ENDOMETRIOSIS

ESHRE GUIDELINE

REVIEW REPORT

2022

ESHRE Guideline Group
Endometriosis

eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

www.eshre.eu/guidelines

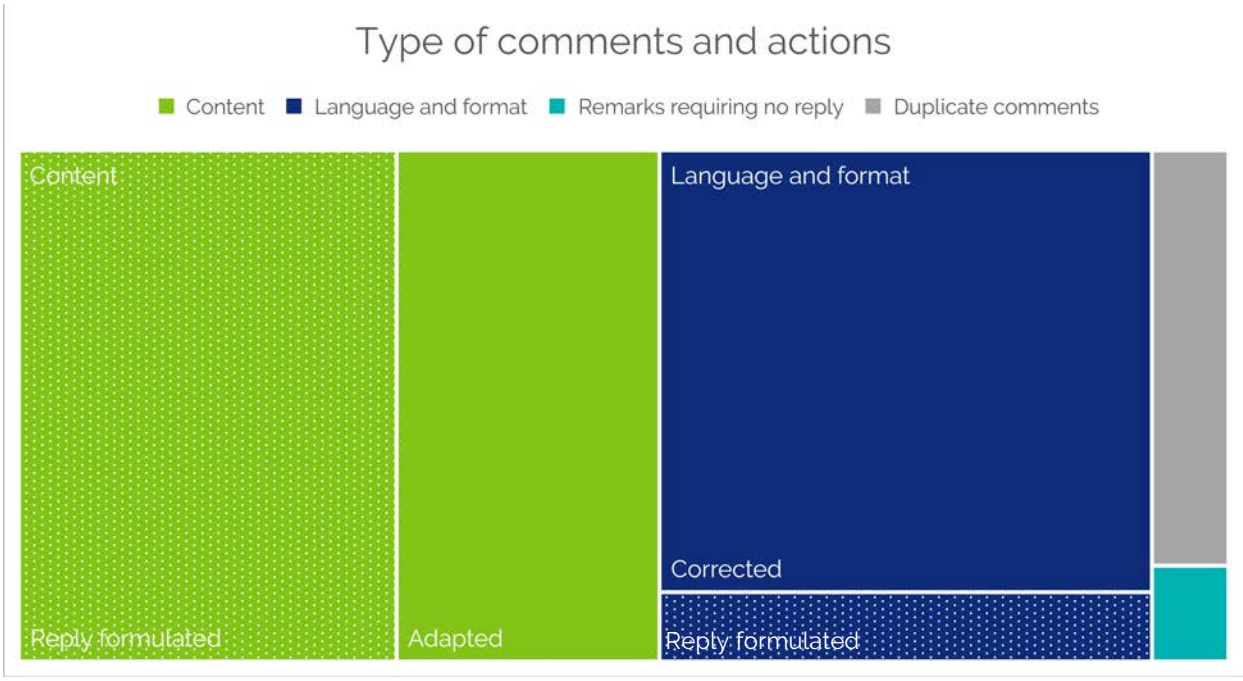
The draft of the guideline "Endometriosis" was published for public review for 6 weeks, between 24 June and 15 August 2021.

This report summarizes all reviewers, their comments and the reply of the guideline development group (GDG) and is published on the ESHRE website as supporting documentation to the guideline (Annex 5).

During the stakeholder review, a total of 253 comments (including 13 duplicates) were received from 20 reviewers. Reviewers included professionals and industry representatives and patients/consumer representatives.

The comments were focused on the content of the guideline (134 comments), or language and style (103 comments). There were 3 comments that did not require a reply. All comments to the language and format were checked and corrected where relevant.

The comments to the content of the paper (n=134) were assessed by the GDG and where relevant, adaptations were made in the paper (n=55; 41.0%). Adaptations included revisions and/or clarifications of the text, and amendments to the recommendations. For a number of comments, the working group considered them outside the scope of the paper or not appropriate/relevant (n=79; 58.9%)



Experts that participated in the stakeholder review

The list of representatives of professional organization, and of individual experts that provided comments to the guideline are summarized below.

Representatives of professional organisations

Organisation	Country	Representative
The Centre for Reproduction Research, De Montfort University, UK	UK	Caroline Law and colleagues
FERRING PHARMACEUTICALS	Denmark	
Gedeon Richer, Myovant and Pfizer		Thierry Schulmann
Department of Fertility and Gynecology, UMC Utrecht	The Netherlands	

Individual experts

Reviewer	Country
Alain Rico	France
Svetlana Dubrovina	Russia
B.C. Schoot	The Netherlands
Celine Bafort	Belgium
Astrid Cantineau	The Netherlands
Linda Giudice	USA
Fleur Blok	The Netherlands
Carlos Calhaz-Jorge	Portugal
Mukhri Hamdan	Malaysia
Velja Mijatovic, Lisette vd Houwen, Anneke Schreurs, Astrid Cantineau on behalf of the COPIE study group	The Netherlands
Pauline de Heer	The Netherlands
Aboubakr Mohamed Elnashar	Egypt
George Pados	Greece
Helen McLaughlin	UK
Ellen Klinkert	The Netherlands
Julie Prilling	

Reviewer comments and replies

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
1	Alain Rico			604	Clinicians could use the measurement of genetic biomarkers and derived polygenic risk score to evaluate the risk of endometriosis.	We consider that for non of the biomarkers, nor for the genetic biomarkers, there are sufficient data from clinical validation studies. We consider such studies are essential before recommending the application of biomarkers in clinical practice.
2	Alain Rico		24	580-582	Since 2016 and Nisenblat's publication there have been at least one mitochondrial biomarkers described by Harbottle et al. (10.2217/bmm-2019-0451) which could potentially be used in the clinic. Also, Kenneth Ward at Juneau Biosciences validated genetic markers leading to an effective polygenic risk score testing (Obstetrics & Gynecology. 135():6S–7S, MAY 2020)	We have checked the suggested papers, but the study of Ward seems to be a conference abstract, and the study by Harbottle is a pilot study. We did not consider it relevant to include the suggested biomarkers but may do in the future when more data become available. We did add a paragraph on more novel biomarkers.
3	Svetlana Dubrovina	76			Maybe it is necessary to make a remark about DIE and estrogens as the component of the combined contraceptive according the opinion of Vercellini? «Oral contraceptives may be used in women with dysmenorrhoea as their main complaint, and when only superficial peritoneal implants or ovarian endometriomas < 5 cm are present, while progestogens should be preferred in women with severe deep dyspareunia and when infiltrating lesions are identified.» Vercellini P, Buggio L, Frattaruolo MP, Borghi A, Dridi D, Somigliana E, Medical treatment of endometriosis related pain, Best Practice & Research Clinical Obstetrics & Gynaecology (2018), doi: 10.1016/j.bpobgyn.2018.01.015.	We are specifically referring to the prevention of recurrence after surgery in this section. Vercellini article refers to medical treatment.
4	Svetlana Dubrovina		36	985-986	Regarding this statement «Notably, none of the hormone treatments used to manage endometriosis are free of side effects. » But later the different side effects of dienogest and GnRH agonist including decrease of bone density (page 39, lines 1117-1130, page 40, lines 1183-85, page 115, lines 4293-4295), weight gain with OCP (page 115, lines 4300) are described. It is self-contradiction).	The sentence copied actually state that there are side effects to each of the treatments (none are free of side effects) and thus there is no contradiction.
5	Svetlana Dubrovina	x	36	994-995	«As there is no evidence that hormonal treatments have a negative effect on disease progression and they generally have limited side effects, prescribing hormonal treatment is recommended (strong recommendation). » In «Comments to the recommendations» I already have stressed that in case of DIE we should avoid any estrogens according the opinion Vercellini.	The sentence copied actually state that there are side effects to each of the treatments (none are free of side effects) and thus there is no contradiction.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
6	Svetlana Dubrovina		58	1940 - 1942	«The GDG recommends that when hysterectomy is performed, a total hysterectomy (i.e., removal of uterus and cervix) is preferred. This recommendation is based on a possible increased risk of prolapse with subtotal hysterectomy. » But there is not any reference regarding this opinion. So, how it could be recommendation. Furthermore, if we consider performance of total hysterectomy aiming at decrease of cervical cancer risk, this also could not be a ground (in this recommendation this reason is explained).	This was due to a typing error and has now been corrected and clarified further. Consideration of the risk of cervical cancer is beyond the scope of this guideline, as women with endometriosis are not known to be at risk of cervical cancer.
7	Svetlana Dubrovina		112	4198	Please, see «Comments to the recommendations»	We have addressed all other comments specifically.
8	Svetlana Dubrovina		125	4716	«It is important to note that some progestogens may decrease bone mineral density. » But this was indicated only for dienogest (lines 4675-4682). So, perhaps, it is necessary to stress that just dienogest not «some progestogens» may decrease bone mineral density (for sure, not all doctors will read all comment in text).	It was decided in the guideline group not to write specific names of medical options in our recommendations and we have done so throughout the guideline. Therefore, the recommendation states "some progestogens" and we have not amended this.
9	B.C. Schoot				As I mentioned in my comments during the first draft round (I think more then a year ago), the association of endometriosis and adenomyosis is poorly emphasized in this draft. Although the discussion of different origin of endometriosis and adenomyosis is going on, it is commonly assumed that there is a high co-occurence rate of the two disease entities. Studies of Kunze/ leyendecker and Brosens underline this coexistence. Both diseases have overlapping complaintsand can thereby influence interpretation, therapy, and counseling. In this guideline the mixture of disease adenomyosis together with endometriosis concerning complaints, diagnosis an treatment is in my opinion (as reported before) not addressed sufficiently. I understand that a guideline on endometriosis is not discussing adenomyosis extensively, however, the complex of this often dual disease of endo and adenomyose might be brought under attention in a more explicit manner. I do not like criticism, but when asked to give input… I would suggest to bring the combined occurrence and its consequences more explicit, adding some sentences.	Although we acknowledge the co-occurrence, we confirm the recently stated definition that adenomyosis is not a type of endometriosis. Furthermore, a guidance document on adenomyosis is under development. This has been clarified in the introduction,

