Observational studies. | |
| Consistency of evidence | Minimal evidence. | |
| Applicability of evidence | Debatable owing to poor quality of evidence. | |
| Effectiveness | Unclear owing to absence of RCTs in the adolescent population. | |
| Adverse effects | Potential for physical, emotional, financial and time costs of empirical medical or surgical treatment. | |
| GRADE – evidence quality | Very low for possible intervention. However there is no down side to consideration of endometriosis as a possible diagnosis in adolescents with suggestive symptoms, with potential major benefit for the adolescent for whom this possible diagnosis is considered, thus a strong statement can be made. | |
| Consensus statement and grading | 9) Endometriosis should be considered as a possible diagnosis in adolescents with suggestive symptoms (strong). | **α** |
| | 10) Currently there is insufficient evidence to make strong recommendations for management amongst adolescents who may have endometriosis (weak). | **γ** |
| References | Yeung *et al.,* 2011; Dovey *et al*., 2010 | |

**ENDOMETRIOSIS AND OBSTETRIC OUTCOMES**

| **5. Endometriosis and obstetric outcomes** | | |
|---|---|---|
| Description | Women with endometriosis have a higher risk of obstetric complications, preterm delivery, antepartum haemorrhage, possibly pre-eclampsia and Caesarean section. | |
| Mechanism of action | Pregnancy complications related to endometriosis may be related to altered implantation receptivity and subsequent placentation deficiencies. | |
| Volume of evidence | Observational studies. | |
| Consistency of evidence | Good. | |
| Applicability of evidence | Good. | |
| Effectiveness | - | |
| Adverse effects | - | |
| GRADE – evidence quality | Moderate – large observational studies. | |
| Consensus statement and grading | 11) Endometriosis should be considered an obstetric risk factor and pregnancies managed accordingly (strong). | γ |
| References | Fernando *et al.,* 2009; Stephansson *et al*., 2009; Mutihir and Nyango, 2010 Brosens *et al.,* 2012 | |

**ENDOMETRIOSIS AND MENOPAUSE**

| **6. Endometriosis and menopause** | |
|---|---|
| Description | A small minority of women remain symptomatic after menopause. |
| Mechanism of action | The cessation of the endogenous cyclic hormonal drive of endometriosis that occurs following menopause means that persistence of problems related to endometriosis is rare after menopause. |
| Volume of evidence | Systematic review of 2 RCTs examining hormone therapy for surgical menopause. |
| Consistency of evidence | Minimal evidence. |
| Applicability of evidence | Good. |
| Effectiveness | Unclear owing to absence of RCTs in the menopausal population. |

| | | |
|---|---|---|
| Adverse effects | Potential for recurrence of endometriosis with hormone replacement therapy. | |
| GRADE – evidence quality | Weak – RCTs assessing different interventions: combined HRT versus no intervention; combined HRT versus tibolone. Trials underpowered to detect differences in endometriosis recurrence, an uncommon event. | |
| Consensus statement and grading | 12) Although endometriosis may occasionally recur, there is no strong evidence to deprive women of hormone replacement treatment (HRT) if they suffer severe menopause symptoms but have a history of endometriosis, although combined oestrogen-progestin hormone therapy is advisable (weak). | γ |
| References | Moen *et al.,* 2010; Al Kadri *et al*., 2010 | |

**ENDOMETRIOSIS AND CANCER**

| **7. Endometriosis and cancer** | |
|---|---|
| Description | There is a recognised association between endometriosis and clear cell, low-grade serous and endometrioid ovarian cancer. Overall odds ratio and relative risk for ovarian cancer ranges 1.3 to 1.9. |
| Mechanism of action | Phylogenetic studies indicate that endometriotic lesions may be a precursor of endometriosis. |
| Volume of evidence | Large cohort studies. |
| Consistency of evidence | Good – however the funnel plot is asymmetric, suggesting publication bias in favour of positive studies. Overall odds ratio and relative risk for ovarian cancer ranges 1.3 to 1.9. |
| Applicability of evidence | Good. |
| Effectiveness | No evidence in favour of ovarian cancer screening amongst women with endometriosis. The other risk factors for ovarian cancer place endometriosis in perspective (for example infertility is associated with an odds ratio of ovarian cancer approximately 2.0). |
| Adverse effects | - |
| GRADE – evidence quality | Moderate – Large cohort studies. |

| | | |
|---|---|---|
| Consensus statement and grading | 13) The relative risk and absolute risk of ovarian cancer amongst women with endometriosis is so low as not to justify routine ovarian cancer screening (strong). | γ |
| References | Sayasneh *et al*., 2011; Pearce *et al*., 2012 | |

**ENDOMETRIOSIS MANAGEMENT OPTIONS FOR WOMEN OF REPRODUCTIVE AGE**

**LIFESTYLE INTERVENTIONS FOR WOMEN WITH ENDOMETRIOSIS**

| **8. Dietary interventions** | | |
|---|---|---|
| Description | Vitamins, minerals, salts, lactic ferments, fish oil (polyunsaturated fatty acids, omega-3 fatty acids). | |
| Mechanism of action | Dietary modulation of symptoms (polyunsaturated fatty acids play a role in menstrual pain) or disease modulation. | |
| Volume of evidence | Endometriosis: 2 RCTs.<br>Dysmenorrhoea: 1 RCT. | |
| Consistency of evidence | No overlap between trials. | |
| Applicability of evidence | Probably applicable, as these treatments are easily accessible. | |
| Effectiveness | Endometriosis: following surgery, combination of vitamins and fish oil was more effective than placebo and similarly effective to hormonal suppression at 12 months for pain relief, but not for endometrioma recurrence.<br>Dysmenorrhoea: one small trial showed fish oil (omega-3 fatty acids) to be more effective than placebo for pain relief. | |
| Adverse effects | Possible with vitamins in high doses. | |
| GRADE – evidence quality | Low – single RCT and not established treatment. | |
| Consensus statement and grading | 14) Dietary intervention following endometriosis surgery in the form vitamins, minerals, salts, lactic ferments, and fish oil appears to be a suitable alternative to hormonal treatment, that is associated with similar pelvic pain reduction and quality of life improvement (weak). | δ |

| | |
|---|---|
| References | Sesti *et al*., 2007; Sesti *et al*., 2009; Proctor and Murphy, 2001 |

**EMPIRICAL MEDICAL TREATMENT FOR WOMEN WITH SYMPTOMS SUGGESTIVE OF ENDOMETRIOSIS**

| **9. First line empirical medical treatment** | | |
|---|---|---|
| Description | Analgesics (non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and opioid analgesics), combined oral contraceptive pill (OCP) or progestins without prior laparoscopic surgical diagnosis. | |
| Mechanism of action | Analgesia or hormonal suppression of endometriosis. | |
| Volume of evidence | No direct evidence, but inferred from RCT evidence of medical treatment of endometriosis. | |
| Consistency of evidence | Variable. | |
| Applicability of evidence | Probably applicable but no direct RCT evidence. | |
| Effectiveness | NSAIDs and other analgesics: insufficient RCT evidence.<br>OCP: effective and continuous treatment probably more effective than cyclic treatment in diagnosed endometriosis.<br>Progestins: RCTs show effectiveness in diagnosed endometriosis. | |
| Adverse effects | Side effects acceptably low incidence and severity. | |
| GRADE – evidence quality | NSAIDs and analgesics: very low.<br>OCP: moderate – RCT evidence but not in population without laparoscopic diagnosis.<br>Progestins: moderate – RCT evidence but not in population without laparoscopic diagnosis. | |
| Consensus statement and grading | 15) Well tolerated, low cost, easily accessible options such as non-steroidal anti-inflammatory drugs (NSAIDs), other analgesics, combined oral contraceptive pill (OCP), and progestins should be considered for use as first line empirical medical treatment (strong) | γ |
| References | Allen *et al.,* 2009; Davis *et al.,* 2007; Harada *et al*., 2008; Guzick *et al.,* 2011; Vercellini *et al.,* 2011; Schlaff *et al.,* 2006; Crosignani *et al.,* 2006; Brown *et al.,* 2012; Cosson *et al.,* 2002; Momoeda *et al.,* 2009; Köhler *et al.,* 2010; | |

