



# The treatment of endometriosis-associated infertility

Stuart Spencer<sup>a</sup>, Alexandros Lazaridis<sup>a</sup>,  
Alexandros Grammatidis<sup>b</sup>, and Martin Hirsch<sup>a</sup>

## Purpose of review

To review the recent evidence around the treatment of infertility in patients with endometriosis.

## Recent findings

The management of endometriosis associated infertility remains challenging. There have been an increasing number of prospective observational studies highlighting the role of surgery to enhance assisted conception amongst those with deep rectovaginal endometriosis. Further validation studies confirm the role of the endometriosis fertility index in prediction of reproductive outcomes after surgery, and confirm that it can be employed in counselling patients prior to surgery on their likelihood of spontaneous conception. Further randomized trials are required to establish the role of surgically treating superficial and deep endometriosis and both spontaneous and assisted conception outcomes.

## Summary

Endometriosis continues to present challenges in counselling patients with regards to their fertility prospects. This article reviews the recent research findings that may assist in the management of patients with endometriosis associated infertility.

## Keywords

assisted reproductive technologies, assisted reproduction technology, endometriosis, fertility, in vitro, infertility, intrauterine insemination, intrauterine insemination, in vitro fertilization, subfertility

## INTRODUCTION

Endometriosis is a recognized cause of infertility, identified in and responsible for 30–47% of cases of delayed conception [1]. In recent years, the approach to endometriosis-associated infertility (EAI) has shifted towards earlier recourse to medically assisted reproduction (MAR) in preference to laparoscopy and surgical treatment. A number of national and international guidelines summarize the evidence base providing recommendations where possible. The most recent, the European Society of Human Reproduction and Embryology (ESHRE) guideline on the diagnosis and management of endometriosis, published in February 2022, summarizes available data up to 1 December 2020 [2]. There are 109 recommendations in the current guideline, however only eight of these have moderate-grade evidence and none have high-grade evidence. The guideline made an additional 30 research recommendations [2].

This article aims to review studies published since the development of the ESHRE guideline, and evaluate how changes in clinical practice could be guided in the future.

## METHOD

We performed a literature review of relevant studies published between 1 January 2020 and 31 March 2022 in Pubmed and Medline (search strategies in [Appendix 1, <http://links.lww.com/COOG/A80>]). These searches included the terms ‘endometriosis’, ‘fertility’, ‘infertility’, ‘assisted reproduction’, ‘IVF’, ‘in vitro’, ‘iui’, ‘fertilization’ and ‘fertilization’. Abstracts were analysed to assess whether outcomes related to EAI were present, and where identified the full text article was obtained and analysed. References in these

<sup>a</sup>Oxford Endometriosis CaRe Centre, Nuffield Department of Women's & Reproductive Health, University of Oxford, Oxford and <sup>b</sup>Centre for Reproductive Medicine, Barts Health NHS Trust, London, United Kingdom

Correspondence to Dr Stuart Spencer, Oxford Endometriosis CaRe Centre, Nuffield Department of Women's & Reproductive Health, University of Oxford, Level 3, Women's Centre, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom. Tel: +44 1865 231571; e-mail: [drstuartspencer@gmail.com](mailto:drstuartspencer@gmail.com)

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## KEY POINTS

- Endometriosis fertility index (EFI) can be used to counsel women prior to surgery for endometriosis on their likelihood of spontaneous conception after surgery.
- EFI can be used to counsel women after surgery for endometriosis on their chances of non-assisted reproductive technologies conception.
- Surgery for deep endometriosis may increase the likelihood of spontaneous and assisted conception.
- Further robust evidence is required to better inform women and clinicians of their choices with regards to treatment of endometriosis-associated infertility.

papers were hand searched for additional articles within the time period. A further supplementary search was performed with terms such as 'endometriosis', 'ivf', 'iui' and 'assisted reproduction'.

## RESULTS

The initial search strategy identified a total of 74 Medline and 87 Pubmed papers. A review of the titles and abstracts found 56 relevant full text articles, and after duplicate articles were excluded a total of 32 unique articles were identified. A further three articles were identified through a supplementary search of CENTRAL resulting in a total of 35 relevant articles. These studies included 39 045 participants from 18 countries.

A summary of the included papers is presented in (Table 1).

## MEDICAL TREATMENT TO ENHANCE SPONTANEOUS CONCEPTION

### Ovarian suppression

The use of medical therapies to suppress ovulation is commonplace for endometriosis-associated pain. Amongst women with EAI, there is no evidence of benefit in the use of ovulation suppression [3]. We did not find any further evidence to support the use of ovulation suppression in these patients.

### Hormone or medical therapies as an adjunct to surgical therapy

The use of hormone therapy prior to or following surgery has historically been unclear. Recent high quality Cochrane data suggests that postsurgical hormone suppression is associated with an

enhanced pregnancy rate when they try to conceive compared to controls who did not undergo post-operative hormone suppression [4<sup>■</sup>]. On this basis, the recent ESHRE guideline advocates postoperative hormone suppression amongst those who do not wish to conceive immediately [2].