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
10	Caroline Law and colleagues		6	130-159	This section provides an important introduction and overview to the main aspects of the condition, but might be enhanced with more reference to both a) the psychosocial impacts of the condition and the impact on quality of life and b) the impacts on women's partners and families, and on the couple/family unit. We suggest that attending to these impacts of the condition, and the way the condition is experienced by both women and those around them, is vital contextual information for the guideline. *Psychosocial impact/impact on quality of life* Our literature review (Culley et al 2013a) and research (Culley et al 2013b, Hudson et al 2015) demonstrates the impact of endometriosis, particularly pain symptoms, on quality of life and on a range of activities and life domains including physical functioning, everyday activities and social life; education and work; sex, intimacy and intimate partnerships; mental health and emotional wellbeing; and in relation to actual and anticipated infertility. This section may be enhanced by referring to such impacts, citing our review and research. *Impact on women's partners and families and the couple/family unit* Our research (Culley et al 2013b) also demonstrates the substantial detrimental impact endometriosis can have on women, and on their male partners and the heterosexual couple unit, in complex and multidimensional ways. Our research with male partners of women with endometriosis demonstrates how the condition impacts them in multiple ways including relating to sex and intimacy, planning for and having children, working lives, household income and emotional wellbeing (Culley et al 2017) as well as the range of 'healthwork' tasks partners engage in to manage the condition and its impacts (Hudson et al 2020). Our research (Hudson et al 2015) also demonstrates how the condition can impact upon and disrupt heterosexual couples' lives and pans for the future (see further detail in 'general comments' below). Our support resources for couples (https://www.endometriosis-uk.org/endometriosis-and-couples) may be of value to practitioners supporting women and their partners. Endometriosis does not just impact upon women's physical bodies – it can have devastating impacts on quality of life; and women do not experience such impacts in isolation but do so alongside partners and family who also experience the impacts of the condition. Enhanced reference to this in the 'clinical need' section would, we suggest, better encapsulate the holistic impact and experience of the condition.	We have added a paragraph on the impact of endometriosis in the introduction and included the references of Culley 2013.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
11	Caroline Law and colleagues		29	736-744	While not specific to the question of whether early or late diagnosis impacts on quality of life, this section may benefit from evidence on the impact a diagnosis can have. Our literature review (Culley et al 2013a) and our own research (Culley et al 2013b) demonstrates that diagnosis can result in feelings of relief, legitimation, liberation and empowerment; can enable women and their partners to better understand the reason for their symptoms, to accept the situation and to be able to make sense of their circumstances; and can enhance access to support services and adjustments e.g. in the workplace. As such, regardless of whether having an early diagnosis impacts on quality of life or not, women may experience significant benefits from being diagnosed - rather than being assumed to have endometriosis and treated as such. This section also makes reference to the impact of endometriosis on quality of life. As discussed directly above, and in the 'general comments' below, our literature review (Culley et al 2013a) and research (Culley et al 2013b, Culley et al 2017, Hudson et al 2015, Hudson et al 2020) provides evidence of such impacts on women and on their partners and the heterosexual couple unit, and may be cited here.	We have added a paragraph and included the references of Culley 2013 a,b,
12	Caroline Law and colleagues		68	2360-2395	This section might include reference to additional ways in which women engage in non-medical management. Our research (Culley et al 2013b) demonstrates the range of self-management strategies women engage in including using hot water bottles, heat pads and wheat sacks, using TENS machines, altering diet, ensuring rest, pacing activities, prayer, altering jobs and work practices and patterns, and positive thinking. Our literature review (Culley et al 2013a) demonstrates the range of ways women attempt to manage their endometriosis and alleviate symptoms through lifestyle changes (e.g. changes to diet and exercise) and through complementary and/or alternative therapies, with some women turning to such approaches due to disenchantment with medical treatment and a rejection of the biomedical approach, seeing the use of alternatives to biomedicine as 'empowering' and enabling them to 'take control' of their management.	We agree with this comment and want to clarify that we have improved on the last guideline (2013) to ensure we do include some text to highlight the need for non-medical treatments. We also have recommended that clinicians should discuss alternatives and non-medical options with women, even though there is no research to identify specific alternatives to base the recommendations on.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
13	Caroline Law and colleagues	Psychosocial impact of endometriosis, and impact on quality of life			While the guideline takes a clinical focus, we suggest that more reference to the psychosocial impact of the condition, and the ways the condition can impact on quality of life, throughout the guideline would be of benefit. While we recognize, as stated in the guideline, that there is limited evidence of how specific non-medical interventions may impact on quality of life, we suggest it is vital that healthcare practitioners understand the sometimes devastating psychosocial impacts of the condition and the emotional distress some women experience, and that healthcare and management take a compassionate, holistic, person-centred approach. As discussed above, our literature review (Culley et al 2013a) and research (Culley et al 2013b, Hudson et al 2015) demonstrates the impact of endometriosis, particularly pain symptoms, on quality of life and on a range of activities and life domains including physical functioning, everyday activities and social life; education and work; sex, intimacy and intimate partnerships; mental health and emotional wellbeing; and in relation to actual and anticipated infertility. Our research (Hudson et al 2015) demonstrates the significant biographical disruptions – that is an event which causes a significant and often distressing disruption to and rethinking of one's life course – the condition can have on women's and on heterosexual couples' lives, particularly relating to sex and intimacy, planning for and having children, working lives and social lives. Our research (Culley et al 2013b) also demonstrates the substantial detrimental impact endometriosis can have on women, and on their male partners and the heterosexual couple unit, in complex and multidimensional ways and recommends that the management of endometriosis addresses the emotional, sexual and relational impact of this disease; that a more holistic, biopsychosocial and gender inclusive approach to endometriosis management and support is urgently needed; and that consultations should be inclusive of the impact of endometriosis on quality of life, and on women, partners and the couple relationship. We suggest that more reference to these impacts and to the ways in which treatment and management can take account of such impacts would better equip healthcare practitioners to provide the best support to women.	We confirm that the scope and the focus of the guideline is medical/clinical. We did expand in the sections on the impact of diagnosis on QoL and have included a significant chapter on non-medical interventions.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
14	Caroline Law and colleagues	Sex and intimacy			The guideline currently makes minimal reference to the impact of the condition on women's (and their partners') experiences of sex and intimacy. However, our research (Culley et al 2013b, Culley et al 2017, Hudson et al 2015, Hudson et al 2020) demonstrates that endometriosis can have a significant and devastating impact for heterosexual couples who struggle to maintain closeness and intimacy in the face of endometriosis. It is commonly assumed that the impact on sex and intimacy is specific to dyspareunia but our research indicates that a wide range of symptoms and experiences can cause difficulties for heterosexual couples in relation to sex and intimacy, including women experiencing general fatigue, reduced sexual desire as a result of medication, low mood, the stress of trying to get pregnant, bleeding during and/or after sex, and women feeling generally unattractive and unfeminine (Culley et al 2013b, Culley et al 2017, Hudson et al 2015). Despite these sometimes intense challenges, very few couples in our research had been given information about the possible impact on sex and intimacy and few had sought or been offered help with the sexual implications of endometriosis or its treatment side-effects (Culley et al 2013b). We suggest the guideline would benefit from enhanced inclusion of the impact on sex and intimacy throughout to ensure healthcare practitioners are aware of these significant and challenging impacts and are better primed to facilitate access to specialist support. Our research (Culley et al 2013b) recommends management of endometriosis must address the holistic impact of the condition including its sexual impact and that healthcare practitioners should consider referring affected women/couples to specialist services including psychosexual counselling. We also suggest the guideline recommends further research into effective interventions that address the impact of the condition on sex and intimacy.	While the current guideline focusses on the clinical management of endometriosis, the significant impact on patients with endometriosis, their partners, family and social circle is acknowledged in the introduction and throughout. We also included psychosocial interventions, including sexual therapy, in the chapter on non-medical approaches; but found only very limited evidence on the relevance/efficacy of such interventions.
15	Celine Bafort		47	1463	Concerning the reference Bafort et al, 2020a: in the reference list this is listed as the Cochrane review however this refers to another article: i.e. Bafort C, van Elst B, Neutens S, Meuleman C, Laenen A, d'Hoore A, Wolthuis A, Tomassetti C. Outcome after surgery for deep endometriosis infiltrating the rectum. Fertil Steril. 2020 Jun;113(6):1319-1327.e3. doi: 10.1016/j.fertnstert.2020.02.108. PMID: 32482260. Bafort et al, 2020b is the reference for the Cochrane review	We have corrected the reference
16	Celine Bafort		54	1808 & 1838	Our group recently published a retrospectively analysis comparing conservative technique and segmental resection specifically for rectal endometriosis. Primary outcome was complication rate, secondary outcome was recurrence rate. Subgroup analysis was done in patients without previous therapeutic laparoscopy. Findings from our paper could be added to these paragraphs. Reference: Bafort C, van Elst B, Neutens S, Meuleman C, Laenen A, d'Hoore A, Wolthuis A, Tomassetti C. Outcome after surgery for deep endometriosis infiltrating the rectum. Fertil Steril. 2020 Jun;113(6):1319-1327.e3. doi: 10.1016/j.fertnstert.2020.02.108. PMID: 32482260	The main conclusion of this article has now been included in the text.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
17	Astrid Cantineau	72			Clinicians should perform ovarian cystectomy or laser vaporization, instead of drainage and electrocoagulation	We can see that this is tempting however the comparisons, outcome points and outcomes are somewhat different. For this reason, we considered it is more correct to keep these as separate recommendations
18	Astrid Cantineau	59			Please consider rephrasing due to the fact that this is a strong recommendation on limited evidence and 'not recommended' sounds different form 'cannot be recommended'. Suggestion: A specific protocol for for pretreatment cannot be recommended or There is insufficient evidence to recommend prolonged administration of GnRH agonist to ART treatment to improve live birth rate.	With unclear benefit of an intervention is it reasonable not to recommend the treatment. We have decided to keep the recommendation as it was formulated.
19	Astrid Cantineau	64			Please remove due to lack of randomized trials since this is the case for almost all recommendations unfortunately…	We agree with the reviewer but considered it important to leave "due to lack of randomized studies" in the recommendation because the data showing a beneficial effect are not from randomized trials, but still, they are often used to promote surgery in these circumstances.
20	Astrid Cantineau	101			Tibolone is not first line treatment of post-menopausal symptoms, because of risk of endometrial cancer.	We have added a few extra data on tibolone, and have removed it from the recommendation,
21	Astrid Cantineau	111			But should perform thorough history and examination, and act on that.	Although we agree with the reviewer, the question on focus is related to the prescription of medical treatment. We considered it not relevant to add this information to the recommendation
22	Astrid Cantineau		27	697	For some women the diagnosis of suggestive endometriosis is enough and there is no need for surgery with a negative ultrasound or MRI.	We agree that surgical confirmation is not always required, and empirical treatment of endometriosis. This is discussed in the diagnosis chapter and the treatment chapter, and hence no further adaptations were made.
23	Astrid Cantineau		32	884	Psychological follow-up is also necessary in some patients	We have added the need for psychological follow-up in the recommendation
24	Astrid Cantineau		78	2867	Omen should be women	This error was corrected
25	Astrid Cantineau		78	2856	This paragraph is based on Hughes latest update of 2009. Did the literature search from 2009-2021 not reveal any new information? It would be adequate to mention this here. Furthermore, aren't there some publications of the positive effect of a GnRH agonist on adenomyosis? Is this worth to mention separately?	The guideline focuses on endometriosis. Adenomyosis was not considered. To our knowledge, there are no new studies published after 2009 focussing on medical treatment to increase natural pregnancy rates in women with endometriosis. Post-operative medical treatment is addressed in another section.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
26	Astrid Cantineau		79	2894	See III.1.a, however this does not underscribe the statement that surgery does increase natural fertility.	Section III.1.a focuses on medical treatment, section III.2 is focused on surgery. Therefore, surgery is not mentioned or explained in section III.1.a
27	Astrid Cantineau		79	2906	RCT of Chen n=262 or n= 273 as noted in line 2909?	The Chen review reported on different comparisons. The OR for the effect of presurgical treatment versus no treatment (surgery alone) was based on 263 patients, while the OR for the comparison of pre- vs postsurgical treatment was based on 273 patients. The information in the guideline is therefore correct,
28	Astrid Cantineau		82	2990	This paragraph gives the idea that this accounts for every degree of endometriosis, which makes it a bit misleading; I would suggest to add here that it concerns only trials on stage I/II endometriosis	We have clarified in the text that the Cochrane review included studies mainly on peritoneal disease, and we have referred to paragraph III.2.a where this is further explained
29	Astrid Cantineau		82	3008	Is it possible to add a sentence that there is no cut-off in size whether or not to operate on endometriomas in the light of fertility? Clinicians are searching for this here, and do not find an answer.	We have added a sentence to the text with regards to the size of the cyst, reading "nor studies exploring the indication for surgery depending on the size of the cyst. "
30	Astrid Cantineau		82	3025	Add year of publication	The reference for the Meuleman 2011 review was added to the text
31	Astrid Cantineau		83	3047	The recommendation that clinicians may consider operative laparoscopy for treatment of endometrioma-associated infertility is not based on the evidence described in paragraph III.2.b. With this statement, one might think that removing an endometrioma of 3 cm without symptoms is the way to go..	This recommendation is correct and does not imply one should perform surgery; hence the word 'may'. We decided to leave it as it is.
32	Astrid Cantineau				We really do not know whether removing a relative small endometrioma might increase the chance of natural pregnancy. I would suggest to remove or at least rephrase this recommendation.	We acknowledge the lack of comparative studies and have clearly mentioned this in the recommendation. We have decided to leave the recommendation unchanged
33	Astrid Cantineau		84	3065	Please add adenomyosis.	We have added "adenomyosis, and other factors affecting fertility"
34	Astrid Cantineau		85	3111	Please state the cut off here based on the publication of Ferrier 2020.	The study of Ferrier does not evaluate acut-offf EFI value in relation to cost-effectiveness but merely reports that using EFI in clinical decision-making could be a cost-effective strategy. We have not amended the text.
35	Astrid Cantineau		85	3113	EFI should be removed.	This was corrected in the text.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
36	Astrid Cantineau		85	3114	This needs a little more explanation for the clinician on how the EFI which is after surgery (resulting in a (hopefully) optimal situation) could be the same as the estimated EFI without therapeutic surgery.	We have rephrased the sentence to make it more clear for the reader.
37	Astrid Cantineau		86	3162	Add whether the endometriosis was removed or not.	We have considered this comment, but the sentence reads "within 6 months of surgical treatment" which we consider is sufficiently clear. For further details on the study, the full paper can be consulted
38	Astrid Cantineau		86	3165	Add whether the endometriosis was removed at surgery or not.	In the study by Van der Houwen, endometriosis was surgically confirmed but the study does not state whether endometriosis was removed. We consider the text correctly reflects the results of the study and have not amended the sentence.
39	Astrid Cantineau		86	3169	Define long and ultralong to increase readability for clinician who is not working in an IVF clinic but performs IUI.	We have considered this comment but decided the terms are clear enough for those performing MAR on endometriosis patients.
40	Astrid Cantineau		87	3189	Low success rate? 50% is not low for IUI. I agree but not based on this argument. It is a small study, the only one, and quite old.	The sentence reports the results of the study while highlighting the different limitations of the study. We have also not based a recommendation on this study.
41	Astrid Cantineau		87	3193	The recurrence rate of endometriosis due to ovarian stimulation + IUI has not been addressed although this concerns patients. T. d'Hooghe once performed research on this. Could this be addressed in this chapter?	We have a separate paragraph on MAR and risks. This paragraph refers to the review of Somigliana 2019, which includes the study of Professor D'Hooghe. We have not further specified this.
42	Astrid Cantineau		88	3237	Patients with endometriosis and unexplained infertility seems a bit odd. Would suggest "endometriosis and no other infertility diagnosis".	The study included a group of patients with endometriosis and compared them to women with unexplained infertility. This was clarified in the sentence,
43	Astrid Cantineau		88	3239	".Compared" should be "compared"	We have checked the paragraph and made some modifications to increase clarity.
44	Astrid Cantineau		88	3259	III4b.1 is not easy to read. A clinician needs to read this twice. To improve reading this paragraph should be restructured. GnRHa versus GnRHanta, prospective-retrospective, stage I/II versus stage III/IV.	The paragraph relates to the OS protocol and summarizes studies comparing GnRH agonist versus GnRH antagonist OS protocols, and next long GnRH agonist versus GnRH antagonist protocols. We have made some modifications to improve the readability of the paragraph and to clarify these 2 comparisons.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
45	Astrid Cantineau		88	3278	III.4b.2. reposition this paragraph.	We have considered this comment, but decided not to reposition the paragraph as we have throughout the guideline started with benefits followed by risks
46	Astrid Cantineau		89	3288	This does not include IUI; this should be clear.	ART is defined as assisted reproduction in which the oocyte is fertilised outside the women's body, whereas MAR includes both ART and IUI. Therefore, this recommendation (using "ART") by definition does not include IUI, and there is no need to further clarify this.
47	Astrid Cantineau		91	3380	Delete "In sharp contrast" It is not that this update showed an opposite effect.	We have removed the word "Sharp" in the sentence
48	Astrid Cantineau		91	3400	"However, when considering RCTs and observational studies" does not make sense unless the meta-analysis mentioned in 3397 also included other type of studies that are excluded for this secondary analysis.	The entire paragraph reports on a single meta-analysis performing 2 sub analyses. This was clarified in the text,
49	Astrid Cantineau		91	3409	Add 'revealed' after pre-treatment	This was corrected in the text
50	Astrid Cantineau		92	3419	There is insufficient evidence to recommend any strategy (GnRHa, COC, nothing!)	We think the recommendation is clear and do not warrant a modification based on this comment.
51	Astrid Cantineau		92	3425	This was a very small study, with problems with inclusion, which does not change the direction of the effect of the review, which should clear for the reader. Is the unpublished data of the Cochrane review study published in the meantime? As this should be stated that the evidence is based on not peer reviewed data.	We clearly state that the study of Tomassetti does not change the direction of the effect of the review. We have added a reference to the text above, where we have mentioned in detail the concerns with the Georgiou review. The unpublished data have, as far as we know, not been published.
52	Astrid Cantineau		95	3546	This recommendation is not in line with the recommendation on page 83, line 3047	Both recommendations look at different outcomes. The recommendations state that surgery for endometrioma may be considered to improve natural pregnancy, but should not be performed before ART to improve the chance of an ART pregnancy.
53	Astrid Cantineau		97	3606	Darai 2017 is missing	We included the review of Hamdan 2015 in the section. Although we have checked out the review by Darai 2017, we consider it focuses on the need for MAR after surgery for colorectal cancer, instead of the need for surgery prior to MAR. We have not added the paper to the chapter

