

Supplementary data

Diagnosis of endometriosis

- R1 Randomised research studies are recommended to verify whether symptom diaries or questionnaires lead to improved or earlier diagnosis of endometriosis.
- R2 The GDG recommends large, multi-centre prospective studies with independent validation sample sets to investigate the potential benefit of biomarkers in the detection and prognosis of endometriosis.
- R3 The GDG recommends research into the development of comprehensive and inclusive consensus criteria for the diagnosis of endometriosis, as an alternative or adjunct to diagnosis via laparoscopy/histology.
- R4 The GDG recommends large longitudinal intervention studies to investigate the potential benefits and best long-term management approaches for women with endometriosis.
- R5 The GDG recommends large longitudinal studies to investigate the effect of early diagnosis on the quality of life of women with endometriosis.

Treatment of endometriosis-associated pain

- R6 Research should investigate the effect of surgery on pain and quality of life (QoL) parameters in different subtypes, preferably via longitudinal population studies.
- R7 The GDG recommends sufficiently powered prospective, randomised and ideally blinded studies to unequivocally determine whether surgical treatment of superficial peritoneal endometriosis improves short and long-term clinical outcomes, such as a reduction in pain symptoms and improvement in quality of life.
- R8 The GDG recommends that nerve-sparing laparoscopy should be performed in centres of expertise and that data are collected in a standardised fashion to assess its potential benefits and risks.
- R9 Studies should evaluate factors that can be assessed prior to surgery and can predict a clinically meaningful improvement of pain symptoms. Such prognostic markers can be used to select patients that may benefit from endometriosis surgery.
- R10 The GDG recommends sufficiently powered randomised clinical trials in different countries and cultural backgrounds to directly compare the risks, costs, and clinical outcomes of laparoscopy and empirical treatment.
- R11 Adequately designed trials are needed to define the potential benefits of non-medical interventions (nutrition, Chinese medicine, electrotherapy, acupuncture, physiotherapy, exercise, and psychological interventions) in endometriosis. Further research into such interventions for women with endometriosis that employ evidence-based protocols with high intervention integrity is recommended.

Treatment of endometriosis-associated infertility and medically assisted reproduction

- R12 In patients without a clear indication for ART, the value of surgery for ovarian and deep endometriosis and its effect on natural pregnancy rates should be evaluated. Such studies should consider patient age, endometrioma bilaterality and size, previous surgeries, adenomyosis and other factors affecting fertility.
- R13 It is suggested that the EFI is used for better patient phenotyping in studies on surgical treatment and/or the place of MAR in endometriosis-related infertility. The role of the EFI as a pre-surgical triage tool should be validated.
- R14 Studies should clarify whether IUI with or without ovarian stimulation is a relevant option for women with (different subtypes of) endometriosis. In addition, the value of EFI to predict the relevance of IUI could be further investigated.

- R15 Studies evaluating IUI and ART should report clinically relevant outcomes (live birth rates and cumulative data), and ideally perform subgroup analysis by stage of endometriosis and type of disease.
- R16 Further studies of both medical and surgical treatments for endometriosis-associated infertility are required to clarify the relative effectiveness of treatments, in particular trials comparing ART and IUI to other treatments.
- R17 The impact of the extent of disease on the outcome of ART should be further studied, as it could provide data for selection of patients that could benefit from ART.
- R18 RCTs are required to answer the question whether surgery for endometrioma prior to ART improves reproductive outcomes.
- R19 Adequately designed trials are needed to define the magnitude of the benefit of non-medical interventions (nutrition, Chinese medicine, electrotherapy, acupuncture, physiotherapy, exercise, and psychological interventions) in endometriosis-associated infertility. Further research into non-medical interventions for women with endometriosis that employ evidence-based protocols with high intervention integrity is recommended.

Impact of endometriosis on pregnancy and pregnancy outcome

- R20 Studies should focus on identification of women with endometriosis who have higher chances of becoming infertile in the future due to endometriosis or endometriosis surgery (and/or who will need ART anyway). These women may have a true benefit from fertility preservation and this evidence would support a future recommendation supporting fertility preservation in selected women with endometriosis.
- R21 Observational studies should be conducted to assess natural evolution of pre-existing endometrioma or other endometriosis lesions during pregnancy.
- R22 There is a need for prospective, well-designed studies to assess the impact of surgery on subsequent pregnancy evolution, disease phenotype and presence of adenomyosis on the rare complications observed during pregnancy in women with endometriosis.
- R23 Larger studies on the evolution of early pregnancy in women with endometriosis versus controls are necessary, particularly with more precise phenotyping including adenomyosis, the role of surgery prior to conception and the mode of conception.
- R24 Prospective observational studies are needed in pregnant women with endometriosis versus controls to better define obstetric risks for women with endometriosis and the potential usefulness of interventions to prevent them.

Endometriosis and menopause

- R25 More evidence is needed on the efficacy and safety (bone health) of aromatase inhibitors or other medical treatments in postmenopausal women with endometriosis-related pain symptoms.

Extrapelvic Endometriosis

- R26 Prospective studies are needed in the field of extrapelvic endometriosis, especially thoracic endometriosis.

Prevention of endometriosis

- R27 Research should further consider the genetic background of endometriosis, which may not be a monogenic disorder, and translate findings into validated tests that can be used in diagnosis and prevention.

Endometriosis and cancer

- R28 Future studies should investigate the association between endometriosis and cancer using a prospective design, with a long duration of follow-up to take into account the temporality

of the association, a population-based sample with standardised collection of data and recognised criteria for the definition of endometriosis, evaluate potential confounding and mediation, and, also importantly, explore heterogeneity by reporting associations according to a) endometriosis and cancer subtypes, and b) patient characteristics (age, menopausal status, etc). When exploring endometriosis macro-phenotypes, results from both exclusive and non-exclusive subtypes should be reported.

R29 More research needs to be performed on the mutational and epigenetic profile of endometriosis tissue, endometrium from endometriosis patients and normal endometrium from women of different ages and reproductive histories. Among women with endometriosis, exclusive macro-phenotypes of endometriosis should be investigated.

R30 More data are needed on the malignant transformation of endometrioma and endometriosis in general to guide the need for monitoring.