### Other medical treatments

Additional medical interventions for spontaneous conception continue to be evaluated. The use of clomiphene or letrozole following laparoscopic treatment of superficial endometriosis has been successful at enhancing rates of ovulation although this does not appear to improve clinical pregnancy rate (CPR) or live birth rate (LBR) [5]. A recent Cochrane systematic review found that there was no evidence for the use of selective estrogen receptor modulators (SERMs) to improve fertility outcomes (LBR, CPR or fertility-related adverse events) in patients with endometriosis [6]. A non-Cochrane systematic review by Peng *et al.* suggests dydrogesterone (an atypical synthetic progestogen) may result in a higher spontaneous pregnancy rate than no treatment. This review had significant statistical heterogeneity and a high or unclear risk of bias, limiting its ability to influence clinical practice guidelines [7]. This is also reflected in the recent ESHRE guideline [2].

## SURGICAL TREATMENT TO ENHANCE SPONTANEOUS CONCEPTION

The decision on whether to proceed with surgery requires careful consultation between the patient and clinician, taking into account the patient's individual characteristics and preferences. Bafort *et al.* and Hodgson *et al.* found that laparoscopic surgery increases the rate of intrauterine pregnancy confirmed by ultrasound compared to diagnostic laparoscopy only (Bafort odds ratio [OR] 1.89, 95% confidence interval [CI] 1.25 to 2.86; Hodgson OR 1.63; 95% CI 1.13–2.35), but lacked a subgroup analysis of disease severity that could better determine which patients may benefit from this intervention [8<sup>■</sup>,9].

The endometriosis fertility index (EFI) has been developed and demonstrated to more accurately predict the likelihood of spontaneous conception after surgery for endometriosis [10]. Vesali *et al.* validated in their systematic review the ability of the EFI to predict non-assisted reproductive technologies (ART) pregnancy after surgery and found that EFI has good predictive value for non-ART pregnancy in women with surgically diagnosed endometriosis, however with significant heterogeneity between studies [11<sup>■</sup>].

**Table 1.** Summary of reviewed papers

Article	Key points	Category	Country	Study design	No. of studies (n)	No. of patients (n)	Mean age of patients (years)	Standard deviation of age (years)	Age range of patients (years)
Almad G, Thompson M, Kim K, Agarwal P, Mackie FL, Dias S, <i>et al.</i> Fluid and pharmacological agents for adhesion prevention after gynaecological surgery. The Cochrane database of systematic reviews. 2020;7:CD001298.	Pharmacological agents can prevent adhesions but no good evidence for improving LBR or CPR	Surgical treatment	Cochrane	Systematic Review	32	3492	-	-	-
Alshahre SM, Narice BF, Fenwick MA, Merwally M. The impact of endometrioma on in vitro fertilization/intra-cytoplasmic injection IVF/ICSI reproductive outcomes: a systematic review and meta-analysis. Archives of gynecology and obstetrics. 2021;303(1):3-16.	Lower number of oocytes and metaphase II oocytes retrieved in women with endometrioma vs controls, but no difference in LBR or CPR	Medically assisted reproduction - Assisted reproductive technology in women with endometriosis	United Kingdom/ Saudi Arabia	Systematic review and meta-analysis	8	428	-	-	-
Bafout C, Beebejaun Y, Tomassetti C, Bosteels J, Duffy JM. Laparoscopic surgery for endometriosis. The Cochrane database of systematic reviews. 2020;10:CD01103	Laparoscopic ablation/excision probably improves pregnancy rate compared to diagnostic laparoscopy alone	Surgical treatment	Cochrane	Systematic Review	14	1563	-	-	-
Bala M, Tahir H, Soomro P, Maqsood S, Nawaz N, Baloch P. A Randomized Control Trial of Combined Surgical and Hormonal Therapy of Endometriosis. Pakistan journal of medical and health sciences. 2022;4(1):1020-3.	No subgroup analysis Uncertain effect on miscarriage For women with endometriosis managed with GnRHα, surgery or combined treatment, no significant difference in CPR or LBR	Surgical treatment - Pakistan Medical treatment - Hormone or medical therapies as an adjunct to surgical therapy	Pakistan	Randomized controlled trial	n/a	360	Not reported	Not reported	Not reported
Cai H, Xie J, Shi J, Wang H. Efficacy of intrauterine insemination in women with endometrioma-associated subfertility: analysis using propensity score matching. BMC Pregnancy Childbirth. 2022;22(1):12.	Per-cycle and cumulative pregnancy rates not significantly different although 'trend towards' lower pregnancy rate with endometrioma IUI with endometrioma more likely to convert to IVF than nonendometrioma patient Looked at CPR not LBR	MAR - Intrauterine insemination in women with endometriosis	China	Retrospective cohort	n/a	129	Endometrioma 30.46 No endometrioma 30.08	Endometrioma 3.72 No endometrioma 3.38	Not reported