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
54	Astrid Cantineau		146	5496	This line is a good addition to the recommendations	We have recommended "The GDG recommends that clinicians should inform and counsel women about any incidental finding of endometriosis." which is very similar to the sentence indicated in the justification section. Therefore, we have not adapted the text/recommendations.
55	Astrid Cantineau		148	5525	But patients can also be informed to come when complaints appear	Yes, we can inform patients to seek fedical advice when they become symptomatic but these cases are not discussed in the asymptomatic chapter. According to the reviewer's comments, a sentence is added covering the aforementioned question.
56	Astrid Cantineau		8		Please provide an explanation to the table on recommendations. What does one bullet mean, what do four bullets mean? I presume level of evidence but this should be more clear to improve the interpretation by clinicians.	We have added a label to the column and a footnote referring to the information in the methodology section.
57	Linda Giudice				I agree that "genetic diagnosis" is in the purview of a research setting and offer that a statement be included that endometriosis is not a monogenic disorder and is rather a complex trait (with loci across the genome identified in GWAS studies with greater effect sizes in more advanced disease). This would strengthen underscoring taking a family history of endometriosis is an important part of the diagnostic work up of disease. The updated Guidelines are likely to be a great resource to clinicians, patients, researchers, and health ministers alike for a few years to come.	We have added a sentence reading "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."
58	FERRING PHARMACEUTICALS	6			The recommendation to use imaging (US and MRI) as diagnostic tools is strongly supported. Non-invasive diagnostic methods are already widely used in clinical practice; however, this is not reflected to the same extent in clinical practice guidelines. As further discussed in the following comments, the acceptance of and recommendation to use non-invasive diagnostic tools in clinical practice is considered important and to be of benefit for patients.	We have checked this comment, but feel that it is supportive of the proposed recommendations and hence, no adaptations were requested
59	FERRING PHARMACEUTICALS		6	150-153	For several reasons (patient safety, access to highly qualified surgeons, financial implications, etc.) the current "gold standard" of diagnosing endometriosis by surgical methods represents a problematic approach for patients. The guidelines should clearly emphasize why laparoscopy/histology are a problematic "gold standard" for diagnosis (page 24 lines 564-568 and page 28 lines 709-716). To that end, we suggest including language in the introduction addressing the urgent need for non-invasive clinical diagnostic criteria for endometriosis, similar to the language used later in the guideline (page 24 lines 564-568 and page 28 lines 709-716).	We did add a paragraph on diagnostic laparoscopy in the introduction of the diagnosis chapter to address this comment

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
60	FERRING PHARMACEUTICALS		16	207-216	It is considered important to further develop non-surgical diagnostic methods and therefore suggested to include an additional research recommendation under the "Diagnosis of Endometriosis" sub-heading. This recommendation would be to encourage research into the development of a comprehensive and inclusive consensus criteria for the diagnosis of endometriosis, as an alternative or adjunct to diagnosis via laparoscopy/histology.	We have added a research recommendation reading "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."
61	FERRING PHARMACEUTICALS	Diagnosis			As a company, doing research and development within the disease area of endometriosis, having close collaboration with clinical experts in the field as well as patients, we believe there should be stronger emphasis on the need for less-invasive clinical diagnostic criteria for endometriosis, in order to move away from reliance on the "gold standard" of laparoscopy with histologic sampling for diagnosis. Less-invasive clinical diagnostic criteria might include a combination of factors such as patient-reported symptoms, clinical exam findings, symptomatic improvement with hormonal therapy, and/or imaging findings; these would serve as an alternative to the more "standard" invasive criteria of laparoscopy with histologic tissue diagnosis. These criteria could be determined ideally through additional research studies, or alternatively through a working group consensus, and could be modeled after the Rotterdam criteria for PCOS or Amsel's criteria for bacterial vaginosis. We believe more inclusive and less invasive criteria would lead to earlier diagnosis and treatment of patients with endometriosis, and could also facilitate research protocols into future therapeutic treatments.	We have added a sentence in the guideline reading "To move away from the reliance of invasive diagnostic means such as laparoscopy, large scale international, multi-centre studies are urgently needed using novel technological platforms, meticulous standardised phenotyping, sufficient funding and an open mind.'
62	Fleur Blok	chapter III			We missed the publications of endometriosis and infertility from Prof dr Tomasetti	We have added the reference to the paper by Dr Tomassetti (Tomassetti C, et al. Endometriosis and infertility: Insights into the causal link and management strategies. Best Pract Res Clin Obstet Gynaecol. 2018 Aug;51:25-33) in the introduction,
63	Fleur Blok	chapter III			Is there any information about the value of GnRH agonists treatment in infertile patients with stage III-IV endometriosis?	We did already mention in the text that the published evidence does not report on more severe disease. Therefore, no further amendments were made.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
64	Fleur Blok	chapter II			We would like to see an additional subject about the use of Plasmajet in patients with superficial endometriosis and endometriomas	As far as we are aware, there are no comparative studies looking at pain outcomes with the use of plasma energy. There is only one small retrospective study comparing plasma energy with cystectomy on ovarian volume and AFC. There is one case-control study looking at fertility outcomes after plasma energy compared to cystectomy. For these reasons, plasma energy was not mentioned specifically in the guideline. However, specific surgical techniques including plasma energy were included in our publications Working Party of ESGE, ESGE and WES documents, and the reader is referred to these documents for these techniques.
65	Fleur Blok				In the draft version it is unclear how the diagnosis of endometriosis is established in the included studies. Can you add this information in the final version?	We have considered studies that define the patient group as women with endometriosis, irrespective of how the diagnosis was established (although in most studies, it was confirmed to laparoscopy/histology). The details of the studies are included in the evidence tables (as an annex to the guideline)
66	Carlos Calhaz-Jorge	General comment			Although some of them look like recommendations it sounds strange to include "Conclusion" statements in the list of recommendations. I suggest either to remove "Conclusion" from the list of recommendations or to name them as either "GPP" or "GDG statement" in this list	We have kept the "conclusions" in the overview as we think it is important to give some information, even if no true recommendation/GPP could be formulated. We did adapt them to GDG statements rather than conclusions.
67	Carlos Calhaz-Jorge	11			Considered here as "Conclusion" but in the text (page 32) it is named GPP	This was corrected in the table
68	Carlos Calhaz-Jorge				"Hormonal treatments" instead of "Hormonal contraceptives" seems more compatible with recommendations 14 and 15	This was corrected in the table
69	Carlos Calhaz-Jorge	25			Text not clear. It needs rephrasing	There was a copy-paste error in this recommendation, which has now been corrected. Thank you for alerting us.
70	Carlos Calhaz-Jorge	41			I suggest to add "if not desiring immediate pregnancy" at the end of the recommendation	We have adapted the recommendation in line with the suggestion of the reviewer