| | |
|---|---|
| | Harada *et al*., 2009; Strowitzki *et al.,* 2010a; Strowitzki *et al.,* 2010b; Petraglia *et al.,* 2012; Strowitzki *et al.,*2012 |

| **10. Second line empirical medical treatment** | | |
|---|---|---|
| Description | Gonadotrophin releasing hormone agonists (GnRH-a) with add-back hormone replacement therapy (HRT), the levonorgestrel-releasing intrauterine system (LNG-IUS). | |
| Mechanism of action | Hormonal suppression of endometriosis. | |
| Volume of evidence | No direct evidence, but inferred from RCT evidence of medical treatment of endometriosis. | |
| Consistency of evidence | Good in context of laparoscopically diagnosed endometriosis. | |
| Applicability of evidence | Probably applicable but no direct RCT evidence in absence of laparoscopic diagnosis. | |
| Effectiveness | GnRH-a with add-back HRT: RCTs show effectiveness in diagnosed endometriosis.<br>LNG-IUS: RCTs show effectiveness in diagnosed endometriosis. | |
| Adverse effects | Side effects important and may carry appreciable treatment burden. | |
| GRADE – evidence quality | GnRH-a with add-back HRT: moderate – RCT evidence but not in population without laparoscopic diagnosis.<br>LNG-IUS: moderate – RCT evidence but not in population without laparoscopic diagnosis. | |
| Consensus statement and grading | 16) In some circumstances, second line medical treatment with gonadotrophin releasing hormone agonists (GnRH-a) with add-back hormone replacement treatment (HRT), or the levonorgestrel intrauterine system (LNG-IUS) may be considered for use as empirical medical treatment for women who are not optimally treated with first line empirical therapy prior to surgical diagnosis and treatment, whilst awaiting laparoscopic surgery (weak). | γ |
| References | Brown *et al.,* 2010; Abou-Setta *et al.,* 2006 | |

**SURGERY FOR WOMEN WITH SYMPTOMATIC ENDOMETRIOSIS**

| **11. Laparoscopic surgical removal of endometriotic lesions** | | |
|---|---|---|
| Description | Laparoscopic ablation of lesions.<br>Laparoscopic excision of lesions. | |
| Mechanism of action | Surgical removal of lesions alleviates pain caused by them. | |
| Volume of evidence | Systematic review examining laparoscopic surgical removal of lesions, with pain outcomes considered:<br>• 1 RCT examining ablation versus no intervention;<br>• 2 RCTs examining excision versus no intervention.<br>• 2 RCTs examining excision versus ablation | |
| Consistency of evidence | Good, although difficulty of surgical trials means small numbers. | |
| Applicability of evidence | Applicable, however the effects of laparoscopic ablation of endometriosis may be indistinguishable from laparoscopic ablation of endometriosis plus uterine nerve ablation, as both were employed together in one RCT. | |
| Effectiveness | Laparoscopic ablation is effective.<br>Laparoscopic excision is effective.<br>No evidence of benefit or harm for laparoscopic excision versus laparoscopic ablation in the short term.<br>Recurrence rates vary following laparoscopic surgical removal of endometriosis, with 10-55% pain recurrence or reoperation rates.<br>First operations tend to produce a better response than subsequent surgical procedures, pain improvements at 6 months in the region of 83% for first excisional procedures versus 53% for second procedures.<br>Whilst no trials have examined outcomes of laparoscopic surgery versus laparotomy, we consider it good practice that a laparoscopic approach to surgery should be undertaken where possible. | |
| Adverse effects | Complications of laparoscopic surgery. | |
| GRADE – evidence quality | Moderate to high. | |
| Consensus statements and grading | 17) Laparoscopic surgical removal of endometriosis is an effective first line approach for treating pain related to endometriosis | **α** |

| | | |
|---|---|---|
| | (strong). | |
| | 18) Although current RCTs have failed to demonstrate benefit of excision over ablation, it is recommended to excise lesions where possible, especially deep endometriotic lesions (weak). | **α** |
| | 19) Laparoscopic surgery for endometriosis should always be undertaken in preference to laparotomy, where possible (strong GPP). | **γ** |
| References | Jacobson *et al.,* 2009; Wright *et al*., 2005; Healey *et al.,* 2010; Vercellini *et al*., 2009; Abbott *et al*., 2004; Koninckx *et al.,* 2012 | |

| **12. Laparoscopic neuroablative surgery** | | |
|---|---|---|
| Description | Laparoscopic uterine nerve ablation (LUNA).<br>Open or laparoscopic presacral neurectomy (PSN). | |
| Mechanism of action | Ablation of afferent nerves carrying pain supply from lesion to central nervous system with its resultant reduction of pain. | |
| Volume of evidence | Systematic review examining laparoscopic neuroablative techniques (5 RCTs examining LUNA and 4 RCTs examining PSN). | |
| Consistency of evidence | Good. | |
| Applicability of evidence | Applicable. | |
| Effectiveness | No evidence of a beneficial effect of adding LUNA to laparoscopic removal of endometriosis.<br>Adding PSN to endometriosis removal may be effective for midline dysmenorrhoea associated with endometriosis. | |
| Adverse effects | Minimal with LUNA; common with PSN, including bowel and bladder problems, painless labour and presacral bleeding complications. | |
| GRADE – evidence quality | High. | |
| Consensus statement and grading | 20) The addition of laparoscopic uterine nerve ablation (LUNA) to laparoscopic removal of endometriosis does not improve pain relief | **β** |

| | | |
|---|---|---|
| | (strong). | |
| | 21) Although presacral neurectomy (PSN) might benefit a small number of women, the benefits are likely to be outweighed by the potential for harmful effects (strong). | γ |
| References | Proctor *et al*., 2005. | |

| **13. Laparoscopic removal of endometriomas** | | |
|---|---|---|
| Description | Laparoscopic excision (or cystectomy) of endometrioma, where the entire cyst wall is completely removed.<br>Laparoscopic ablation (or drainage/fenestration and electrocoagulation) of endometrioma, where the endometriotic cyst is opened, its contents drained and surgical electrocautery is applied to the cyst wall. | |
| Mechanism of action | Removal of ovarian endometriotic cyst, preferably retaining as much normal ovary tissue as possible. | |
| Volume of evidence | Systematic review of 2 RCTs examining laparoscopic cystectomy versus drainage and coagulation of ovarian endometriomas.<br>Other studies have assessed the impact of ovarian surgery for endometriomas on ovarian reserve. | |
| Consistency of evidence | Good. | |
| Applicability of evidence | Applicable. | |
| Effectiveness | Laparoscopic cystectomy for endometriomas is associated with lower rates of symptom recurrence and endometrioma recurrence than drainage and coagulation.<br>Laparoscopic excision is effective.<br>No evidence of benefit or harm for laparoscopic excision versus laparoscopic ablation in the short term. | |
| Adverse effects | Complications of laparoscopic surgery. | |
| GRADE – evidence quality | High. | |
| Consensus statement and | 22) Laparoscopic excision (cystectomy) for ovarian endometriomas | |