**Table 1 (Continued)**

Article	Key points	Category	Country	Study design	No. of studies (n)	No. of patients (n)	Mean age of patients (years)	Standard deviation of age (years)	Age range of patients (years)
Cantineau AE, Ruiten AG, Cohlen BJ. Agents for ovarian stimulation for intrauterine insemination (IUI) in ovulatory women with infertility. <i>Cochrane Database Syst Rev.</i> 2021;11(11):Cd005356.	No recent studies looking at IUI specifically for women with endometriosis - therefore significant heterogeneity and cannot apply to this population	MAR - Intrauterine insemination in women with endometriosis	Cochrane	Systematic review	82	12614	-	-	-
Casals G, Carrera M, DomÍnguez JA, Abrao MS, Carmona F. Impact of Surgery for Deep Infiltrative Endometriosis before In Vitro Fertilization: A Systematic Review and Meta-analysis. <i>J Minim Invasive Gynecol.</i> 2021;28(7):1303-12.e5.	Increased pregnancy and LBR with IVF after operating on DE Greater effect when bowel involvement - CI for surgery when no bowel involvement crosses 1 Lack of info on complications and IVF Lack of RCTs	Surgical therapies as an adjunct to MAR	Spain/Brazil	Systematic review and meta-analysis	4	493	31.1-33.1	-	-
Chen I, Veih VB, Choudhry AJ, Muri A, Zakhari A, Black AY, <i>et al.</i> Pre and postsurgical medical therapy for endometriosis surgery. The Cochrane database of systematic reviews. 2020;11:CD003678.	Pregnancy rate probably increased with postsurgical medical hormonal suppression, unsure if presurgical increases, uncertain if pre and post increases	Medical treatment - Cochrane Hormone or medical therapies as an adjunct to surgical therapy	Cochrane	Systematic review	25	3378	-	-	-
Chung JW, Law TSM, Mak JSM, Sahota DS, Li TC. Ovarian reserve and recurrence 1 year postoperatively after using haemostatic sealant and bipolar diathermy for haemostasis during laparoscopic ovarian cystectomy. <i>Reprod Biomed Online.</i> 2021;43(2):310-8.	In patients that use Floseal instead of bipolar diathermy for haemostasis at cystectomy: Increased AFC but no difference in spontaneous pregnancy rate Lower rate of recurrence	Surgical treatment - Hong Kong ovarian endometriosis	Hong Kong	Retrospective cohort	n/a	75	31.95	4.99	Not reported
Dong P, Ling L, Hu L. Systematic review and meta-analysis of traditional Chinese medicine compound in treating infertility caused by endometriosis. <i>Annals of palliative medicine.</i> 2021;10(12):1263-142.	TCM is effective in increasing response rate and pregnancy rate compared to 'western' medicine Heterogeneity in control and intervention substances Possible selection and attrition bias Outcomes not clear - how is response rate or pregnancy evaluated	Nonmedical treatment strategies	China	Systematic review and meta-analysis	11	1071	TCM 28.5-33.91 Control 27.1-34.82	TCM 1.3-7.3 Control 1.4-76.02	Not reported

**Table 1 (Continued)**

Article	Key points	Category	Country	Study design	No. of studies (n)	No. of patients (n)	Mean age of patients (years)	Standard deviation of age (years)	Age range of patients (years)
Ferrero S, Scala C, Biscaldi E, Raccia A, Leone Roberti Maggiore U, Barra F. Fertility in patients with untreated rectosigmoid endometriosis. <i>Reprod Biomed Online</i> . 2021;42(4):757-67.	48% pregnancy rate and 45% LBR in women with deep endometriosis not treated with surgery Median follow up 31 months Time to pregnancy - 10 months (spontaneous), 25 months (ART)	Medically assisted reproduction	Italy	Retrospective cohort	n/a	215	33.4	4.1	Not reported
Guo H, Li J, Shen X, Cong Y, Wang Y, Wu L, et al. Efficacy of Different Progesterins in Women With Advanced Endometriosis Undergoing Controlled Ovarian Hypersimulation for in vitro Fertilization-A Single-Center Noninferiority Randomized Controlled Trial. <i>Frontiers in endocrinology</i> . 2020;11:129.	No difference in clinical or ongoing pregnancy rate between medroxyprogesterone acetate, dydrogesterone and progesterone in women with advanced endometriosis	Medical therapies as an adjunct to MAR	China	Randomized controlled trial	n/a	455	MPA 32.8 Dydrogesterone 33.0 Progesterone 33.1	MPA 3.4 Dydrogesterone 3.2 Progesterone 3.4	Not reported
Javaheri A, Ashkezar SK, Eftekhari M, Tafii SZG. Ovarian reserve in women with endometriosis under total cystectomy compared to partial cystectomy: A randomized clinical trial. <i>International Journal of Reproductive BioMedicine</i> . 2021;19(7):619-24.	In women with endometrioma, partial cystectomy results in less reduction in AMH than total cystectomy	Surgical treatment - ovarian endometriosis	Iran	Randomized controlled trial	n/a	50	Total cystectomy 29.88 Partial cystectomy 29.58	Total cystectomy 5.4 Partial cystectomy 5.7	Not reported
Kaponis A, Chaizopoulos G, Paschopoulos M, Georgiou I, Paraskevaïdis V, Zikopoulos K, et al. Ultralong administration of gonadotropin-releasing hormone agonists before in vitro fertilization improves fertilization rate but not CPR in women with mild endometriosis: a prospective, randomized, controlled trial. <i>Fertility and sterility</i> . 2020;113(4):828-35.	GnRH increases fertilization rate but not CPR in women with mild endometriosis	MAR - ART in women with endometriosis	Greece	Randomized controlled trial	n/a	600	GnRH 34.8 No GnRH 32.8 Control 36.4	GnRH 3.8 No GnRH 2.9 Control 2.1	Not reported