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
71	Carlos Calhaz-Jorge	49			I suggest consider removing the last part of the sentence. It is in the justification text and not really part of a recommendation. Clinicians may consider operative laparoscopy for the treatment of endometrioma-associated infertility as it may increase their chance of natural pregnancy, although no data from comparative studies exist.	We agree that the reference to the existing data is not required in the recommendation. Still, for this particular recommendation, we consider that removing "although no data from comparative studies exist" may make the recommendation for surgery stronger than it should be.
72	Carlos Calhaz-Jorge	73 and 75			Recommendation 75 "recommended to offer long-term hormonal treatment…" includes recommendation 73 "Clinicians should consider prescribing combined hormonal contraceptives for prevention…". Maybe rephrasing Rec 75 allows to delete Rec 73	We have combined the 2 recommendations as suggested
73	Carlos Calhaz-Jorge	77			No reference to the strength of the recommendation. Is it intended?	This was corrected in the table
74	Carlos Calhaz-Jorge	78			Not a GPP?	There was indeed an inconsistency in this recommendation, which was labelled as a weak recommendation based on low quality evidence, but formulated as a GPP. This has now been corrected in the guideline
75	Carlos Calhaz-Jorge	81			The text of the recommendation is not clear. Maybe it could be rephrased	The recommendation has been reformulated, now reading; In adolescents, clinicians should take a careful history and consider the following symptoms as indicative of the presence of endometriosis: - chronic or acyclical pelvic pain, particularly combined with nausea, dysmenorrhea, dyschezia, dysuria, dyspareunia - cyclical pelvic pain,
76	Carlos Calhaz-Jorge	87			Why not to add "although negative histology does not entirely rule out the disease" to Rec 86 and delete GPP 87?	We have merged the 2 recommendations, as suggested by the reviewer
77	Carlos Calhaz-Jorge	92			Suggestion: "In adolescents with endometriosis, clinicians may consider surgical removal of endometriosis lesions to manage endometriosis-related symptoms. However symptom recurrence rates may be considerable, especially when surgery is not followed by hormonal treatment."	We have amended the recommendation as suggested by the reviewer
78	Carlos Calhaz-Jorge	97			No reference to the strength of the recommendation. Is it intended?	This was a conclusion, and therefore no strength of the recommendation was added. This has been corrected.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
79	Carlos Calhaz-Jorge	120			Reading the current text of the recommendation we could infer that endometriosis protects against cancers and the usual standard screening related to cervical cancer and breast cancer is not needed any more	We have adapted the recommendation, now reading that "In women with endometriosis, clinicians should not systematically perform cancer screening beyond the existing population-based cancer screening guidelines "
80	Carlos Calhaz-Jorge		6	155	#123, to be removed?	This is an error in the Endnote conversion of the references and has been resolved in the final version.
81	Carlos Calhaz-Jorge		6 and 7		The statement that this is an update of a previous document is repeated in lines 154-155 and 177-178. Maybe not needed the duplication.	The duplication of information was resolved
82	Carlos Calhaz-Jorge		7	183	I guess the meaning of "cis" needs to be made clearer. Probably not understandable in the whole world.	We have revised this sentence. "Individuals who are not cis-female" (or Cisgender female) was replaced by "individuals who are transgender".
83	Carlos Calhaz-Jorge		16	222-223	This sentence has not a format of recommendation. Maybe to be reformulated?	The research recommendation was reformulated.
84	Carlos Calhaz-Jorge		17	282, 287, 291	Titles with no specific research recommendations. Are they needed? To be removed?	The empty headings were included in the draft version (awaiting possible additions from the stakeholder review), but they have been removed in the final version.
85	Carlos Calhaz-Jorge		20	363	Which is the meaning of "()"?	This was an error and has been corrected.
86	Carlos Calhaz-Jorge		20	367-368	The information "(1 symptom: OR 5.0; 95%CI 4.4 to 5.7); 7 symptoms: OR 84.7; 95%CI 58.8 to 121.8)" would make more sense at the end of the previous paragraph	This was adapted as suggested.
87	Carlos Calhaz-Jorge		26	638-639	I suggest to introduce "and" in the sentence "However, because of the small size of the studies and large confidence intervals interpretation of the data was cautioned."	This was adapted as suggested.
88	Carlos Calhaz-Jorge		40	1180	Sentence needed?	This was adapted as suggested.
89	Carlos Calhaz-Jorge		40-41	1181 - 1185	This paragraph refers to safety and not efficacy. I suggest to be moved to the next section	This was adapted as suggested. We added the data on efficacy from the Tang et al 2017 study and moved the study on BMD to the safety section.
90	Carlos Calhaz-Jorge		42		No word about the decrease in bone loss resulting from the use of GnRH antagonists. I suggest a clear statement about bone loss when referring to "considerable side effects" (line 1261)	We have added the "potential impact on bone density" when discussing the side effects of GnRH antagonists.
91	Carlos Calhaz-Jorge		43	1306	The text of the recommendation is not clear. Can it be rephrased, please?	We have rewritten the recommendation in reply to this comment.
92	Carlos Calhaz-Jorge		47	1464	I suppose it should be "formulated" instead of "formulating"	This was an error and has been corrected

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
93	Carlos Calhaz-Jorge		48	1472	Suggestion: "More data are needed on the effect of surgery in different subtypes of endometriosis via longitudinal population"	This research recommendation has been revised and reformulated based on another comment.
94	Carlos Calhaz-Jorge		50	1601	"and a trend to lower lower AFC at …". Please remove one of the words "lower".	This was an error and has been corrected.
95	Carlos Calhaz-Jorge		50	1614 - 1615	Unclear sentence: "but there are data comparing impact of different techniques should be interpreted with caution". I think it should be "there are no data". Please, check.	This sentence has been revised and corrected.
96	Carlos Calhaz-Jorge		51	1632 - 1633	Please reconsider the sentence: "Deep endometriosis involving the bowel has been reported to be 5-12% of women affected by endometriosis"	This sentence has been revised and corrected.
97	Carlos Calhaz-Jorge		53	1740	Maybe the word "both" is not needed.	This sentence has been revised and corrected.
98	Carlos Calhaz-Jorge		55	1849 - 1852	The text of this paragraph does not relate with the title of the section: "Complications of surgery for bowel endometriosis".	This paragraph was a copy-paste error, which has been corrected
99	Carlos Calhaz-Jorge		56	1877	"Results are stratified by whether concurrent a hysterectomy…". I guess the "a" should be removed	This sentence has been revised and corrected
100	Carlos Calhaz-Jorge		56	1881 - 1884	The text of this paragraph is not consistent with the title of the section: "Surgery for posterior compartment endometriosis excluding bowel endometriosis"	We have moved this paragraph into a new section on endometriosis of the bladder and ureter
101	Carlos Calhaz-Jorge		57	1941 - 1942	"This recommendation is based on a possible increased risk of prolapse with subtotal hysterectomy". Are there any data that base this statement?	This was a typing error and has now been corrected and clarified.
102	Carlos Calhaz-Jorge		64	2244	Please, can you clarify the origin of the "previous GPP"?	We have added the reference to the Dunselman 2013 guideline for clarification
103	Carlos Calhaz-Jorge		64	2253	I guess it should be "considering" instead of "considered"	This sentence has been revised and corrected
104	Carlos Calhaz-Jorge		64	2265	I suggest "from the previous guideline"	This was adapted as suggested
105	Carlos Calhaz-Jorge		65	2285	I suggest to add "if not desiring immediate pregnancy" at the end of the recommendation	We have amended the recommendation in line with the suggestion of the reviewer
106	Carlos Calhaz-Jorge		66	2316 - 2318	The study by Vercellini et al (2012) is a parallel cohort study, not a RCT. Please, check.	The reviewer makes a valid point, and the error has been corrected
107	Carlos Calhaz-Jorge		69	243 6- 2437	This text is repeated in lines 2445-2447	This sentence has been revised and corrected