| | | |
|---|---|---|
| grading | is preferred where possible to minimise symptom recurrence and endometrioma recurrence (strong). | γ |
| References | Hart *et al*., 2008 | |

| **14. Surgery for deep endometriosis** | | |
|---|---|---|
| Description | Conservative surgery involves removal of endometriosis that can safely be undertaken without risking surgery to the pelvic viscera.<br>If deep endometriosis involves the bowel wall, particularly the rectum, the surgical approaches are shaving, disc excision, or excision and re-anastomosis.<br>If deep endometriosis involves the urinary tract or vaginal walls, similar principles apply. | |
| Mechanism of action | Removal of deep endometriosis designed to relieve pain related to its occurrence. | |
| Volume of evidence | Primarily small observational studies. | |
| Consistency of evidence | Poor. | |
| Applicability of evidence | Difficult to apply owing to study design, poor description of disease extent including depth of penetration, heterogeneous patient populations, inconsistency of access to appropriate surgical expertise, variable radicality of surgery in the same studies, variable experience and expertise of surgeons, short follow up, poor description of drop-outs, variable use of postoperative medical therapy. | |
| Effectiveness | Suggestion of symptomatic benefit. | |
| Adverse effects | Variable reports of incidence of major intra- and post-operative complications from the radical surgical approaches, ranging from 0-13%. | |
| GRADE – evidence quality | Very low, owing to study design, as well as volume, consistency and applicability of evidence issues. | |
| Consensus statement and grading | 23) The best surgical approach to deep endometriosis is unclear (weak). | γ |
| | 24) Highly specialised surgical expertise is required by surgeons who undertake surgery for deep endometriosis, and it should be | α |

| | | |
|---|---|---|
| | undertaken only within centres of expertise (strong GPP). | |
| References | Vercellini *et al*., 2006; Vercellini *et al*., 2009 | |

**MEDICAL THERAPY FOR WOMEN WITH SYMPTOMATIC ENDOMETRIOSIS**

| **15. First line medical treatment** | |
|---|---|
| Description | Analgesics (non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and opioid analgesics), combined oral contraceptive pill (OCP), or progestins without prior laparoscopic surgical diagnosis. |
| Mechanism of action | Analgesia or hormonal suppression of endometriosis. |
| Volume of evidence | 1 RCT NSAID (naproxen).<br>2 RCTs – 1 RCT OCP versus placebo; 1 RCT OCP versus GnRH analogue.<br>1 RCT OCP for recurrent endometrioma prevention.<br>4 RCTs for dienogest.<br>Other progestins |
| Consistency of evidence | Variable. |
| Applicability of evidence | Applicable. |
| Effectiveness | NSAIDs and other analgesics: insufficient RCT evidence.<br>OCP: effective versus placebo; similar effectiveness to GnRH analogue; continuous treatment probably more effective than cyclic treatment in diagnosed endometriosis.<br>Dienogest: dose finding study suggests 2mg daily dose; dienogest more effective than placebo and similar effectiveness to GnRHa.<br>Progestins: Effective versus placebo; similar efficacy to other medical treatment options.<br>Dydrogesterone: no evidence of benefit. |
| Adverse effects | Possible unintended side effects from all drugs in this category. |
| GRADE – evidence quality | NSAIDs and analgesics: low – 1 very small RCT.<br>OCP: low – no comparison with placebo.<br>Dienogest: high |

| | | |
|---|---|---|
| | Other progestins: high. | |
| Consensus statement and grading | 25) Well tolerated, low cost, easily accessible options such as non-steroidal anti-inflammatory drugs (NSAIDs), other analgesics, combined oral contraceptive pill (OCP), and progestins should be considered for first line medical treatment of laparoscopically diagnosed endometriosis (strong). | **γ** |
| | 26) The combined oral contraceptive pill (OCP) is an effective medical treatment to minimise the endometrioma recurrence rate after surgical removal of the cyst (strong). | **α** |
| References | Allen *et al.,* 2009; Davis *et al.,* 2007; Harada *et al*., 2008; Guzick *et al.,* 2011; Vercellini *et al.,* 2011; Schlaff *et al.,* 2006; Crosignani *et al.,* 2006; Brown *et al.,* 2012; Cosson *et al.,* 2002; Momoeda *et al.,* 2009; Köhler *et al.,* 2010; Harada *et al*., 2009; Strowitzki *et al.,* 2010a; Strowitzki *et al.,* 2010b; Petraglia *et al.,* 2012; Strowitzki *et al.,* 2012; Serrachioli *et al*., 2010. | |

| **16. Second line medical treatment** | |
|---|---|
| Description | Gonadotrophin releasing hormone analogues (GnRH-a) with add-back hormone replacement therapy (HRT), the levonorgestrel-releasing intrauterine system (LNG-IUS), depot progestins, gestrinone, Danazol. |
| Mechanism of action | Hormonal suppression of endometriosis. |
| Volume of evidence | GnRH-a +/- add-back HRT: 41 RCTs including 4,935 women for GnRH-a alone; 2 RCTs GnRH-a + add-back HRT: subgroup of the RCTs outlined above.<br>LNG-IUS: 2 RCTs<br>Depot progestins:<br>Gestrinone: RCTs comparing to other medical treatments.<br>Danazol: 6 RCTs |
| Consistency of evidence | Variable. |
| Applicability of evidence | Probably applicable but no direct RCT evidence. |
| Effectiveness | GnRH-a: Effective with or without add-back; similar efficacy to other second |

| | | |
|---|---|---|
| | line medical treatment options; significantly lower side effects and reduced loss of bone mass with add-back HRT; adherence to GnRH-a treatment improved with add-back.<br>LNG-IUS: RCTs show effectiveness in diagnosed endometriosis.<br>Depot progestins: Enhanced benefit compared to some other treatments, but more side effects.<br>Gestrinone: Insufficient RCT evidence of effectiveness; some androgenic side effects.<br>Danazol: Effective, but androgenic side effects. | |
| Adverse effects | Side effects very important, especially with gestrinone, Danazol, depot progestins, and GnRH-a without add-back HRT. | |
| GRADE – evidence quality | GnRH-a with add-back HRT: moderate – 2 RCTs.<br>GnRH-a alone: high.<br>LNG-IUS: low – 2 RCTs with conflicting results.<br>Depot progestins: low – conflicting results and high treatment burden.<br>Danazol: moderate – very high treatment burden through androgenic side effects<br>Gestrinone: very low. | |
| Consensus statement and grading | 27) Second line medical treatments could include gonadotrophin releasing hormone analogues (GnRH-a, which should be used with add-back hormone replacement treatment, HRT, routinely), the levonorgestrel intrauterine system (LNG-IUS) and depot progestins (weak). | **γ** |
| | 28) Danazol and gestrinone should not be used, other than for women, established on these treatments in the absence of side effects, for whom other treatments have proven ineffective (strong). | **α** |
| References | Brown *et al*., 2010; Farmer *et al*., 2009; Abou-Setta *et al.,* 2006; Bayoglu *et al.,* 2011; Vercellin *et al.,* 2010; Selak *et al*., 2007. | |