**Table 1 (Continued)**

Article	Key points	Category	Country	Study design	No. of studies (n)	No. of patients (n)	Mean age of patients (years)	Standard deviation of age (years)	Age range of patients (years)
Kashani L, Moini A, Esfidani T, Yamini N, Mohiti S. Effect of intrauterine granulocyte-colony stimulating factor administration on in vitro fertilization outcome in women with moderate-to-severe endometriosis: an rct. International journal of reproductive biomedicine. 2021;19(8):733-40.	In women with moderate-to-severe endometriosis, granulocyte-colony stimulating factor prior to IVF/ICSI does not improve the CPR	Medical therapies as an adjunct to MAR	Iran	Randomized controlled trial	n/a	66	G-CSF 31.34 Control 30.92	G-CSF 5.4 Control 3.2	Not reported
Khalifa E, Mohammad H, Abdullah A, Abdel-Rasheed M, Khairy M, Hasni M. Role of suppression of endometriosis with progestins before IVF-ET: a noninferiority randomized controlled trial. BMC pregnancy and childbirth. 2021;21(1):264.	Dienogest similar to GnRH for downregulation before IVF	Medical therapies as an adjunct to MAR	Egypt	Randomized controlled trial	n/a	134	GnRH 35.6 Dienogest 36.1	GnRH 3.5 Dienogest 2.7	Not reported
Lier MCI, Ozcan H, Schreurs AMF, Van De Ven PM, Dreyer K, Van Der Houwen LEE, <i>et al.</i> Uterine bathing with sonography gel prior to IVF/ICSI-treatment in patients with endometriosis, a multicentre randomized controlled trial. Human reproduction open. 2021;2020(4).	No difference in ongoing pregnancy rate or LBR with uterine bathing with sonography gel prior to IVF/ICSI-treatment in patients with endometriosis Trial stopped early - slow recruitment	Medical therapies as an adjunct to MAR	Netherlands	Randomized controlled trial	n/a	112	Gel 35 Control 36	Not reported	IQR Gel 33-39 IQR Control 33-38
Liu S, Xie Y, Li F, Jin L. Effectiveness of ultra-long protocol on in vitro fertilization/intracytoplasmic sperm injection-embryo transfer outcome in infertile women with endometriosis: A systematic review and meta-analysis of randomized controlled trials. The journal of obstetrics and gynaecology research. 2021;47(4):1232-42.	Ultra-long GnRHa downregulation protocol 2+ months had a higher CPR	Medical therapies as an adjunct to MAR	China	Systematic review and meta-analysis	9	943	30.3-34.8	0.67-5.37	Not reported



Table 1 (Continued)

Article	Key points	Category	Country	Study design	No. of studies (n)	No. of patients (n)	Mean age of patients (years)	Standard deviation of age (years)	Age range of patients (years)
Moreno-Sepulveda J, Romeral C, Nino G, PÓrez-Benavente A. The Effect of Laparoscopic Endometrioma Surgery on Anti-Müllerian Hormone: A Systematic Review of the Literature and Meta-Analysis. <i>JBRA Assist Reprod.</i> 2022;26(1):88-104.	Decrease in AMH with endometrioma surgery no difference in short- and long-term AMH after surg Greater decrease with bilateral compared to unilateral Greater decrease with cystectomy compared to vaporization Greater decrease with bipolar haemostasis compared to suture/haemostatic agents	Surgical treatment - ovarian endometriosis Surgical therapies as an adjunct to MAR	Spain/Chile	Systematic review and meta-analysis	36	4349	-	-	-
Nankali A, Kazemina M, Jamshidi PK, Shohaimi S, Salari N, Mohammadi M, et al. The effect of unilateral and bilateral laparoscopic surgery for endometriosis on Anti-Müllerian Hormone (AMH) level after 3 and 6 months: a systematic review and meta-analysis. <i>Health and quality of life outcomes.</i> 2020;18(1):314.	Unilateral and bilateral treatment of endometrioma affects AMH levels	Surgical treatment - ovarian endometriosis Surgical therapies as an adjunct to MAR	Iran	Systematic review and meta-analysis	19	Not reported	Not reported	Not reported	Not reported
Peng C, Huang Y, Zhou Y. Dydrogesterone in the treatment of endometriosis: evidence mapping and meta-analysis. <i>Archives of gynecology and obstetrics.</i> 2021;304(1):231-52.	Dydrogesterone has a higher pregnancy rate than gestrinone Heterogenic studies, high risk of bias (unclear blinding), outcome (pregnancy) not clearly defined - CPR or live birth?	Medical treatment	China	Systematic review and meta-analysis	19	1709	28.8-35.2	Not reported	18-51
Rius M, Gracia M, Ros C, MartÚnezZamora M, deGuirior C, Quintas L, et al. Impact of endometrioma surgery on ovarian reserve: a prospective, randomized, pilot study comparing stripping with CO(2) laser vaporization in patients with bilateral endometriomas. <i>J Int Med Res.</i> 2020;48(6):300060520927627.	Cystectomy with excision reduces ovarian volume and AFC more than CO2 laser vaporization ovarian reserve: a prospective, randomized, pilot study comparing stripping with CO(2) laser vaporization in patients with bilateral endometriomas. J	Surgical treatment - ovarian endometriosis Surgical therapies as an adjunct to MAR	Spain	Randomized controlled trial - pilot study	n/a	16	32.13 (inclusion 18-45 years)	6.56	Not reported