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
108	Carlos Calhaz-Jorge		73	2656	Maybe better "intake of antioxidant vitamins A, C and E in women with endometriosis" instead of "intake of antioxidants A, C and E in women with endometriosis"	This was adapted as suggested.
109	Carlos Calhaz-Jorge		78	2845-2846	This chapter deals also with MAR (as stated in the following sentence). Maybe better to rephrase the initial sentence.	We have revised this paragraph to make it more clear.
110	Carlos Calhaz-Jorge		78	2867	The text of this line is not clear. Maybe to be improved	There was an error in this sentence, which has been corrected.
111	Carlos Calhaz-Jorge		79	2894	Maybe better "fertility as pointed out above (see III.1.a), and surgery does increase natural fertility, it is still of" instead of "fertility as pointed out above, and surgery does increase natural fertility (see III.1.a), it is still of"	This was adapted as suggested.
112	Carlos Calhaz-Jorge		83	3056	I guess it should be "evaluating" instead of "evaluation"	This was adapted as suggested.
113	Carlos Calhaz-Jorge		85	3113	Please remove "it" in "prior to surgery, it EFI"	This was adapted as suggested.
114	Carlos Calhaz-Jorge		96	3580	I guess the word "still" should be removed in "…endometriosis still had a lower"	This was adapted as suggested.
115	Carlos Calhaz-Jorge		98	3654	The number "46015%" is not correct	This typo was corrected in the text.
116	Carlos Calhaz-Jorge		102	3788-3789	"Leone Roberti Maggiore, 2016 #563]". I guess #563 must to be removed	This is an error in the Endnote conversion of the references and has been resolved in the final version.
117	Carlos Calhaz-Jorge			3790	"Leone Roberti Maggiore, 2016 #563]" I guess #563 must to be removed	This is an error in the Endnote conversion of the references and has been resolved in the final version.
118	Carlos Calhaz-Jorge		103	3831	"(Leone RM 2016)". This is a different reference format. Is it intended?	This is an error in the references and has been corrected
119	Carlos Calhaz-Jorge		104	3860	"well-designed studies to assess: the impact of surgery". Maybe the ":" is not needed.	This was corrected in the text.
120	Carlos Calhaz-Jorge			3886	"pregnancy outcomes in women with endometriosis versus controls Scotland, Saraswat at al.," Please remove the word Scotland	This was corrected in the text.
121	Carlos Calhaz-Jorge		105	3930-3931	Unclear text. Can you check, please?	This was corrected in the text.
122	Carlos Calhaz-Jorge			3936	I guess "#544" must to be removed	This is an error in the Endnote conversion of the references and has been resolved in the final version.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
123	Carlos Calhaz-Jorge		106	3983-3985	The sentence starts "Lalani et al and Horton et al" but the references at the end are "(Lalani, et al., 2018, Leone Roberti Maggiore, et al., 2016)." Maybe it needs to be changed.	This was corrected in the text.
124	Carlos Calhaz-Jorge		110	4126	"disease recurrence, compared to controls for OCP (RR 0.32; 95%CI 0.23 to 0.44; 6 studies; n=854;". I guess that "for OCP" is to be removed	This was corrected in the text.
125	Carlos Calhaz-Jorge		111	4191	"rate of recurrence was lower in women who conceived after pregnancy and used postpartum". I guess it should be "conceived after surgery"	This was corrected in the text.
126	Carlos Calhaz-Jorge		112	4211	"availability, and side effects. When prescribing such treatment, there contraceptive properties". It should "the" instead of "there"	This was corrected in the text.
127	Carlos Calhaz-Jorge		115	4291	Suggestion: "randomized to dienogest) or depot leuprolide acetate. There was no difference between VAS"	This was corrected in the text.
128	Carlos Calhaz-Jorge			4292	Suggestion: "treatments" instead of "treatment"	This was corrected in the text.
129	Carlos Calhaz-Jorge			4312	Suggestion: "cystectomy were treated with dienogest (2mg) at detection of recurrence of symptoms (dysmenorrhea"	This was corrected in the text.
130	Carlos Calhaz-Jorge		116	4339	letrozole is here referred for the first time regarding endometriosis recurrence prevention. Is it correct?	This was corrected in the text.
131	Carlos Calhaz-Jorge		118	4452	Divasta must be DiVasta	This was corrected in the text.
132	Carlos Calhaz-Jorge		124	4695	"equine estrogens 0.625 mg daily (CEE) (combined with add-back), or NA plus placebo. Quality of"	We have checked this and clarified the sentence.
133	Carlos Calhaz-Jorge		126	4755-4756	The sentence "No risk factors for recurrence were identified, including the use of postoperative hormonal suppression therapy" suggests that postop hormonal treatment may be a risk factor for recurrence of endometriosis which is not correct.	The sentence was rewritten to avoid misinterpretation.
134	Carlos Calhaz-Jorge		129	4856	"± 6.5 retrieved oocytes per cycle, and storage time was 1.7 ± 0.4 years. Clinical live birth ratio (CLBR)". I guess it is "Cumulative live birth rate" instead of "Clinical.."	This was corrected in the text, it indeed referred to cumulative live birth rate.
135	Carlos Calhaz-Jorge		131	4906	Suggestion: "There are very scarce data on the prevalence of endometriosis after menopause."	This was corrected in the text.
136	Carlos Calhaz-Jorge		134	5003-5004	In the conclusion, it is said that "as data are limited to surgically induced menopause." However, patients included in the described series are not limited to post-BSO. Can you clarify, please?	We have corrected the text, stating that data are mainly based on BSO patients.
137	Carlos Calhaz-Jorge		135	5031	I guess it should be "estrone" instead of "estriol"	This was corrected in the text.
138	Carlos Calhaz-Jorge		135	5036	Please remove "#188"	This is an error in the Endnote conversion of the references and has been resolved in the final version.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
139	Carlos Calhaz-Jorge		143	5370-5374	Appendicular, bladder and ureteral endometriosis do not fit under the title of the section: "Extrapelvic endometriosis of the abdominal wall, the umbilicus, and the inguinal region". And they are mainly not extrapelvic	We have covered bladder and ureter endometriosis in the surgery chapter and removed it from the extrapelvic endometriosis section.
140	Carlos Calhaz-Jorge		146	5475	I suggest the removal of the word "asymptomatic" in "By definition, patients with an incidental finding of asymptomatic endometriosis do not"	This was corrected in the text
141	Carlos Calhaz-Jorge		154	5726	I guess it should be "medication" instead of "mediation"	The sentence refers to mediation analyses, and hence it was correct
142	Carlos Calhaz-Jorge		157	2834-5835	Exactly the same text is repeated two lines below. Maybe better to avoid the repetition.	We have revised this paragraph and removed the repetition.
143	Carlos Calhaz-Jorge		160	5956-5959	Long sentence and unclear sentence. Please, check.	We have revised this sentence to increase the readability.
144	Carlos Calhaz-Jorge			5962-5963	I understand the idea is to state that patients with endometriosis don't need specific cancer screening. But they still need the usual screening for the general female population (ie, screening of cervical cancer and breast cancer). I suggest the recommendation to state it.	We have amended the recommendation, now reading that "In women with endometriosis, clinicians should not systematically perform cancer screening beyond the existing population-based cancer screening guidelines "
145	Carlos Calhaz-Jorge				A deep thanks to all involved in this overwhelming work. This is an amazing text that I'm sure will be widely used to improve clinical care and, hopefully, to stimulate research in many still obscure areas of this intriguing disease. Congratulations	Thank you for these kind words
146	Mukhri Hamdan	Surgical treatment			Recommendation on the management of recurrent endometrioma. Or specify in the text whether the surgery for endometrioma is primary or a recurring endometrioma.	This section is clearly for recurrent endometriosis or endometriomas as specified in the section title.
147	Mukhri Hamdan			2867	Missing 'w' for women	This was corrected in the text
148	Mukhri Hamdan			3259	III.4.b.1 Type of OS protocol Would be good to include the recent study published in HR on using ultralong protocol which was not found more superior than long protocol in women undergoing ART after had surgery https://doi.org/10.1093/humrep/deab163	We have added the study by Tomassetti 2021 in the text, in section III.5

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
149	Mukhri Hamdan			4675	What is the long term effect on the BMD for patients on progestins. What are the recommended monitoring needed in such patients	In this article, follow up was one year. There are no long term data about this. For this reason we have added in the text what the effects were after one year.
150	Mukhri Hamdan	General comment			It would be nice to include the protocol of management during the covid pandemic Covid 19 in this guideline. This will include empirical treatment, delay/avoid surgical treatment and optimization of medical treatment. Also, would be good touch on vaccination and the precaution needed.	Although we understand the rationale for this comment, it is outside the scope of the current guideline to discuss management of endometriosis during the COVID19 pandemic
151	Mukhri Hamdan	General comment			Otherwise very well written guideline	Thank you for these kind words
152	Gedeon Richer, Myovant and Pfizer		42	1224	Given the benefit of ABT on minimizing bone loss in women with hormonal therapy, could we add: "GnRH agonist monotherapy/without ABT should be used after careful consideration..."	We do state "Clinicians should consider prescribing combined hormonal add-back therapy alongside GnRH agonist therapy to prevent bone loss and hypoestrogenic symptoms". We consider the text covers the issue raised by the reviewer
153	Gedeon Richer, Myovant and Pfizer		42	1231	Shouldn't we add a paragraph on ABT also under the GnRH antagonist chapter? A short introduction of benefit of ABT on minimization of bone loss and reduction of AE such as flushs could help to explain why ABT is beneficial in the treatment of EM? ie: add back therapy may partially prevent bone loss while not stimulating endometrial growthsome. e.g "The estrogen threshold hypothesis" (Barbieri RL. Am J Obstet Gynecol 1992;166:740–5) Although there is no drug approved yet in endometriosis with ABT, in the SmPC of the recent European approval of relugolix in uterine fibroids (RYEQO) for moderate to severe symptoms of uterine fibroids, there were no clinically meaningful difference between placebo and relugolix combination therapy (40 mg relugolix, 1 mg estradiol (as hemihydrate), and 0.5 mg norethisterone acetate) on BMD loss (RYEQO SmpC- July 2021)	There is very little on antagonists in the guideline because these are new treatments with limited data. We do not think the data are strong enough to allow us to add specifics about when to give addback HRT (or not) at this moment in time. We have added a comment in the justification section.
154	Gedeon Richer, Myovant and Pfizer		42	1248	In the section above, BMD concerns for GnRH agonists are highlighted. We suggest to including the BMD changes that were seen in the ELARIS EM trials for to be balanced and consistent	We have mentioned the side effects with regards to BMD in the justification section