**EMERGING MEDICAL THERAPIES FOR WOMEN WITH SYMPTOMATIC ENDOMETRIOSIS**

| **17-a. Aromatase inhibitors** | | |
|---|---|---|
| Description | Anastrazole, fadrozole, formestane, exemestane, letrozole. | |
| Mechanism of action | Suppression of the physiological conversion of androgens to oestrogens. | |
| Volume of evidence | Systematic review identified 4 RCTs. | |
| Consistency of evidence | Uncertain. | |
| Applicability of evidence | Small volume of evidence. | |
| Effectiveness | Appears to be effective in reducing pain symptoms; similar effectiveness to GnRH-a. | |
| Adverse effects | Minimal; not contraceptive. | |
| GRADE – evidence quality | Low – No consistency of evidence and not in widespread use in clinical practice. | |
| Consensus statement and grading | 29) Aromatase inhibitors might be reasonable as a second line medical treatment, but more research is required (weak) | γ |
| References | Ferrero *et al.,* 2011 | |

| **17-b. Selective progesterone receptor modulators (SPRMs)** | | |
|---|---|---|
| Description | Mifepristone, Asoprisnil, Megestrol. | |
| Mechanism of action | Progesterone receptor modulation. | |
| Volume of evidence | 1 RCT of n=126: Mifepristone versus Danazol.<br>Asoprisnil, Megestrol: observational studies only. | |
| Consistency of evidence | Only 1 RCT; other observational study | |
| Applicability of evidence | Limited. | |
| Effectiveness | Mifepristone is as effective as Danazol in reducing symptoms, with better oestrogen levels. | |
| Adverse effects | Minimal. | |
| GRADE – evidence quality | Low – only one RCT and not in widespread clinical use. | |
| Consensus statement and grading | 30) Selective progesterone receptor modulators (SPRMs) might be a reasonable second line medical treatment, but more research is required (weak). | γ |

| | |
|---|---|
| References | Guo *et al.,* 2011; Spitz, 2009 |

| **17-c. GnRH antagonists** | | |
|---|---|---|
| Description | Elagolix | |
| Mechanism of action | Pituitary suppression of gonadotrophin release. | |
| Volume of evidence | 1 RCT of n=252: Elagolix versus Depo Provera. | |
| Consistency of evidence | Only 1 RCT | |
| Applicability of evidence | Limited. | |
| Effectiveness | As effective as Depo Provera in reducing symptoms, with fewer side effects. | |
| Adverse effects | Possible bone loss and menopause type side effects. | |
| GRADE – evidence quality | Low – only one RCT and not in widespread clinical use. | |
| Consensus statement and grading | 31) Gonadotrophin releasing hormone (GnRH) antagonists might be reasonable as second line medical treatment, but more research is required (weak). | **γ** |
| References | Struthers *et al.,* 2009 | |

| **17-d. Pentoxifylline** | | |
|---|---|---|
| Description | Oral anti-inflammatory agent. | |
| Mechanism of action | Competitive non-selective phosphodiesterase inhibitor that inhibits tumour necrosis factor α (TNF-α) and reduces inflammation. | |
| Volume of evidence | Systematic review identified 4 RCTs. | |
| Consistency of evidence | Poor. | |
| Applicability of evidence | Applicable. | |
| Effectiveness | No evidence of benefit on pain or disease recurrence. | |
| Adverse effects | Unclear. | |
| GRADE – evidence quality | Moderate – conflicting results. | |
| Consensus statement and grading | 32) There is no evidence of a benefit of pentoxifylline on the reduction of pain (strong). | **α** |
| References | Lu *et al*., 2012 | |

| **17-e. Anti-TNFα agents** | | |
|---|---|---|
| Description | Infliximab | |
| Mechanism of action | Suppression of lesion growth. | |
| Volume of evidence | 1 RCT of 21 women with stage IV endometriosis. | |
| Consistency of evidence | Only 1 RCT | |
| Applicability of evidence | Limited, as only trialled in women with stage IV disease. | |
| Effectiveness | No evidence of benefit on pain reduction. | |
| Adverse effects | Minimal. | |
| GRADE – evidence quality | Low – very small RCT, restricted to stage IV. | |
| Consensus statement and grading | 33) There is no evidence of a benefit of anti-TNFα (anti-tumour necrosis factor alpha) on the reduction of pain (weak). | **γ** |
| References | Koninckx *et al*.,2008 | |

| **17-f. SERMs** | | |
|---|---|---|
| Description | Raloxifene | |
| Mechanism of action | Modulation of oestrogen receptor. | |
| Volume of evidence | 1 RCT of 93 women with laparoscopically excised endometriosis. | |
| Consistency of evidence | Only 1 RCT | |
| Applicability of evidence | Limited. | |
| Effectiveness | Pain returned earlier with raloxifene. | |
| Adverse effects | Minimal. | |
| GRADE – evidence quality | Low – single RCT, worse outcome with treatment. | |
| Consensus statement and grading | 34) There is no benefit from raloxifene on prevention of recurrence of pain (strong). | **α** |
| References | Stratton *et al*., 2008 | |

| **17-g. Thiazolidinediones** | |
|---|---|
| Description | Rosiglitazone |
| Mechanism of action | Peroxisome proliferator-activated receptor-γ. |

| | | |
|---|---|---|
| Volume of evidence | Case series of 3 women only. | |
| Consistency of evidence | Minimal evidence. | |
| Applicability of evidence | Limited information. | |
| Effectiveness | Insufficient evidence, as 2 out of 3 women had improvement of pain. | |
| Adverse effects | Possible. | |
| GRADE – evidence quality | Very low – tiny case series. | |
| Consensus statement and grading | 35) There is insufficient evidence of a benefit of rosiglitazone on the reduction of pain (weak). | γ |
| References | Moravek *et al.,* 2009 | |

| **17-h. Valproic acid** | | |
|---|---|---|
| Description | Anticonvulsant. | |
| Mechanism of action | Membrane stabilising drug | |
| Volume of evidence | 2 non-randomised studies. | |
| Consistency of evidence | Limited. | |
| Applicability of evidence | Limited. | |
| Effectiveness | Insufficient evidence. | |
| Adverse effects | Minimal. | |
| GRADE – evidence quality | Very low – no RCT evidence. | |
| Consensus statement and grading | 36) There is insufficient evidence of benefit of valproic acid on the reduction of pain (weak) | γ |
| References | Liu and Guo, 2008 | |

| **17-i. Anti-angiogenesis agents** | |
|---|---|
| Description | Cabergoline, endostatin, sirolimus, thalidomide, vascular endothelial growth factor inhibitors. |
| Mechanism of action | Suppression of the vascular proliferation that accompanies endometriosis. |
| Volume of evidence | Experimental animal models. |
| Consistency of evidence | No evidence in humans. |

| | | |
|---|---|---|
| Applicability of evidence | Applicability limited by impact on reproductive function and other organ systems. | |
| Effectiveness | Effective in prevention of development of endometriotic lesions in animal models; no effect on established disease. | |
| Adverse effects | Detrimental effects on reproductive function and other organ systems. | |
| GRADE – evidence quality | Very low – not applicable for women. | |
| Consensus statement and grading | 37) Anti-angiogenesis agents are at research level only (strong). | **α** |
| References | Laschke and Menger, 2012 | |