**Table 1 (Continued)**

Article	Key points	Category	Country	Study design	No. of studies (n)	No. of patients (n)	Mean age of patients (years)	Standard deviation of age (years)	Age range of patients (years)
Rodriguez-Tarrega E, Monzo AM, Quiroga R, Polo-Sanchez P, Fernandez-Colom P, Monterde-Estrada M, <i>et al.</i>	GnRH <sub>a</sub> downregulation for 3 months before IVF did not improve CPR, and increased length of controlled ovarian stimulation, lower estradiol level, higher rate of cancellation, lower rate of cleavage embryos	MAR - ART in women with endometriosis	Spain	Single blinded randomized controlled trial	n/a	200	GnRH 33.86 Control 33.72	GnRH 3.08 Control 3.25	Not reported
Rodriguez-Tarrega E, Monzo AM, Quiroga R, Polo-Sanchez P, Fernandez-Colom P, Monterde-Estrada M, <i>et al.</i>	Surgery for DE with bowel involvement gives increase in wellbeing Pregnancy rate 28% after surgery Not an RCT - qualitative study, variable length of follow up	Surgical treatment to enhance spontaneous conception Medically assisted reproduction	Brazil	Cross-sectional with structured	n/a	77	questionnaire	n/a	77
Shi J, Dai Y, Zhang J, Li X, Jia S, Leng J.	Women with adenomyosis and endometriosis have higher LBR if lower age, endometrioma size and uterine size Higher rate of peritoneal and ovarian endometriosis leads to lower LBR EFI positively correlated with LBR	24-54 Surgical treatment	China	Retrospective cohort study	n/a	226	Live Birth 32.52 Control 33.53	Live birth 3.20 Control 3.95	Not reported
Stojkowska S, Dimitrov G, Stojkowski J, Sallirovski S, Lega MH.	For IVF, women with endometrioma >3 cm treated surgically had similar CPR and LBR as women with unexplained infertility Not an RCT (although describes itself as such)	Surgical therapies as an adjunct to MAR	Macedonia	Prospective case-control study	n/a	120	Endometrioma 32.10 Unexplained 31.20	Endometrioma 4.35 Unexplained 3.81	Not reported



Table 1 (Continued)

Article	Key points	Category	Country	Study design	No. of studies (n)	No. of patients (n)	Mean age of patients (years)	Standard deviation of age (years)	Age range of patients (years)
Tian Z, Zhang Y, Zhang C, Wang Y, Zhu HL. Antral follicle count is reduced in the presence of endometriosis: a systematic review and meta-analysis. <i>Reprod Biomed Online</i> . 2021;42(1):237-47.	Reduced AFC, AMH and increased FSH in women with endometriosis, especially those with endometrioma or advanced age	Medically assisted reproduction	China	Systematic review and meta-analysis	15	Not reported	29.0-36.5	0.4-5.99	Not reported
Tomassetti C, Bafout C, Vanhie A, et al. Estimation of the Endometriosis Fertility Index prior to operative laparoscopy. <i>Hum Reprod</i> . 2021;36(3):636-46	EFI can be estimated based on clinical/ultrasound data only without the need for any surgical data, and could be used to counsel women prior to surgery for endometriosis on their likelihood of conception after surgery with ART	Assessing the need for assisted reproduction after surgery	Belgium	Single-cohort prospective	n/a	observational study	n/a	n/a	82
31.5±4.65	Not reported	Not reported							
Tomassetti C, Beukelaers T, Conforti A, Debrock S, Peeraer K, Meuleman C, et al. The ultra-long study: a randomized controlled trial evaluating long-term GnRH downregulation prior to ART in women with endometriosis. <i>Human reproduction (Oxford, England)</i> . 2021;36(10):2676-86.	Ultra-long GnRHa does not improve CPR. Trial was stopped prematurely due to low recruitment	Medical therapies as an adjunct to MAR	Belgium	Open-label randomized controlled trial	n/a	42	Control 32.4 Ultralong 31.4	Control 3.7 Ultralong 3.9	
Tsiampa E, Spartalīs E, Isouroufīs G, Dimitroulīs D, Nikiteas N. Impact on ovarian reserve after minimally invasive single-port laparoscopic ovarian cystectomy in patients with benign ovarian cysts: A systematic review and meta-analysis. <i>International journal of clinical practice</i> . 2021;75(12):e14875.	Single port laparoscopy can be an alternative to MPL. Only looks at 'benign cysts', not endometriomas specifically	Surgical treatment - ovarian endometriosis	Greece	Systematic review and meta-analysis	4	336	29.4-34.73	5.0-10.18	Not reported
van Hoesel MH, Chen YL, Zheng A, Wan Q, Mourad SM. Selective oestrogen receptor modulators (SERMs) for endometriosis. <i>The Cochrane database of systematic reviews</i> . 2021;5:CD011169.	No evidence for SERMs and fertility	Medical treatment	Cochrane	Systematic Review	1	93	SERM 31.1 Placebo 32.0	SERM 1.1 Placebo 1.1	18-45