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
155	Gedeon Richer, Myovant and Pfizer		42	1264	GnRH antagonist - Same suggestion as for GnRH agonist (monotherapy/without ABT)	There is very little on antagonists in the guideline because these are new treatments with limited data. We do not think the data are strong enough to allow us to add specifics about when to give addback HRT (or not) at this moment in time. We have added a comment in the justification section.
156	Gedeon Richer, Myovant and Pfizer		64	2275	II.4.b Postoperative medical treatment: homrSome additional references to support this section: Postoperative hormonal suppressive medical treatment has been demonstrated to decrease risk of recurrences of EM after surgery 1. Seracchioli R et al. Fertil Steril 2010;94:464–71 2. Vercellini P et al. Fertil Steril 2003;80:305–9 3. Tanmahasamut P et al. Obstet Gynecol 2012;119:519–26	We have based this section on the recent systematic review by Chen 2020. The study from Seracchioli R 2010 is included in the review meta-analysis The study by Vercellini 2003 was excluded from this review (a pilot study) Also, Tanmahasamut 2012 was not included in the review. We have added the study to the text.
157	Gedeon Richer, Myovant and Pfizer		66	2308	II.5. Medical versus surgical treatment for endometriosis 1. Medical and surgical treatments are often complementary to one another and should be considered in all patients who present with EM-associated symptoms. Singh SS et al. Fertil Steril. 2017 Mar;107(3):549–554 2. Also, surgery does not cure the systemic cause of the disease, even if the endometriotic lesions are successfully removed. Vercellini P et al. Hum Reprod. 2009;Update 15, 177–188 3. And, surgery is associated with a high rate of recurrence, and recurrence of pain requiring therapy is common (30-60% of pts) within 6-12 months of surgical treatment - Vercellini P et al. Hum Reprod. 2009;Update 15, 177–188 - Giudice L. N Engl J Med. 2010 June 24; 362(25): 2389–2398 4. Reducing the number of surgeries for EM would be desirable, as they entail a risk of complications, including infertility Sibiude J et al. Obstet. Gynecol. 2014;124, 709–717.	The literature focussed on studies directly comparing medical versus surgical treatment, and therefore the suggested studies were not added. We do acknowledge the benefits and side effects/harms of both surgical and medical treatment in the justification section and the recommendation.
158	Gedeon Richer, Myovant and Pfizer	Section 14: Hormonal contraceptives			We have identified several main areas that may benefit from further development and clarity: Section 14: Hormonal contraceptives a. We think hormonal therapies could be referred as empirical treatment like analgesics. b. Is there a possibility of separating out the recommendation level by individual treatment type? For example, there is little evidence that combined hormonal contraceptives are effective in treating endometriosis-associated pain (so should really be a weak recommendation) vs some other hormonal methods that have much more data (i.e.: GnRH agonists or antagonists). The idea would be to split this section into two parts (1) weak recommendation and (2) strong recommendation	Regarding splitting the recommendation per treatment, we clarified that the individual treatments are discussed below. Still, as it was decided not to recommend a certain treatment over another, as all have, as the reviewers state, different strengths of evidence supporting them, but also different benefits, side effects, we decided to keep the overarching recommendation.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
159	Gedeon Richer, Myovant and Pfizer	Section 24			2. Section 24: We think there is a need to add specifics about add-back therapy being used alongside GnRH antagonists (both Relugolix combination therapy and linzagolix), specifically highlighting the benefit of ABT on QoL and BMD a. Currently there is very little about relugolix in the guidelines and the data cited includes monotherapy only. However, although no GnRH therapy with ABT is approved for endometriosis, in the recent European approval of relugolix combination therapy in uterine fibroids, no clinically significant difference was observed on bone loss vs placebo	There is very little on antagonists in the guideline because these are new treatments with limited data, We do not think the data are strong enough to allow us to add specifics about when to give addback HRT (or not) at this moment in time.
160	Gedeon Richer, Myovant and Pfizer	Sections 41 and 42			3. Sections 41 and 42: it appeared to us, that we could further strengthen the benefit of hormonal therapy in the post op setting in minimizing the recurrences of endometriosis and repeated surgeries., that may have an impact of fertility. Medical and surgical treatments are often complementary to one another and should be considered in all patients who present with endometriosis -associated symptoms. We think it is important to mention that surgery doesn't cure the systemic (underlying) cause of the disease.	We consider that the comment of the reviewer is covered in the updated version of the text.
161	Velja Mijatovic, Lisette vd Houwen, Anneke Schreurs, Astrid Cantineau on behalf of the COPIE study group	59			Please consider rephrasing this recommendation. The way in which this is formulated in the updated guideline may well raise barriers for currently enrolling randomized controlled trials, like the COPIE (Continuous use of Oral contraceptives as an alternative for long term Pituitary desensitization with a GnRH agonist prior to IVF/ICSI in Endometriosis patients) study 1 which is registered in the Dutch Trial Register (Ref. No. NTR6357, http://www.trialregister.nl), comparing different pre-treatments for in vitro fertilization. We strongly believe this research question is relevant, as you do too, stated in line 3424. Especially in the light of patients who are unable to interrupt their hormonal treatment due to pain symptoms and prefer to start their fertility treatment straight away. The fact that this is formulated as a strong recommendation on limited high quality evidence we suggest the following alternative wording: "Based on the current literature a specific protocol for pre-treatment cannot be recommended". 1 Van der Houwen et al. Hum Reprod Open 2019	We state that the benefit of GnRH agonist prior to ART treatment is uncertain, which opens the door for more research, Still, we considered that GnRH agonist prior to ART treatment should currently not be applied in clinical practice
162	Velja Mijatovic, Lisette vd Houwen, Anneke Schreurs, Astrid Cantineau on behalf of the COPIE study group		91	3380	Please delete "In sharp contrast" The latest update of the Cochrane review did not show an opposite effect which this wording suggest.	We have removed the word 'sharp" in the text.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
163	Velja Mijatovic, Lisette vd Houwen, Anneke Schreurs, Astrid Cantineau on behalf of the COPIE study group		92	3419	Please consider rephrasing to give currently ongoing studies the opportunity to finish inclusion based on the fact that there is insufficient evidence to recommend any medical pre-treatment strategy (GnRHa, COC or nothing) prior to IVF-ICSI.	We state that the benefit of GnRH agonist prior to ART treatment is uncertain, which opens the door for more research, Still, we considered that GnRH agonist prior to ART treatment should currently not be applied in clinical practice
164	Velja Mijatovic, Lisette vd Houwen, Anneke Schreurs, Astrid Cantineau on behalf of the COPIE study group		92	3425	This study of Tomassetti et al 2021 was a very small study, with problems with inclusion, which does not change the direction of the effect of the review, which should be clear for the reader. Is the unpublished data of the Cochrane review study published in the meantime? As this should be stated that the evidence is based on not peer reviewed data.	We clearly state that the study of Tomassetti does not change the direction of the effect of the review. We have added a reference to the text above, where we have mentioned in detail the concerns with the Georgiou review. The unpublished data have, as far as we know, not been published.
165	Pauline de Heer	1			Request to add cyclical / catamenial rectal bleeding; it is a seemingly rare symptom (although I personally know several patients with this symptom), but one that – in the absence of hemorrhoids – almost always points towards endometriosis. I would add this symptom to this recommendation, since it can also occur when DE is not visualized on ultrasound/MRI, and it can speed up diagnosis and treatment. Some sources: http://dx.doi.org/10.1136/bcr-2015-209464 https://doi.org/10.1111/j.1445-2197.1989.tb07635.x https://doi.org/10.1186/s13256-020-02386-w https://dx.doi.org/10.14309/01.ajg.0000596200.57284.05	We have checked, but "rectal bleeding" was already included in the recommendation
166	Pauline de Heer	24			GnRH antagonists: I am surprised to not read anything about the poor cost-effectiveness of these new drugs. On the basis of the prohibitive cost and poor side effect profile as compared to combined oral contraceptives, I would at least expect a word of caution in the recommendation, and advice to do stepped care. I would like to refer to the ICER analysis of elagolix: https://icer.org/wp-content/uploads/2020/10/ICER_Elagolix_Final_Evidence_Report_080318.pdf	Cost-effectiveness of treatments (medical or surgical) was not part of the remit of this guideline. Still, we have added a good practice point to reflect the uncertainties of GnRH antagonist and stating they should not be used as first line treatment
167	Pauline de Heer	25			Incomplete sentence in the recommendation on page 9.	This copy-paste error was corrected
168	Pauline de Heer	36			Linguistically, you suggest in this recommendation that clinicians can consider hysterectomy without removing all visible endometriosis lesions; I assume (hope) that this is not the case. Could you rephrase this recommendation to: "Clinicians can consider hysterectomy with removal of all visible endometriosis lesions, and with or without removal of the ovaries […]"? Too often I've come across patients who were told by their doctor that removal of the uterus while leaving the lesions in place would suffice, which was (obviously) not the case	It is clear that the text recommends removal of all visible endometriotic lesions in its current format.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
169	Pauline de Heer	73 & 75			"not immediately seeking conception." – I'd put 'immediately' between brackets, since there are plenty of women not seeking conception at all.	The recommendation states that these medical treatments should be considered by all women, except those that will aim to get pregnant immediately after the surgery (as the medical treatment will prevent pregnancy). As such, we have decided not to adapt the recommendation.
170	Pauline de Heer	74			Why 'at least 18-24 months'? Does the risk decrease after that? Or is this all we know from the follow-up that was done?	This duration based on published data.
171	Pauline de Heer	79			Why only obstructive genital malformations? This signals to me that you see retrograde menstruation as a (leading) cause for endometriosis in these patients, while the mulleriosis/mullerianosis theory of origin would point towards a higher prevalence of endometriosis in patients with all genital malformations, due to the fact that both stem from the mullerian ducts. Although not much research has been done in this field, I propose placing 'obstructive' between brackets.	This was copied from the studies. In case of an obstruction, the menstrual debris is not shed vaginally, which may give a higher chance on developing endometriosis. We have not made any amendments to the guideline
172	Pauline de Heer	90			This recommendation seems to deem the risks of GnRH agonist use in adolescence as low, but I can't find any literature with long-term studies on this 'low' risk. Could you provide large studies with long-term effects of GnRH agonist use with/without addback in adolescents with information on bone density, brain development, etcetera?	We have addressed the high quality studies which are available on this topic, and we concluded that GnRH agonists are safe to use for up to one year
173	Pauline de Heer	93			The term 'laparoscopic removal' is used here; in other parts of the guideline the term 'excision' is used. Since no guarantee can be given of complete removal when using ablation/cauterization techniques (since you don't have the opportunity for pathological analysis of the removed lesion), I would like to suggest replacing 'removal' with 'excision'.	We have used laparoscopic removal, because during our discussions we agreed that we do not have enough evidence to state that excision is the only right way to treat endometriosis effectively and safe,
174	Pauline de Heer	97			What do you mean with 'active'? If this means 'symptomatic', please use the term 'symptomatic'.	We have adapted the recommendation to active/symptomatic.
175	Pauline de Heer	98			Why is this a weak recommendation? Why would this be different from recommendation 26?	The justification for this recommendation is mentioned in the text. In comparison to younger women, there are much less data showing benefit, while the risks of surgery could hypothetically be higher. No modification was made to the recommendation or the grading
176	Pauline de Heer	100			It is not clear to me when surgery is not feasible in post-menopausal patients.	What we mean by not feasible, is when there is a contra-indication or higher risk due to comorbidities. No modification was made to the recommendation, but we clarified this in the justification.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
177	Pauline de Heer	110			Because of the phrasing 'at the time of surgery' it seems as if this recommendation only pertains to incidental findings during a surgery for a different medical reason, which I completely understand, since there is also a high probability that the surgeon doesn't have the necessary skills to excise the endometriosis tissue. I would, however, expect this recommendation to also pertain to situations in which diagnostics (ultrasound, CT, MRI) show signs of endometriosis. Did you mean to include these situations?	When endometriosis is detected during US, the patient can be counselled with regards to appropriate actions; When identified during surgery, counselling is not possible, and treatment should not routinely be performed. ,
178	Pauline de Heer	113			See my comment below about page 149.	(duplicate comment)
179	Pauline de Heer	116			This recommendation is unclear about whether it mentions an absolute or relative risk increase (the narrative on page 154 shows that these are absolute increases, which is very confusing). In chapter X.1. also opens with the conclusion that there is no statistically significant risk increase for all cancers among endometriosis patients as compared to the whole population. Can this be added to the recommendation, and can the "+0.5% to +1.2%" be clarified?	We have adapted the recommendation to make it more clear. Also, we included a section "What information could clinicians provide to women with endometriosis regarding their risk of developing cancer?" in the guideline which explains and clarifies the message and the percentages.
180	Pauline de Heer		6	132-133	There is no proof that endometriosis is estrogen-dependent. If you do have proof, please supply a dependable source here. Otherwise, I would like to suggest changing this sentence into: "Female hormones seem to influence the (symptoms of) the disease, thus it is mostly found in women of reproductive age although it is not limited to this age group, nor this sex."	We have considered this comment, but consider there is proof that endometriosis is an estrogen-dependent disease. We have included a reference in the text
181	Pauline de Heer		6	138	The 190 million women is a gross underestimate; this estimate is based on only women in their reproductive age, and neglects the fact that endometriosis is also found in girls and in post-menopausal women (and an unknown number of men). I would remove this sentence from the text.	We did included a recent estimation for this sentence. Even if an underestimation, it does emphases the importance of endometriosis (and the guideline). Therefore we decided to keep the sentence. We did slightly modify the sentence, now reading that "it is estimated that currently approximately at least 190 million women worldwide are affected by the disease"
182	Pauline de Heer		6	147-148	"hormonal suppression of endogenous estrogen levels" – this statement ignores the fact that many patients experience more symptoms due to progestogens, and the fact that oophorectomies in many patients do not resolve symptoms	In reply to the comment, we have rewritten the sentence, now reading "Therapeutic options range from improving pain symptoms and fertility prospects by means of hormonal suppression of endogenous estrogen levels, pro-apoptotic and anti-inflammatory effects on endometriotic tissue, surgical removal, or destruction of endometriotic lesions and division of adhesions to management of chronic pain syndromes."

