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ORIGINAL ARTICLE *Gynaecology*

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/.

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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.