**Table 1 (Continued)**

Article	Key points	Category	Country	Study design	No. of studies (n)	No. of patients (n)	Mean age of patients (years)	Standard deviation of age (years)	Age range of patients (years)
Vesali S, Razavi M, Rezaeinejad M, Maleki-Hajjagha A, Maroufizadeh S, Sepidarkish M. Endometriosis fertility index for predicting nonassisted reproductive technology pregnancy after endometriosis surgery: a systematic review and meta-analysis. <i>BJOG: an international journal of obstetrics and gynaecology.</i> 2020;127(7):800-9.	EFI has good predictive value for non-ART pregnancy in women with surgically diagnosed endometriosis. Significant heterogeneity between studies.	Surgical treatment to enhance spontaneous conception	Iran	Systematic review and meta-analysis	17	4598	-	-	-
Yilmaz N, Ceran MU, Ugurlu EN, Gulerman HC, Ustun YE. Impact of endometrioma and bilaterality on IVF/ICSI cycles in patients with endometriosis. <i>J Gynecol Obstet Hum Reprod.</i> 2021;50(3):101839.	Retrospective analysis of IVF/ICSI MAR - ART in women with endometriosis. Lower number of AFC, dominant follicles, total oocytes and MI oocytes in endometrioma groups. Numbers of embryos achieved, CPRs and LBRs were found to be similar.	MAR - ART in women with endometriosis	Turkey	Retrospective case-control	n/a	159	Endometrioma 30.5 No endometrioma 31.0	Not reported	Endometrioma 23-42 No endometrioma 24-41
Younis JS, Shapso N, Ben-Sira Y, Nelson SM, Izhaki I. Endometrioma surgery-a systematic review and meta-analysis of the effect on antral follicle count and anti-Müllerian hormone. <i>Am J Obstet Gynecol.</i> 2022;226(1):33-5e7.	Endometrioma cystectomies associated with reduction in AMH no antral follicle count. In women with endometrioma, AMH may be more accurate to measure depletion of ovarian reserve.	Surgical treatment of ovarian endometriosis. Surgical therapies as an adjunct to MAR.	Israel	Systematic review and meta-analysis	14	650	28.6	5.0	-
Zhou L, Fu J, Liu D, Wang Q, Chen H, Yang S, <i>et al.</i> Ovarian induction with clomiphene citrate or letrozole following laparoscopy in infertile women with minimal to mild endometriosis: a prospective randomized controlled trial. <i>Journal of Obstetrics and Gynaecology.</i> 2022;42(2):316-2	Clomiphene or letrozole offer laparoscopic treatment of superficial endometriosis. Increases rate of ovulation, but not CPR or live birth rate.	Medical Treatment to enhance spontaneous conception - Other medical treatments	China	Randomized controlled trial	n/a	210	Control 28.8 Letrozole 28.9 Clomiphene 28.7	Control 3.9 Letrozole 3.3 Clomiphene 3.4	-

AFC, antral follicle count; AMH, anti-Müllerian hormone; ART, assisted reproductive technologies; DE, deep endometriosis; EFI, endometriosis fertility index; FSH, follicle stimulating hormone; GnRH, gonadotropin-releasing hormone; GnRHα, gonadotropin-releasing hormone agonist; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilization; MAR, medically assisted reproduction; RCT, randomized controlled trial; SERM, selective estrogen receptor modulators; TCM, traditional Chinese medicine.

Tomassetti *et al.* further assessed the ability of noninvasive test models to predict the EFI compared to surgical findings. This demonstrated a high level of agreement that may enable more accurate counselling of a person's likelihood of conception without requiring surgical intervention [12<sup>11</sup>].

Shi *et al.* reported that women with co-existing adenomyosis and endometriosis have a higher LBR when they are of lower age, smaller endometrioma and uterine size. Additionally, they described that a higher rate of peritoneal and ovarian endometriosis leads to a lower LBR, and that the EFI is positively correlated with the LBR in these patients [13].

In their randomized controlled trial (RCT), Bala *et al.* found no difference between GnRHa, surgery or combined treatment on the CPR or LBR [14]. However, there are uncertainties in the method of randomization, patient demographics and fertility outcomes and firm conclusions cannot be drawn on the basis of this study.

With regards to endometriosis surgical techniques and fertility, Ahmad *et al.* found that neither antiadhesive barriers nor steroid treatment improve the LBR or CPR [15].

These recent findings highlight the challenges in counselling women on surgery for endometriosis, but encourage the use of EFI in counselling women on the likelihood of fertility even if they do not plan on undergoing ART [10,11<sup>11</sup>,12<sup>11</sup>,13].

### Peritoneal endometriosis

The ESHRE guideline recommends operative laparoscopy as a treatment option for EAI in rASRM stage I/II endometriosis, as it improves the rate of ongoing pregnancy.

The ESHRE recommendation was based on Bafort *et al.*, who identified and included trials on rASRM stage I/II endometriosis and found an increase in the intrauterine pregnancy rate but not LBR.

We did not identify any studies that stratified patients with superficial endometriosis by EFI. We are aware that the ESPriT2 trial plans to assess fertility as a secondary outcome after treatment of superficial endometriosis [16].

### Ovarian endometriosis

There is ongoing interest in assessing the effect of surgery and different surgical techniques for endometrioma on surrogate markers of ovarian reserve including antral follicle count (AFC), follicle-stimulating hormone (FSH) and anti-Müllerian hormone (AMH). Many studies evaluated these surrogate markers and consistently found a

reduction in AFC [17,18] and AMH [17,19–21], and an increase in FSH [17]. Bilateral endometrioma surgery had a greater effect on these surrogate markers than unilateral [19] and total cystectomy reduced AMH more than partial cystectomy [22].