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
183	Pauline de Heer		6	148	"decidualisation of endometriotic tissue" – by what means? I have not seen any proof that this can be achieved with endometriosis tissue in real patients. Can you supply a source (not using mouse models, since they use man-made implants of either foreign endometriosis tissue or their own endometrial tissue, which is very different from endometriosis tissue)?	In reply to the comment, we have rewritten the sentence, now reading "Therapeutic options range from improving pain symptoms and fertility prospects by means of hormonal suppression of endogenous estrogen levels, pro-apoptotic and anti-inflammatory effects on endometriotic tissue, surgical removal, or destruction of endometriotic lesions and division of adhesions to management of chronic pain syndromes."
184	Pauline de Heer		17	301	Endometriosis is not ectopic endometrium (as you state yourselves on page 6); many cell differences have been described in literature, so I would like to suggest you call it 'endometriosis tissue' here.	We have adapted the research recommendation, now reading "More research needs to be performed on the mutational and epigenetic profile of endometriosis tissue, endometrium from endometriosis patients ectopic, eutopic, and normal endometrium from women of different ages and reproductive histories. "
185	Pauline de Heer		36	980 - 988	Since we see so many individual differences in symptom reduction when using these hormonal therapies – part of patients even experience worsening of symptoms while on these hormonal therapies (often to the disbelief of their doctors, which is very frustrating) – I think it would be good to mention that both the efficacy and side-effect profiles of these therapies are highly individual, and unfortunately finding a good therapy is trial and error.	We have added a sentence in line with the reviewers' comment to the text
186	Pauline de Heer		36	993-994	"As there is no evidence that hormonal treatments have a negative effect on disease progression"; could you also emphasize that they don't have a positive effect on disease progression either? Too often, patients hear from their (non-expert) gynaecologists that taking hormones will prevent the endometriosis lesions from getting bigger, while we know that this isn't true. Case studies have described the growth of DE while using hormones continuously, and the only aim of hormones is to suppress symptoms, as can be seen in all trials for these hormones, and for example in the ACOG bulletin on endometriosis.	The statement that there is no evidence that the listed treatments have a negative effect on disease progression is correct, and supports the recommendation for offering medical treatment. Whether or not these treatment have a positive effect on disease progression is not known (and only suggested by low quality case reports)

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
187	Pauline de Heer		36	994	"they generally have limited side effects" – could you add a recommendation to do stepped care here? We know that the side effect profile of GnRH agonists is worse than that of combined hormonal contraceptives, for example.	We have added a sentence that these overarching recommendations should be read and applied in consideration of the remainder of this section which provides more detailed information on the different medical treatments including their efficacy and side-effect profile." In fact, we have a recommendation stating that "The GDG recommends that GnRH agonists are prescribed as second line (for example if combined oral contraceptives or a progestogen have been ineffective) due to their side-effect profile.' in line with the suggestion of the reviewer.
188	Pauline de Heer		42-43	1231 - 1269	GnRH antagonists: I am surprised to not read anything about the poor cost-effectiveness of these new drugs. On the basis of the prohibitive cost and poor side effect profile as compared to combined oral contraceptives, I would at least expect a word of caution in the recommendation, and advice to do stepped care. In addition to that, I would note that GnRH antagonists aren't available in all countries (just like you did with the aromatase inhibitors in line 1298). I would like to refer to the ICER analysis of elagolix: https://icer.org/wp-content/uploads/2020/10/ICER_Elagolix_Final_Evidence_Report_080318.pdf	Cost-effectiveness of treatments (medical or surgical) was not part of the remit of this guideline.
189	Pauline de Heer		47-48	1477 - 1501	Ablation versus excision: aside from the available evidence, I am missing a statement on the characteristics of ablation versus excision when it comes to the depth of lesions; with ablation it is impossible to know whether you destroyed the whole lesion, so you risk leaving part of it behind (and covering it with scar tissue). Can something be said (as an expert opinion) on using excision to be able to remove the complete lesion, and to check for this radical resection of the lesion afterwards during pathology assessment? (personal background: my own largest superficial endometriosis lesion ended up being 3-4mm deep; something that would have been missed doing ablation)	We have added a sentence to address this, in the justification section
190	Pauline de Heer		51	1624	'not rarely detected'; to patients this is an important point: endometrioma often are a sign of more extensive disease. Is it possible to rephrase this sentence to make it less ambiguous and more clear to all readers?	We have modified the text to make it less ambiguous.
191	Pauline de Heer		51	1656	'recurrence rate': is this recurrence of symptoms or histologically proven presence of DE? Can you clarify this?	We have clarified in the text that this refers to the total recurrence rate (recurrence of symptoms or lesions).

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
192	Pauline de Heer		57	1924 - 1925	"Many clinicians believe that surgical castration would lead to regression of remaining endometriotic lesions." – why is this statement in the text? It doesn't seem to be supported by evidence, and it is not clarified what the opinion of the GDG is. I am afraid that readers of the guideline will interpret this sentence as a recommendation, especially since I heard from many patients that their clinician gave this explanation to suggest hysterectomy, even in young patients with a wish to become pregnant. Can you remove this sentence?	Surgical castration may indeed work in a similar way to medical treatment with GnRHa or natural menopause. There is some evidence that recurrence/persistence of pain and the need for further surgery after preservation of ovaries is higher.
193	Pauline de Heer		102	3779	"as 'pseudopregnancy' induced through hormonal therapies has a positive effect on symptoms" – I understand that you are refuting this statement later on, but I think it would be good to add the word 'statistically' here, as we know definitely not all patients experience a positive effect on symptoms. So: "as 'pseudopregnancy' induced through hormonal therapies statistically has a positive effect on symptoms"	We agree; it is clear that it is a common 'belief' that is described by this sentence, and the scientific data follow later. We decided to leave this unchanged.
194	Pauline de Heer		117	4382-4385	I am missing a reference to even earlier cases of endometriosis, such as: - Endometriosis found in fetuses (eg. https://doi.org/10.1002/jcp.22888 , https://doi.org/10.1016/j.rbmo.2010.04.002) - Endometriosis found in very young girls (eg. https://doi.org/10.1016/j.fertnstert.2004.08.025 https://doi.org/10.1159/000181185)	The guideline and key questions focus on endometriosis in women of reproductive age, adolescents, and postmenopausal women. Endometriosis in foetuses or very young girls is outside the scope of the current guideline.
195	Pauline de Heer		131	4892-4893	It seems that you use the term 'disease' to mean 'tissue', while I think this sentence is about endometriosis tissue becoming less symptomatic.	Endometriosis (the disease) is considered "steroid-dependent", not the tissue. The sentence is correct as is and we have not made any amendments
196	Pauline de Heer		131	4896 & 4899 & 4921	"reactivation of residual disease" and "still be active after menopause" and "can still be active after menopause" – what do you mean with 'reactivation' / 'be active'? If you mean that it is symptomatic, could you make this explicit?	We have considered this comment but we consider that the text and terms used are clear for the readers.
197	Pauline de Heer		131	4921	"Clinicians should be aware that endometriosis, however rare, can still be active after menopause." – a prevalence of 2-5% is not rare; it is around half of the total estimated prevalence of endometriosis. Why this conclusion?	The conclusion and statement want to ensure clinicians are knowledgeable that endometriosis after menopause can occur, can be symptomatic, and needs management. We have removed "however rare", but kept the remainder of the sentence as is.
198	Pauline de Heer		133	4959	Why are only NSAIDs mentioned as pain killers? There are also other pain killers that could help.	We agree and have adapted the "NSAIDs" to the more general term "analgesics".

