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. Diagnosis may commence with two simple questions about pain and infertility. 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. 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. 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. OCP: effective and continuous treatment probably more effective than cyclic treatment in diagnosed endometriosis. Progestins: RCTs show effectiveness in diagnosed endometriosis.	
Adverse effects	Side effects acceptably low incidence and severity.	
GRADE – evidence quality	NSAIDs and analgesics: very low. OCP: moderate – RCT evidence but not in population without laparoscopic diagnosis. 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. 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. 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	

11. Laparoscopic surgical removal of endometriotic lesions		
Description	Laparoscopic ablation of lesions. 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: • 1 RCT examining ablation versus no intervention; • 2 RCTs examining excision versus no intervention. • 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. Laparoscopic excision is effective. No evidence of benefit or harm for laparoscopic excision versus laparoscopic ablation in the short term. Recurrence rates vary following laparoscopic surgical removal of endometriosis, with 10-55% pain recurrence or reoperation rates. 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. 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). 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. 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. 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. 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. Laparoscopic excision is effective. 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. If deep endometriosis involves the bowel wall, particularly the rectum, the surgical approaches are shaving, disc excision, or excision and re-anastomosis. 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). 2 RCTs – 1 RCT OCP versus placebo; 1 RCT OCP versus GnRH analogue. 1 RCT OCP for recurrent endometrioma prevention. 4 RCTs for dienogest. Other progestins
Consistency of evidence	Variable.
Applicability of evidence	Applicable.
Effectiveness	NSAIDs and other analgesics: insufficient RCT evidence. OCP: effective versus placebo; similar effectiveness to GnRH analogue; continuous treatment probably more effective than cyclic treatment in diagnosed endometriosis. Dienogest: dose finding study suggests 2mg daily dose; dienogest more effective than placebo and similar effectiveness to GnRHa. Progestins: Effective versus placebo; similar efficacy to other medical treatment options. 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. OCP: low – no comparison with placebo. 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. LNG-IUS: 2 RCTs Depot progestins: Gestrinone: RCTs comparing to other medical treatments. 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. LNG-IUS: RCTs show effectiveness in diagnosed endometriosis. Depot progestins: Enhanced benefit compared to some other treatments, but more side effects. Gestrinone: Insufficient RCT evidence of effectiveness; some androgenic side effects. 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. GnRH-a alone: high. LNG-IUS: low – 2 RCTs with conflicting results. Depot progestins: low – conflicting results and high treatment burden. Danazol: moderate – very high treatment burden through androgenic side effects 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. 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. 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. 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. 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. 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. Vitamin B6 related to prostaglandin E2 production, assists with myometrial relaxation and utilisation of magnesium. Vitamin E has analgesic and anti-inflammatory properties.	
Volume of evidence	Endometriosis: no RCTs. Dysmenorrhea: 1 RCT for each of vitamins B1, B6 and E respectively.	
Consistency of evidence	Some.	
Applicability of evidence	Applicable.	
Effectiveness	Endometriosis: no evidence. Dysmenorrhoea: Vitamins B1 and B6 more effective than placebo; vitamin E not effective.	
Adverse effects	Vitamin B1safe. Vitamin B6 sensory neural adverse effects >100mg/day. 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. Dysmenorrhea: 3 small RCTs.	
Consistency of evidence	Moderate.	
Applicability of evidence	Applicable.	
Effectiveness	Endometriosis: no evidence. 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.

	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. 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

	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. 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. 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: - 2 RCTs examining ablation/excision +/- adhesiolysis versus no intervention in stage I and II endometriosis. - No RCTs in stage III and IV endometriosis.

	Observational studies of repeat surgery. 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. 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. Low for impact of repeat surgery – observational studies only. 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. 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

	drainage and coagulation of ovarian endometriomas. 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. 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. Harmful effects on ovarian reserve may accompany stripping endometriomas, although there is insufficient evidence that this is worse for stripping versus drainage and coagulation. 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. If deep endometriosis involves the bowel wall, particularly the rectum, the surgical approaches are shaving, disc excision or excision and re-anastomosis. If deep endometriosis involves the urinary tract or vaginal walls, similar principles apply.
Mechanism of action	Removal of deep endometriosis designed to improve fertility.

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. No evidence of benefit of pre- and postoperative medical therapy versus postoperative medical therapy alone (1 RCT). No trials compared preoperative medical therapy to surgery alone. 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.

Consistency of evidence	Limited.	
Applicability of evidence	Applicable.	
Effectiveness	Limited evidence that IUI is successful, especially if used in conjunction with controlled ovarian stimulation. Multiple pregnancy is a key hazard of ovarian stimulation and all reasonable steps should be employed to avoid multiple pregnancy. 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. One RCT comparing IVF versus expectant management. No RCTs comparing IVF with other fertility treatments in endometriosis.
Consistency of evidence	Limited.
Applicability of evidence	Applicable.
Effectiveness	IVF effectiveness lower with endometriosis. IVF effective versus expectant management. Short course antagonist and long course agonist protocols give similar results.

	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. 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	

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	