Moreno-Sepulveda *et al.* found a greater decrease in the AMH level with cystectomy than vaporization, and with bipolar haemostasis than haemostatic suturing or haemostatic agents [19]. Conversely, Rius *et al.* compared cystectomy with stripping of the cyst wall against CO<sub>2</sub> laser vaporization and found a reduced ovarian volume and AFC in the cystectomy group [18]. This may not translate into a reduced fecundity, as the Candiani *et al.* paper cited in the ESHRE guideline found a higher spontaneous pregnancy rate after laparoscopic stripping compared to CO<sub>2</sub> laser vaporization [23].

Chung *et al.* reported that using FloSeal when performing ovarian cystectomy for ovarian endometrioma had a higher AFC at one year, but no difference in the FSH or AMH compared to patients receiving haemostasis with diathermy. There was no difference in the spontaneous pregnancy rate and the rate of endometrioma recurrence was not significantly different [24].

Reduced surrogate markers of ovarian reserve do not predict spontaneous conception but are associated with reduced response to ovarian stimulation during MAR. Where a reduced ovarian reserve is detected in advance of surgery, a discussion needs to take place for the patient to consider fertility preservation ahead of any further interventions that may reduce ovarian reserve.

One study found single-port laparoscopic cystectomy did not statistically affect the AMH level compared to multiport cystectomy, but only looked at 'benign cysts' rather than endometrioma specifically [25]. Reference should be made to the ESHRE guideline for the surgical management of endometriosis with regards to performing surgery in an appropriate centre of expertise, minimal handling of ovarian tissue, being aware of the risk of damage to ovarian reserve with a consideration of fertility preservation, and considering antiadhesion measures or ovarian suspension [26].

### Deep endometriosis

There is ongoing discussion on whether fertility improvement benefits from deep endometriosis surgery outweigh the risks of surgical morbidity. Ferrero *et al.* found that there was a persistent lack of evidence for surgery to improve fertility in women with endometriosis with bowel involvement without significant bowel occlusion or other indications

for surgery [27<sup>¶</sup>]. This is consistent with the ESHRE recommendation that operative laparoscopy may be offered to symptomatic patients with deep endometriosis wishing to conceive [2]. One observational study concluded that surgery for deep endometriosis with bowel involvement provided an increase in wellbeing and a pregnancy rate of 28% after surgery amongst those with infertility [28].

## ASSESSING THE NEED FOR ASSISTED REPRODUCTION AFTER SURGERY

The use of predictive tools such as the EFI enables clinicians and patients to accurately discuss the likelihood of spontaneous conception after surgery. It is proposed to be the principal tool for postoperative fertility counselling/management of women with endometriosis [1] and this was validated by Vesali *et al.* in their 2020 meta-analysis [11<sup>¶¶</sup>]. This tool can enable those with a low likelihood of spontaneous pregnancy to promptly access MAR while those with a high likelihood can avoid invasive, costly, and unnecessary interventions. This approach may complement the ESHRE recommendation to use EFI after endometriosis surgery to counsel the likelihood of reproductive outcomes with ART [2].

## MEDICALLY ASSISTED REPRODUCTION

Counselling of women with infertility prior to embarking on a treatment pathway is imperative. Ferrero *et al.* found a 48% pregnancy rate and 45% LBR in women with deep endometriosis not treated with surgery, with a median time to follow up of 31 months [27<sup>¶</sup>]. Time to conception was shorter in women attempting spontaneous conception (10 months) compared to ART (25 months), suggesting it is reasonable to attempt spontaneous pregnancy before undergoing ART in the absence of other indications for prompt ART.

### Intrauterine insemination in women with endometriosis

Intrauterine insemination (IUI) may be considered in women with endometriosis. Cai *et al.* concluded that IUI may be a viable approach for subfertile women with endometrioma and no other identifiable infertility factors. Per-cycle and cumulative pregnancy rates were not significantly different compared to women with unexplained infertility and this rate was not different with associated ovarian stimulation. The same study concluded that IUI with endometrioma was more likely to convert to IVF, however the authors chose to collect and report the CPR rather than the LBR [29]. These findings

confirm the ESHRE suggestion that IUI with ovarian stimulation may be suitable for women with endometrioma and no other identified infertility factors [2].

In a recent Cochrane review, Cantineau *et al.* found no studies looking at agents for ovarian stimulation in IUI specifically for women with endometriosis [30].

### Assisted reproductive technology in women with endometriosis

ART is a common treatment strategy for EAI. Alshehre *et al.* found a lower number of oocytes and metaphase II oocytes were retrieved in women with endometrioma vs. controls, without a corresponding significant difference in the CPR or LBR [31]. In a retrospective analysis of IVF (in-vitro fertilization) and ICSI (intra-cytoplasmic sperm injection) in women with and without endometrioma, Yilmaz *et al.* found a lower AFC, dominant follicles, total oocytes and metaphase II oocytes in the endometrioma group. It is important to note that the number of embryos achieved, CPR and LBR were found to be similar between the groups [32]. These findings should not alter the current ESHRE recommendations with regards to endometriosis and ART [2].