**COMPLEMENTARY THERAPIES FOR WOMEN WITH SYMPTOMATIC ENDOMETRIOSIS**

| **18-a. Acupuncture** | | |
|---|---|---|
| Description | Fine needles inserted into specific points on the skin according to meridian points. | |
| Mechanism of action | Traditional Chinese Medicine theory. Possible modulation of endogenous opioids such as β-endorphins, serotonin and dopamine. Possible anti-inflammatory actions via prostaglandins. | |
| Volume of evidence | Endometriosis: 2 RCTs.<br>Dysmenorrhoea: 6 RCTs for acupuncture; 4 RCTs for acupressure. | |
| Consistency of evidence | Good. | |
| Applicability of evidence | Acupuncture available in most parts of the world. | |
| Effectiveness | Lowered pain in both endometriosis and dysmenorrhea groups who received acupuncture. | |
| Adverse effects | Nil. | |
| GRADE – evidence quality | Very low – not blinded, small studies, poor description of acupuncture method. | |
| Consensus statement and grading | 38) There is some evidence of effectiveness of acupuncture, but it requires repeated treatments and effects are unlikely to be long-lasting (weak). | **γ** |
| References | Zhu *et al.,* 2011 | |

| **18-b. Transcutaneous electrical nerve stimulation (TENS)** | | |
|---|---|---|
| Description | Stimulation of the skin using electrical currents at various pulse rates (frequencies) and intensities. | |
| Mechanism of action | Alteration of the body's ability to receive or perceive pain signals. | |
| Volume of evidence | Endometriosis: 1 RCT.<br>Dysmenorrhea: 4 RCTs of high or low frequency TENS versus placebo. | |
| Consistency of evidence | Good for high frequency TENS. | |
| Applicability of evidence | Not necessarily easy to use amongst all populations. | |
| Effectiveness | Endometriosis: no data.<br>Dysmenorrhea: High frequency TENS reduces pain, but no evidence of effectiveness for low frequency TENS. | |
| Adverse effects | Minor. | |
| GRADE – evidence quality | Moderate. | |
| Consensus statement and grading | 39) There is evidence of effectiveness of high frequency transcutaneous electrical nerve stimulation (TENS) for short-term pain management for women with dysmenorrhoea (weak). | γ |
| References | Proctor *et al*., 2002 | |

| **18-c. Traditional Chinese medicine (TCM)** | |
|---|---|
| Description | Range of herbs used according to principles of traditional Chinese medicine (TCM) and tailored to patient's needs. |
| Mechanism of action | Most TCM contain more than one active compound. Possible improvements in haemocytologic parameters. |
| Volume of evidence | Endometriosis: 1 RCT versus acupuncture; 1 RCT versus gestrinone.<br>Dysmenorrhoea: Cochrane review of 39 RCTs, including 3,495 participants, few well designed. |
| Consistency of evidence | Good, but varying herbs. |
| Applicability of evidence | Applicable for Chinese women, but uncertain outside of TCM setting. |
| Effectiveness | Highly applicable for Chinese women, but identification of active ingredient |

| | | |
|---|---|---|
| | not possible. | |
| Adverse effects | Poorly reported but no evidence of harm. | |
| GRADE – evidence quality | Low – not blinded, poorly reported. | |
| Consensus statement and grading | 40) There is insufficient evidence of effectiveness of traditional Chinese medicine (TCM) and applicability is uncertain outside of TCM settings (weak). | **α** |
| References | Zhu *et al*.,2008; Flower *et al*., 2012 | |

| **18-d. Vitamins** | | |
|---|---|---|
| Description | Vitamin B1, Vitamin B6, Vitamin E. | |
| Mechanism of action | Vitamin B1 protects from muscle cramps and various pains.<br>Vitamin B6 related to prostaglandin E2 production, assists with myometrial relaxation and utilisation of magnesium.<br>Vitamin E has analgesic and anti-inflammatory properties. | |
| Volume of evidence | Endometriosis: no RCTs.<br>Dysmenorrhea: 1 RCT for each of vitamins B1, B6 and E respectively. | |
| Consistency of evidence | Some. | |
| Applicability of evidence | Applicable. | |
| Effectiveness | Endometriosis: no evidence.<br>Dysmenorrhoea: Vitamins B1 and B6 more effective than placebo; vitamin E not effective. | |
| Adverse effects | Vitamin B1safe.<br>Vitamin B6 sensory neural adverse effects >100mg/day.<br>Vitamin E heart failure >400IU/day. | |
| GRADE – evidence quality | Low - single study in each category; quality poor. | |
| Consensus statement and grading | 41) Vitamin B1 and B6 can be used to relieve pain for women with dysmenorrhea but there is limited evidence of effectiveness and there are safety concerns with vitamin B6 at higher doses (weak). | **γ** |
| References | Proctor and Murphy, 2001 | |

| **18-e. Magnesium** | | |
|---|---|---|
| Description | Trace element supplement. | |
| Mechanism of action | Possible role in pain reduction by inhibiting calcium entry into the cell. | |
| Volume of evidence | Endometriosis: no RCTs.<br>Dysmenorrhea: 3 small RCTs. | |
| Consistency of evidence | Moderate. | |
| Applicability of evidence | Applicable. | |
| Effectiveness | Endometriosis: no evidence.<br>Dysmenorrhea: 3 RCTs report reduced pain and reduction in the need for additional analgesics. | |
| Adverse effects | Nil. | |
| GRADE – evidence quality | Moderate. | |
| Consensus statement and grading | 42) There is some evidence of effectiveness of magnesium in reduction of pain for women with dysmenorrhea (weak). | γ |
| References | Proctor and Murphy, 2001 | |

| **18-f. Topical heat** | |
|---|---|
| Description | Superficial heat such as hot water bottles, heated stones, soft heated packs filled with grain, heat pads, and infra-red heat lamps. Deep heat modalities include short wave or microwave diathermy and ultrasound. |
| Mechanism of action | Superficial heat elevates the temperature of tissues and provides the greatest effect at 0.5cm or less from the surface of the skin. However, deep heating is achieved by converting another form of energy to heat, such as shortwave diathermy, microwave diathermy and ultrasound. |
| Volume of evidence | No studies identified for endometriosis or dysmenorrhoea, but some studies in low back pain. |
| Consistency of evidence | Moderate. |
| Applicability of evidence | Could be used. |
| Effectiveness | Endometriosis and dysmenorrhoea: no data. |

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|---|---|---|
| | Low back pain: reduces pain and disability for patients with back pain that lasts < 3 months. The relief has only been shown to occur for a short time and the effect is relatively small. | |
| Adverse effects | Mild pink tinge of skin. | |
| GRADE – evidence quality | Moderate. | |
| Consensus statement and grading | 43) There is no evidence of effectiveness for topical heat (weak). | γ |
| References | French *et al.,* 2006 | |

| **18-g. Spinal manipulation** | | |
|---|---|---|
| Description | Involves mobilisation and manipulation, techniques applied to a joint to normalise function. | |
| Mechanism of action | Manipulation may improve spinal mobility and pelvic blood flow. Possible action through neural networks or by decreasing prostaglandin F2α levels. | |
| Volume of evidence | Endometriosis: no RCTs.<br>Dysmenorrhea: 4 RCTs. | |
| Consistency of evidence | Almost all studies do not show benefit. | |
| Applicability of evidence | Not applicable. | |
| Effectiveness | Only one small study suggested benefit. A larger study, with sham manipulation as a control group, concluded no evidence for the use of spinal manipulation for women with dysmenorrhea. | |
| Adverse effects | Severe adverse events reported infrequently. | |
| GRADE – evidence quality | Low – not blinded, studies heterogeneous and not able to be pooled. | |
| Consensus statement and grading | 44) There is no evidence to support spinal manipulation (weak). | γ |
| References | Proctor *et al.,* 2006 | |

| **18-h. Behavioral interventions** | |
|---|---|
| Description | Physical and cognitive procedures with a focus on both physical and |

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|---|---|---|
| | psychological coping strategies for painful symptoms – relaxation, biofeedback, pain management and coping skills. | |
| Mechanism of action | The behavioural approach assumes that psychological and environmental factors interact with, and influence, physiological processes. | |
| Volume of evidence | Endometriosis: no RCTs.<br>Dysmenorrhea: 5 RCTs, each of different interventions. | |
| Consistency of evidence | Relaxation showed inconsistent results. | |
| Applicability of evidence | Could be difficult to replicate. | |
| Effectiveness | Endometriosis: no data.<br>Dysmenorrhoea: 1 RCT of pain management training reported a reduction in pain; 3 RCTs of relaxation reported varied results (1 RCT reported effectiveness for pain; 2 RCTs reported no evidence of a difference in pain); 1 RCT reported pain management training versus a control was effective. | |
| Adverse effects | Possibly. | |
| GRADE – evidence quality | Very low – inconsistency in the reporting of data, small trial size, poor methodological quality and age of the trials. | |
| Consensus statement and grading | 45) There is insufficient evidence to support behavioural interventions (weak). | γ |
| References | Proctor *et al.,* 2007 | |

**SURGERY FOR INFERTILITY IN WOMEN WITH ENDOMETRIOSIS**

| **19. Laparoscopic surgical removal of endometriotic lesions** | |
|---|---|
| Description | Laparoscopic ablation/excision of lesions. |
| Mechanism of action | Surgical removal of lesions improves fertility. |
| Volume of evidence | Systematic review examining laparoscopic surgical removal of lesions, with pain outcomes considered:<br>- 2 RCTs examining ablation/excision +/- adhesiolysis versus no intervention in stage I and II endometriosis.<br>- No RCTs in stage III and IV endometriosis. |

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|---|---|---|
| | Observational studies of repeat surgery.<br>Observational studies of laparoscopic surgery following failed IVF. | |
| Consistency of evidence | Poor – the results from the 2 RCTs differed. | |
| Applicability of evidence | Applicable. | |
| Effectiveness | Systematic review and meta-analysis suggests fertility benefit from laparoscopic removal of endometriosis.<br>First operations tend to produce a better response than subsequent surgical procedures, the pregnancy rates after repeat surgery being approximately half that with primary surgery. | |
| Adverse effects | Complications of laparoscopic surgery. | |
| GRADE – evidence quality | Moderate for primary surgery – trial results not consistent.<br>Low for impact of repeat surgery – observational studies only.<br>Low for laparoscopic surgery following failed IVF – observational studies only. | |
| Consensus statement and grading | 46) Laparoscopic surgical removal of endometriosis improves fertility in stage I and II endometriosis (strong). | γ |
| | 47) Although RCTs have failed to demonstrate benefit of excision over ablation, it is recommended to excise lesions where possible, especially where pain is present (weak). | γ |
| References | Jacobson *et al.* 2010; Vercellini *et al.,* 2009; Koninckx *et al.,* 2012 | |

| **20. Laparoscopic removal of endometriomas** | |
|---|---|
| Description | Laparoscopic excision (or cystectomy) for endometrioma, where the entire cyst wall is completely removed.<br>Laparoscopic ablation (or drainage/fenestration and electrocoagulation) of endometrioma, where the endometriotic cyst is opened, its contents drained and surgical electrocautery is applied to the cyst wall. |
| Mechanism of action | Removal of ovarian endometriotic cyst, preferably retaining as much normal ovary tissue as possible, designed to enhance fertility. |
| Volume of evidence | Systematic review of 2 RCTs examining laparoscopic cystectomy versus |

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|---|---|---|
| | drainage and coagulation of ovarian endometriomas.<br>Other studies have assessed the impact of ovarian surgery for endometriomas on ovarian reserve. | |
| Consistency of evidence | Good. | |
| Applicability of evidence | Applicable. | |
| Effectiveness | Laparoscopic cystectomy for endometriomas ≥4cm is associated with improved fertility and lower recurrence rates compared to drainage and coagulation.<br>If IVF is required, ovarian access may be improved and it is believed that pelvic infection rates may be reduced by prior surgery for endometriomas.<br>Harmful effects on ovarian reserve may accompany stripping endometriomas, although there is insufficient evidence that this is worse for stripping versus drainage and coagulation.<br>One small RCT examining suturing versus electrosurgical diathermy for haemostasis, with adhesions as outcome. | |
| Adverse effects | Complications of laparoscopic surgery. | |
| GRADE – evidence quality | High. | |
| Consensus statement and grading | 48) Laparoscopic excision (cystectomy) where possible for endometriomas is preferredto laparoscopic ablation (drainage and coagulation) to enhance fertility (strong). | **α** |
| References | Hart *et al*., 2008; Pellicano *et al.,* 2008 | |

| **21. Surgery for deep endometriosis** | |
|---|---|
| Description | Conservative surgery involves removal of endometriosis that can safely be undertaken without risking surgery to the pelvic viscera.<br>If deep endometriosis involves the bowel wall, particularly the rectum, the surgical approaches are shaving, disc excision or excision and re-anastomosis.<br>If deep endometriosis involves the urinary tract or vaginal walls, similar principles apply. |
| Mechanism of action | Removal of deep endometriosis designed to improve fertility. |

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|---|---|---|
| Volume of evidence | Primarily observational studies. | |
| Consistency of evidence | Poor. | |
| Applicability of evidence | Difficult to apply owing to study design, poor description of disease extent including depth of penetration, heterogeneous patient populations, inconsistency of access to appropriate surgical expertise, variable radicality of surgery in the same studies, variable experience and expertise of surgeons, short follow up, poor description of dropouts, variable use of postoperative medical therapy. | |
| Effectiveness | Suggestion of improved fertility in observational studies. | |
| Adverse effects | Variable reports of incidence of major intra- and post-operative complications from the radical surgical approaches, ranging from 0-13%. | |
| GRADE – evidence quality | Very low, owing to study design, as well as volume, consistency and applicability of evidence issues. | |
| Consensus statement and grading | 49) The best surgical approach to deep endometriosis in women with infertility is unclear (weak). | γ |
| References | Chapron *et al.*, 1999; Vercellini *et al*., 2006; Barri *et al*., 2010; Donnez and Squifflet, 2010 | |

| **22. Adjunct medical therapy before or after surgery for infertility** | |
|---|---|
| Description | Pre- and/or postoperative adjunct hormonal medical therapy. |
| Mechanism of action | Designed to suppress endometriosis and enhance fertility. |
| Volume of evidence | Systematic review of 16 RCTs. |
| Consistency of evidence | Good. |
| Applicability of evidence | Applicable. |
| Effectiveness | No evidence of any fertility benefit from postoperative medical therapy.<br>No evidence of benefit of pre- and postoperative medical therapy versus postoperative medical therapy alone (1 RCT).<br>No trials compared preoperative medical therapy to surgery alone.<br>No trials compared pre- and postoperative medical therapy to surgery alone. |

| | | |
|---|---|---|
| Adverse effects | Side effects common amongst women on hormonal suppressive therapy. | |
| GRADE – evidence quality | High. | |
| Consensus statement and grading | 50) Medical adjunct therapy in conjunction with laparoscopic surgery has not been shown to have fertility benefit (strong). | **α** |
| References | Furness *et al.,* 2009. | |