## MEDICAL THERAPIES AS AN ADJUNCT TO MEDICALLY ASSISTED REPRODUCTION

The evidence of benefit for extended gonadotropin-releasing hormone agonist (GnRHa) administration remains uncertain. In their systematic review of nine studies including 943 patients between 2002 and 2019, Liu *et al.* concluded that an ultra-long GnRHa downregulation protocol of two or more months had a higher CPR but not LBR [33]. Subsequent trials have also failed to show an increase in the CPR with GnRHa downregulation of 3 months or more before IVF [34,35<sup>¶</sup>,36<sup>¶</sup>].

Khalifa *et al.* suggest that the use of Dienogest for suppression of endometriosis provided similar results to a three month GnRHa downregulation prior to IVF, with no difference in the CPR and less adverse effects in the dienogest group [37].

ESHRE do not recommend the use of prolonged GnRHa or progestogens prior to ART due to insufficient evidence [2] and these studies reinforce this recommendation.

With regards to other medical therapies prior to MAR, Kashani *et al.* found that in women with moderate-to-severe endometriosis, granulocyte-colony stimulating factor prior to IVF/ICSI does not improve the CPR [38]. The RCT of Guo *et al.* found

no difference in the clinical or ongoing pregnancy rate for women with advanced endometriosis treated with medroxyprogesterone acetate, dydrogesterone or progesterone prior to IVF [39]. Lier *et al.* did not find a difference in the ongoing pregnancy rate or LBR for women with endometriosis undergoing uterine bathing with sonography gel prior to IVF/ICSI treatment [39].

## **SURGICAL THERAPIES AS AN ADJUNCT TO MEDICALLY ASSISTED REPRODUCTION**

### **Surgery prior to medically assisted reproduction in women with peritoneal endometriosis**

The Cochrane systematic review by Bafort *et al.* considering laparoscopic surgery for endometriosis found 3 studies looked at the viable intrauterine pregnancy rate after surgery but all were non-ART pregnancies [8<sup>11</sup>].

### **Surgery prior to medically assisted reproduction in women with ovarian endometrioma**

The effect of surgery for ovarian endometriosis on markers of ovarian reserve has been previously discussed in this article. The results of those studies [17–22,24] reinforce the ESHRE recommendation to avoid surgery for ovarian endometrioma unless required to improve endometriosis-associated pain or accessibility of follicles [2]. A study looking at the surgical treatment of endometrioma >3 cm prior to IVF found a similar CPR and LBR as in women with unexplained infertility, however this was a prospective case-control study despite identifying itself as an RCT [40].

### **Surgery prior to medically assisted reproduction in women with deep endometriosis**

Surgery for deep endometriosis with or without gastrointestinal involvement may be hypothesized to improve the inflammatory environment of the pelvis, leading to an improvement in MAR outcomes, although data remains limited.

A systematic review by Casals *et al.* concluded that there was an increased pregnancy and LBR with IVF after surgery for deep endometriosis. This study demonstrated the greatest positive effect when the excised endometriosis involved the bowel [41<sup>11</sup>]. Surgery for deep endometriosis prior to ART has previously been recommended by ESHRE on the

basis of pain symptoms and patient preference only [2], but this study indicates that ART outcomes may be improved after surgery to deep endometriosis, particularly when it involves the bowel. There remains a lack of information on complications of surgery and IVF, and limited high-quality data on this topic [41<sup>11</sup>].

Further research is needed to better inform a decision on whether to surgically treat deep endometriosis prior to ART.

## **NON-MEDICAL TREATMENT STRATEGIES**

Nonmedical treatment of EAI has limited evidence. The non-Cochrane systematic review by Dong *et al.* concluded that traditional Chinese medicine may be effective in increasing the response rate and pregnancy rate compared to 'Western' medicine. However, these outcomes were not clearly defined within the article, with significant heterogeneity between studies and possible selection and attrition bias in their analysis [42].

## **FUTURE RESEARCH**

It is widely acknowledged that there are many unanswered questions regarding endometriosis and infertility for which robust data is required. Two randomized trials are of particular interest. The ESPriT2 trial is a randomized controlled trial assessing laparoscopic treatment of superficial endometriosis versus no surgical treatment with plans to assess a secondary outcome of pregnancy events at 3, 6 and 12 months [16]. The EFFORT study plans to assess the effect of surgical management of deep endometriosis and its effect on the CPR and LBR at 18 months when compared to ART [43].

## **CONCLUSION**

We believe this paper provides a comprehensive summary of the latest research findings regarding the treatment of endometriosis associated infertility. The strengths of this article are the comprehensive search, synthesis, and discussion of how the results relate to our most up-to-date clinical practice guideline for the management of endometriosis. Weaknesses include the breadth of the topic and the recent paucity of robust RCT data, which may have been negatively influenced by the COVID-19 pandemic.

We feel that the most significant findings include the use of preoperative imaging techniques to generate an EFI score which is reproducible with surgical findings. This will continue to be a useful tool in the counselling of women with endometriosis on their



prospects of spontaneous conception. The role of surgery continues to grow as expertise and skills reduce complication rates. The recent observational data suggests that treatment for deep endometriosis may improve both spontaneous and MAR outcomes during ART.

We feel that the most significant findings are that EFI has been shown to be useful in the counselling of women with endometriosis on their prospects of fertility prior to surgery and for non-ART reproduction, and that surgery for deep endometriosis may improve the outcomes of ART. As usual, we will continue to await further significant research findings to better inform our treatment of women with EAI.

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## Conflicts of interest

There are no conflicts of interest.

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- of special interest
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