**ASSISTED CONCEPTION FOR INFERTILITY IN WOMEN WITH ENDOMETRIOSIS**

| **23-a. Controlled ovarian stimulation** | | |
|---|---|---|
| Description | Letrozole versus gonadotrophins. | |
| Mechanism of action | Different methods of stimulating ovarian follicle development. | |
| Volume of evidence | Letrozole versus gonadotrophins: 1 RCT including 20 women. | |
| Consistency of evidence | Minimal evidence. | |
| Applicability of evidence | Applicable. | |
| Effectiveness | Letrozole versus gonadotrophins: higher total number of follicles with gonadotrophins, but no evidence of a difference in pregnancy rate per completed cycle. | |
| Adverse effects | Multiple pregnancies. | |
| GRADE – evidence quality | Low – single very small RCT n=20. | |
| Consensus statement and grading | 51) There is no evidence to support the use of controlled ovarian stimulation alone and insufficient evidence to recommend one agent over another (weak). | **γ** |
| References | Aygen *et al.,* 2010 | |

| **23-b. IUI** | |
|---|---|
| Description | A fertility treatment originally designed for male factor or unexplained infertility. |
| Mechanism of action | Mechanically introduces the highest quality sperm closer to more than one egg ideally. |
| Volume of evidence | Numerous RCTs. |

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|---|---|---|
| Consistency of evidence | Limited. | |
| Applicability of evidence | Applicable. | |
| Effectiveness | Limited evidence that IUI is successful, especially if used in conjunction with controlled ovarian stimulation.<br>Multiple pregnancy is a key hazard of ovarian stimulation and all reasonable steps should be employed to avoid multiple pregnancy.<br>Double insemination might be superior to single insemination. | |
| Adverse effects | Minimal. | |
| GRADE – evidence quality | Moderate – RCTs but consistency of evidence limited. | |
| Consensus statement and grading | 52) Intrauterine insemination (IUI) with controlled ovarian stimulation (COS) is effective in improving fertility in minimal and mild endometriosis, but the role of unstimulated IUI is uncertain (strong). | **γ** |
| | 53) Double insemination should be considered for intrauterine insemination (IUI) (weak). | **δ** |
| References | Tummon *et al.,* 1997; Costello*,* 2004; Subit *et al.,* 2011 | |

| **23-c. IVF/ICSI** | |
|---|---|
| Description | IVF/ICSI – hi-tech expensive treatment, more invasive. |
| Mechanism of action | Replaced embryo designed to implant. |
| Volume of evidence | Systematic review of observational studies for effectiveness of IVF in endometriosis versus other causes of infertility.<br>One RCT comparing IVF versus expectant management.<br>No RCTs comparing IVF with other fertility treatments in endometriosis. |
| Consistency of evidence | Limited. |
| Applicability of evidence | Applicable. |
| Effectiveness | IVF effectiveness lower with endometriosis.<br>IVF effective versus expectant management.<br>Short course antagonist and long course agonist protocols give similar results. |

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|---|---|---|
| | No apparent increase in endometriosis occurrence post-IVF. | |
| Adverse effects | Invasive fertility treatment with high physical, emotional, financial and time costs. | |
| GRADE – evidence quality | Moderate – RCTs but consistency of evidence limited. | |
| Consensus statement and grading | 54) Although in-vitro fertilization (IVF) may be less effective for endometriosis than for other causes of infertility, it should be considered for use to improve the success rate above expectant management (strong). | **γ** |
| References | Barnhart *et al.,* 2002; Benschop *et al*., 2010; Soliman *et al.,* 1993; D'Hooghe *et al.,* 2006 | |

**ADJUNCTS TO ASSISTED CONCEPTION FOR INFERTILITY IN WOMEN WITH ENDOMETRIOSIS**

| **24-a. GnRH analogue treatment prior to IUI** | | |
|---|---|---|
| Description | Pre-treatment with GnRH-a for 6 months prior to IUI. | |
| Mechanism of action | Suppresses endometriosis; alters endometrial expression of implantation markers including integrins. | |
| Volume of evidence | 1 RCT, n=110, both IVF and IUI patients. | |
| Consistency of evidence | Only one RCT | |
| Applicability of evidence | Applicable. | |
| Effectiveness | Single RCT suggests benefit in IVF and IUI, but limited evidence of effectiveness in IUI. | |
| Adverse effects | Physical, emotional, financial and time costs. | |
| GRADE – evidence quality | Low – only one RCT, mixed population and substantial treatment burden. | |
| Consensus statement and grading | 55) There is insufficient evidence of benefit of gonadotrophin releasing hormone (GnRH-a) treatment before intrauterine insemination (IUI) (weak). | **α** |
| References | Rickes *et al.,* 2002 | |

| **24-b. Laparoscopic surgery prior to IUI** | | |
|---|---|---|
| Description | Prior laparoscopic surgery with removal of endometriosis before IUI. | |
| Mechanism of action | Removal of endometriosis designed to improve fertility and thus success rate through IUI. | |
| Volume of evidence | Two retrospective studies. | |
| Consistency of evidence | Good. | |
| Applicability of evidence | Doubtful owing to poor quality data. | |
| Effectiveness | No evidence of benefit. | |
| Adverse effects | Potential complications of surgery. | |
| GRADE – evidence quality | Very low. | |
| Consensus statement and grading | 56) There is insufficient evidence of benefit of laparoscopic surgery prior to IUI/COS (weak). | γ |
| References | Tanahatoe *et al.,* 2005 | |

| **24-c. Ultra-long IVF protocol with prior GnRH analogue** | | |
|---|---|---|
| Description | Pre-treatment with GnRH analogue for 3-6 months prior to IVF. | |
| Mechanism of action | Suppresses endometriosis; alters endometrial expression of implantation markers including integrins. | |
| Volume of evidence | Systematic review of 3 RCTs. | |
| Consistency of evidence | Good. | |
| Applicability of evidence | Applicable, however some of the success rates in these trials seem unusually high. | |
| Effectiveness | Increases the odds of clinical pregnancy fourfold. | |
| Adverse effects | Data for adverse effects on mother and foetus not available. | |
| GRADE – evidence quality | Moderate – RCTs but variable quality and differing success rates. | |
| Consensus statement and grading | 57) GnRH analogue administered for 3-6 months prior to IVF/ICSI in women with endometriosis increases the clinical pregnancy rate (strong). | γ |
| References | Sallam *et al.,* 2006 | |

| **24-d. OCP prior to IVF/ICSI** | | |
|---|---|---|
| Description | Pre-treatment with OCP for 6-8 weeks prior to IVF/ICSI. | |
| Mechanism of action | Suppresses endometriosis prior to IVF/ICSI. | |
| Volume of evidence | Controlled non-randomised study. | |
| Consistency of evidence | Little available data. | |
| Applicability of evidence | Doubtful owing to poor quality data. | |
| Effectiveness | Suggestion of improved results with prior OCP | |
| Adverse effects | Minimal. | |
| GRADE – evidence quality | Very low – non-randomised. | |
| Consensus statement and grading | 58) There is insufficient evidence to support the use of the combined oral contraceptive pill (OCP) prior to IVF/ICSI (weak). | γ |
| | 59) There are no data to compare the approach of pre-treatment with the combined oral contraceptive pill (OCP) versus gonadotrophin releasing hormone agonists (GnRH-a) (weak). | γ |
| References | de Ziegler *et al.,* 2010 | |

| **24-e. Laparoscopic surgery prior to IVF/ICSI** | | |
|---|---|---|
| Description | Prior laparoscopic surgery with removal of endometriosis and/or endometriomas (by aspiration or cystectomy) before IVF/ICSI. | |
| Mechanism of action | Removal of endometriosis designed to improve fertility and thus success rate through IVF/ICSI. | |
| Volume of evidence | Systematic review of 4 RCTs.<br>Many observational and non-randomised studies. | |
| Consistency of evidence | Good. | |
| Applicability of evidence | Good. | |
| Effectiveness | No improvement in pregnancy rates. | |
| Adverse effects | Physical, emotional, financial and time costs of surgery. | |
| GRADE – evidence quality | High. | |
| Consensus statement and | 60) There is no evidence that surgical removal of endometriosis or | |

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|---|---|---|
| grading | surgical treatment of endometriomas (by aspiration or cystectomy) improves success rates through IVF (weak). | **γ** |
| | 61) Ovarian response might be reduced in some women who have undergone surgery (weak). | **α** |
| | 62) Since endometriomas may damage the ovary, and since complications can arise in women with endometriomas undergoing ART, laparoscopic ovarian cystectomy may sometimes be recommended for women with endometriomas larger than 3cm diameter (weak). | **α** |
| References | Bianchi *et al.,* 2009; Benschop *et al*., 2010 | |

**MEDICAL THERAPY FOR INFERTILITY IN WOMEN WITH ENDOMETRIOSIS**

| **25. Ovulation suppression** | | |
|---|---|---|
| Description | Combined oral contraceptive pill (OCP), danazol or gonadotrophin releasing hormone agonist (GnRH-a). | |
| Mechanism of action | Ovulation suppression proposed to promote regression of endometriosis with possible fertility benefit. | |
| Volume of evidence | Meta-analysis of 25 RCTs. | |
| Consistency of evidence | Good. | |
| Applicability of evidence | Applicable. | |
| Effectiveness | No evidence of any fertility benefit from any medical therapy suppressing ovulation. | |
| Adverse effects | Common. | |
| GRADE – evidence quality | High. | |
| Consensus statement and grading | 63) There is no evidence of fertility benefit from medical treatment – ovulation suppression may delay pregnancy and this is not recommended (strong). | **α** |
| References | Hughes *et al*., 2007 | |

**EMERGING THERAPIES FOR INFERTILITY IN WOMEN WITH ENDOMETRIOSIS**

| **26-a. Lipiodol** | | |
|---|---|---|
| Description | Oil soluble contrast medium (OSCM) administered by hysterosalpingography (HSG). | |
| Mechanism of action | Possible effects on endometrial receptivity, peritoneal immuno-biology or tubal flushing. | |
| Volume of evidence | Sub-population of 1 RCT, including 62 women with endometriosis. | |
| Consistency of evidence | Only 1 RCT. | |
| Applicability of evidence | Applicable. | |
| Effectiveness | Increased live birth rate from pregnancies occurring within 6 months (OR 3.70, 95%CI 1.30 to 10.50). | |
| Adverse effects | Minimal | |
| GRADE – evidence quality | Low – Single RCT n=62; no a priori hypothesis for endometriosis sub-population. | |
| Consensus statement and grading | 64) Lipiodol hysterosalpingogram improves live birth rates in women with endometriosis, but otherwise unexplained infertility, who are attempting natural conception (weak). | γ |
| References | Johnson *et al*., 2004; Reilly *et al.,* 2011 | |

| **26-b. Pentoxifylline** | |
|---|---|
| Description | Oral anti-inflammatory agent. |
| Mechanism of action | Competitive non-selective phosphodiesterase inhibitor that inhibits tumour necrosis factor α (TNF-α) and reduces inflammation. |
| Volume of evidence | Meta-analysis of 4 RCTs, including 334 women. |
| Consistency of evidence | Good. |
| Applicability of evidence | Applicable. |
| Effectiveness | No evidence of an increase in pregnancy rate (RR 1.54, 95%CI 0.89 to 2.66); no data for live birth. |
| Adverse effects | Unclear. |
| GRADE – evidence quality | High. |

| | | |
|---|---|---|
| Consensus statement and grading | 65) There is no evidence of fertility benefit from pentoxifylline for women with mild to moderate endometriosis (strong). | **α** |
| References | Lu *et al.,* 2012 | |

| **26-c. Traditional Chinese Medicine (TCM)** | | |
|---|---|---|
| Description | Range of herbs used according to principles of Traditional Chinese Medicine (TCM) and tailored to patient's needs. | |
| Mechanism of action | Most TCM contain more than one active compound. Possible improvements in haemocytologic parameters. | |
| Volume of evidence | Meta-analysis of 2 RCTs in Chinese traditional setting – 1 RCT compared TCM versus Danazol; 1 RCT compared TCM versus gestrinone. | |
| Consistency of evidence | No overlap in RCT interventions. | |
| Applicability of evidence | Applicable for Chinese women, but uncertain outside of TCM setting. | |
| Effectiveness | No evidence of benefit of TCM over gestrinone or Danazol. | |
| Adverse effects | Poorly reported but no evidence of harm. | |
| GRADE – evidence quality | Low – questionable applicability; compared versus treatments not known to improve chance of pregnancy. | |
| Consensus statement and grading | 66) There is no evidence of fertility benefit of traditional Chinese medicine (TCM) over gestrinone or Danazol (weak). | **γ** |
| References | Flower *et al.,* 2012 | |

| **26-d. Vitamins** | |
|---|---|
| Description | Vitamin C and vitamin E. |
| Mechanism of action | Possible effects on oxidative stress and thus fertility. |
| Volume of evidence | 1 RCT, including 34 women. |
| Consistency of evidence | Only 1 RCT. |
| Applicability of evidence | Applicable. |
| Effectiveness | No significant difference in pregnancy rates. |
| Adverse effects | No evidence of harm. |

| | | |
|---|---|---|
| GRADE – evidence quality | Low – very small RCT. | |
| Consensus statement and grading | 67) There is insufficient evidence of increased pregnancy rates from the use of vitamins (weak). | **α** |
| References | Mier-Cabrera *et al.,* 2008 | |

| **26-e. Mifepristone** | | |
|---|---|---|
| Description | Variety of regimes. | |
| Mechanism of action | Selective progesterone receptor modulator. | |
| Volume of evidence | 104 reports on clinical trials and trial-like studies conducted in China and published in the last 11 years. | |
| Consistency of evidence | Trial quality generally well below acceptable level. | |
| Applicability of evidence | Highly questionable owing to trial quality. | |
| Effectiveness | Sub-optimal trial quality makes it impossible to assess whether mifepristone is effective. | |
| Adverse effects | Unlikely. | |
| GRADE – evidence quality | Very low – many areas deficient including informed consent, choice and evaluation of outcome measures, data analysis and randomisation. | |
| Consensus statement and grading | 68) There is insufficient reliable evidence of improved fertility with mifepristone (weak). | **α** |
| References | Guo *et al.,* 2011 | |

| **26-f. Rosiglitazone** | |
|---|---|
| Description | An oral thiazolidinedione. |
| Mechanism of action | Reduces endometriotic lesions in animal models and does not impede conception. |
| Volume of evidence | Case series of 3 women with endometriosis as part of an open label prospective phase 2a clinical trial. |
| Consistency of evidence | Minimal evidence. |
| Applicability of evidence | Applicable. |

| | | |
|---|---|---|
| Effectiveness | No evidence on fertility outcomes. | |
| Adverse effects | Unlikely. | |
| GRADE – evidence quality | Very low – no evidence from a very small number of women. | |
| Consensus statement and grading | 69) There is no evidence of impact of rosiglitazone on fertility (weak). | **α** |
| References | Moravek *et al.,* 2009 | |