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
199	Pauline de Heer		134	5026	"Estrogen is one of the predominant drivers of endometriotic growth." – can you provide a source for this claim?	We have adapted the sentence a little to "Estrogen is considered to be one of the predominant drivers of endometriotic growth". A reference for the statement has been included in the introduction of the guideline
200	Pauline de Heer		139	5220-5236	Can anything be said about the influence of hormonal therapies on the increased cardiovascular risks, and especially the (long-term) use of GnRH agonists? I suspect this must be an important factor, but you only mention hysterectomy/BSO. Mu et al, 2016, note: "We did not have information on other hormonal treatments for endometriosis, such as danazol (a synthetic androgen) and Leuprolide (lupron, gonadotropin-releasing hormone analog) to assess to what extent the association between endometriosis and CHD could have been explained by those treatments.", which I think is a very important remark to be made in this section of the guideline.	Interesting comment, however, this is outside the scope of this guideline.
201	Pauline de Heer		143	5393-5394	"Hormonal treatment (OCP or GnRH agonist) has been shown to be effective in a significant proportion of patients, although with high recurrence rates." – what is meant by 'recurrence'? Of symptoms? Of lesions? During hormone treatment or after cessation? Can you make this explicit? I would also like to mention that many studies, including trials of for example GnRH (ant)agonists looked at dysmenorrhea to see whether symptoms were suppressed / stayed away. When suppressing the menstrual cycle, suppressing dysmenorrhea is a simple feat. This doesn't say anything about more specific endometriosis symptoms.	In the respective section, we specifically discuss thoracic endometriosis, and follow the sentence on "recurrent pneumothorax". We do not think there is a need for further clarification. We discuss the recurrence rates in general since there are no more specific data available.
202	Pauline de Heer		146	5471-5497	I would expect that DE with severe bowel or bladder involvement for example would lead to a different conclusion; could you make this explicit?	We have no data on the natural progress of the disease neither peritoneal nor DE. However, surgeons should inform patients regarding the extent of the disease as clearly stated in the guideline.
203	Pauline de Heer		148	5515-5517	With large endometriomas I would be worried about the possibility of ovarian torsion if the endometrioma gets even bigger. The recommendation seems quite 'relaxed' about monitoring, though. Which indications actually require monitoring, in your opinion?	We agree with the reviewer's comments, however, due to the lack of unequivocal evidence on the endometrioma size and frequency of monitoring we were not able to create a more specific recommendation.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
204	Pauline de Heer		149	5545 - 5602	Recommending a healthy lifestyle to people worried about getting endometriosis seems like a fine recommendation, since a healthy lifestyle is good for everyone, but to patients this chapter can be read as a 'blaming' chapter, while all of the 'evidence' that is presented only describes associations, no causal links (or perhaps causal links are the other way around – we don't know), and most studies are self-reported. On behalf of patients, I would really appreciate a more modest tone of voice, simply stating that we don't yet know the origin of endometriosis, so we also don't know how to prevent it. And that a healthy lifestyle is always a good idea, but that this cannot give any guarantee.	We have added a sentence to the justification in reply to this comment. The entire sentence now reads "To the best of our knowledge, the proposal of healthy lifestyle/diet could be considered a feasible and acceptable option to improve general health, and it may also be beneficial towards the risk of endometriosis. "
205	Pauline de Heer		156-157	5785-5841	Why use the term 'OCP' in the first part of this text, and then switch to 'CHC', while you mean the same thing?	Thank you for alerting this inconsistency. We have corrected this in the text.
206	Pauline de Heer	Layout			Please add the recommendation numbers to the recommendations in the text (so not only in the overview on the first pages) – this helps navigating the guideline.	We will add the recommendation numbers also in the full guideline
207	Pauline de Heer	Recurrence			Throughout the guideline, the term 'recurrence' is used in different meanings, sometimes with adjectives, which also differ (while apparently meaning the same thing). In the definition on page 109, line 4067, it is very clear that it should be about visualized lesions, while throughout the guideline, recurrence is also mentioned in the meaning of symptom recurrence. And in lines 4083-4086 you state that you will define recurrence as one of both… This is extremely confusing, and can (and probably will) lead to patients continuing medical therapies while they suffer from very ill side effects, because their clinician told them this will keep the endometriosis from growing. This does not contribute to quality of life. I've come across 'pain recurrence' and 'symptom recurrence', 'disease recurrence' (which in layman's terms could very well mean 'recurrence of experiencing disease', so equal to symptom recurrence) and 'histological recurrence', and very often, the term 'recurrence' without explaining the type of recurrence. Is it possible to clarify this throughout the guideline (or show explicitly that in some studies, the meaning of 'recurrence' wasn't clear)? And finally: it would also be good to acknowledge somewhere that any type of 'recurrence' can very well be due to missed lesions or incomplete resection of lesions.	As explained in the introduction of the chapter, recurrence refers both to the recurrence of pain/symptoms, and the recurrence of disease/lesions. For most studies, it was already specified whether they reported on pain or disease recurrence. We did double-check to make sure it is mentioned for each study in the evidence section.
208	Pauline de Heer	Conservative surgery			It seems throughout the guideline the term 'conservative surgery' has different meanings. Could you explicitly define it in each occurrence in the guideline?	In the surgery section, conservative surgery refers to 'organ-preserving or fertility-preserving surgery'. This has now been clarified in this section. In the surgery for deep endometriosis section conservative surgery refers to surgery without bowel resection and this is also clarified in the relevant section.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
209	Aboubakr Mohamed Elnashar	17			Women suffering from endometriosis-associated dysmenorrhea . Dysmenorrhea to be replaced by pain	In the recommendation, we have kept 'dysmenorrhoea' as this was the study 'endpoint' in the trials, not simply 'pain'.
210	Aboubakr Mohamed Elnashar	21			No studies have evaluated the value of using GnRH agonist for more than 12 months (the licensed treatment duration)	We agree with the comment but consider this is covered by the recommendation ("evidence is limited regarding dosage or duration of treatment")
211	Aboubakr Mohamed Elnashar	22			GnRH agonist are prescribed after age 17y, after completion of bone formation	In the justification section, the following information has been included, which addresses the reviewers' comments and further amendments can be waived: "Considering the possible impact on BMD, The GDG recommends that in young women and adolescents, GnRH agonist should be used after careful consideration and as second line of therapy and after discussion with a practitioner in a secondary or tertiary care setting, considering potential side effects and long-term health risks (e.g., bone health). More information is covered in chapter V.2 Treatment for endometriosis in adolescents."
212	Aboubakr Mohamed Elnashar	31			Before surgery assessment of ovarian reserve (AMH or AFC) is recommended	We have modified the text to cover this
213	Aboubakr Mohamed Elnashar	36			Removal of ovaries is recommended after menopause or at 51 years	The text recommends the removal of all visible endometriotic lesions and was not further adapted.
214	Aboubakr Mohamed Elnashar	49			Infertility associated endometrioma To be replaced by infertility associated endometriosis	The recommendation refers specifically to endometrioma and therefore has not been adapted. Specific recommendations for peritoneal and deep endometriosis have also been formulated.
215	Aboubakr Mohamed Elnashar	74			Clinicians should consider prescribing the postoperative use of a levonorgestrel releasing intrauterine system (52 mg LNG-IUS) or a combined hormonal contraceptive for at least 18–24 months for the secondary prevention of endometriosis-associated dysmenorrhea Or progestogen	The recommendation was based on published evidence. We do not have evidence of the preventive efficacy of progestogens at the moment.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
216	Aboubakr Mohamed Elnashar	91			GnRH agonist is not recommended before 17 years	we have slightly adapted the GPP, stating that "in young women and adolescents, if GnRH agonists are considered, they should be used only after careful consideration and discussion with a practitioner in a secondary or tertiary care setting, considering potential side effects and long-term health risks."
217	George Pados	Recommendation 77 (Chapter IV)			No recommendation has been provided	We have corrected this error in the table
218	George Pados	Treatment of asymptomatic endometriosis (line 5483) 5483			It is mentioned that …surgical treatment of asymptomatic endometriosis cannot be recommended. Since associated risks of excision or ablation of asymptomatic endometriosis are minimal even for a less skilled endoscopist, I think that the phrase should be modified as follows: surgical treatment of asymptomatic endometriosis should be provided with caution	This is what we exactly are saying in the first GPP. We fully agree with the reviewer that any surgical procedure should be provided with caution and it is not possible to carry out without the informed consent of the patient.
219	George Pados	II.3.e. Surgery for ovarian endometrioma			We have shown in a prospective randomised trial (Pados G. et al., Hum Reprod 25(3),672-677, 2010; Tsolakidis D. et al., Fertil Steril 94(1), 71-76, 2010) that the ovarian reserve is better after ablation compared with excision technique, while the recurrence rate is higher with the ablation technique.	The studies by Pados 2010 and Tsolakidis 2010 mainly focussed on ovarian reserve/fertility. This topic is covered in section III.2.b. Both studies have been included in the review by Dan et al 2013, listed as the primary source of evidence for that section. As such, the studies have not been specifically mentioned in the guideline, but the data have been considered (through the inclusion of the review by Dan et al 2013)
220	Helen McLaughlin		11.6.b.1	2455 / 245 6 / 2457	I feel the commentary regarding pelvic physio to be quite unclear. My takeaway is that based on studies pelvic floor physiotherapy addressing pelvic floor dysfunction should be taken with caution and has no / little supporting evidence from trials? Or is the point targeted towards general physiotherapists? Lines 2455 and 2456 discuss pelvic health physios and then line 2457 addresses physiotherapists – should there be a distinction between the two or is it intended they are the same? Pelvic physiotherapy has also been addressed here as a pain management option, and not as a tool to aid recovery from surgery. Has it been considered to address it is a post-operative treatment? My personal experience of pelvic floor physiotherapy has been the opposite of the conclusion described (combined with excision surgery) and I worry for the lack of clarity I question above, and the dismissive tone taken.	We have made significant adaptations to the section on physiotherapy in reply to the comment of the reviewer.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
221	Department of Fertility and Gynecology, UMC Utrecht	25			What is the indication to use a second drug next to an aromatase inhibitor?	The studies evaluating aromatase inhibitors in endometriosis have done so in combination with other medications and we have recommended accordingly. We have slightly reformulated the recommendation, now reading "In women with endometriosis-associated pain refractory to other medical or surgical treatment, it is recommended to prescribe aromatase inhibitors, as they reduce endometriosis-associated pain. Aromatase inhibitors may be prescribed in combination with oral hormonal contraceptive pills, progestogens, GnRH agonists, or GnRH antagonists."
222	Department of Fertility and Gynecology, UMC Utrecht	41 AND 46			41 is a weak recommendation and 46 a strong recommendation to prescribe hormones postoperatively? Shouldn't they both be weak or strong?	We have adapted both recommendations, which are now formulated as weak recommendations
223	Department of Fertility and Gynecology, UMC Utrecht	72			In the 2013 guideline there was a statement about CO2laser. What is the recommendation about CO2laser vaporization? And.. is cystectomy also advised for the secondary prevention of recurrence of an endometrioma?	The recommendations for surgery include both cystectomy and laser vaporisation. With regards to secondary prevention, we have, based on available data, recommended cystectomy, This is covered in section IV.1.a
224	Department of Fertility and Gynecology, UMC Utrecht	73			Shouldn't it be 'secondary prevention'?	The recommendation reads "prevention of endometrioma recurrence" which equals secondary prevention, but clarifies that this is endometrioma recurrence (rather than symptom recurrence). It was considered not required to amend the recommendation.
225	Department of Fertility and Gynecology, UMC Utrecht	Rec 72-75			Please reconsider the order of recommendations. Rec 72,73 is about endometriomas, rec 74 about endometriosis in general, rec 75 again about endometriomas.	The sections first describe the surgical treatment and next medical treatment for the prevention of recurrence. The recommendations have been checked based on other comments, which also resolves this comment.
226	Department of Fertility and Gynecology, UMC Utrecht	80			this recommendation seems a bit odd; in this way, every adolescent can be considered to have endometriosis. Either this should be narrowed down ('consider endometriosis in adolescents that don't respond adequately on hormonal treatment + NSAID's), or broadened; 'clinicians may discuss the possible presence of endometriosis in adolescents with severe dysmenorrhea'.	Based on the literature, (cyclical) absenteeism from school and use of OC for dysmenorrhoea are risk factors for endometriosis in adolescents. We have based this recommendation entirely on the evidence available from the studies.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
227	Department of Fertility and Gynecology, UMC Utrecht	83			the last 'where appropriate' should be removed	We have removed the second "where appropriate" in the recommendation
228	Department of Fertility and Gynecology, UMC Utrecht		19	357	this sentence is repeated in line 360, therefore does not seem relevant in the text	We have checked the paragraph and made some minor corrections to remove any duplication
229	Department of Fertility and Gynecology, UMC Utrecht		20	390	dyschezia is not mentioned in the study results (nor are cyclical cough/chest pain, fatigue, dysuria, haematuria), what is the scientific basis and OR for these symptoms?	Based on the limitations of the available data, but also the limitations of observational/epidemiological data in general, we have formulated the recommendation based on the data combined with expert opinion. The recommendation is labelled a GPP. In this GPP, we considered it more relevant towards earlier diagnosis to be inclusive, and not to miss any symptoms, rather than be limited only very specific and published symptoms.
230	Department of Fertility and Gynecology, UMC Utrecht		24	566	the paper cited is quite old (1998) and possibly not representative of current practice in laparoscopy. For such a guideline, more caution or nuance may be considered before stating diagnostic laparoscopy is associated with mortality	We have added a more recent references to the sentence, to reinforce the message that even if laparoscopy has been the gold standard, it is not without risks
231	Department of Fertility and Gynecology, UMC Utrecht		39	1132 - 1141	what are the corresponding references?	The section reports the results and conclusion of the review of Lan, et al., 2013. The reader is referred to the review for more details about the trials included in the review
232	Department of Fertility and Gynecology, UMC Utrecht		39	1132 - 1141	it seems like these papers are better discussed under subsection II.2.c (GnRH agonists), as the current subsection appears to be aimed at the comparison between intrauterine en subdermal implant progesterone treatment. Also, in these lines GnRH agonists are described to be comparable to LNG-IUS, whereas in line 1177 GnRH agonists were found to be inferior to LNG-IUS in a Cochrane review. It might be better to discuss these results collectively.	While we acknowledge that the data could also have been included under the GnRHa section, the review by Lan et al 2013 (Analysis of the levonorgestrel-releasing intrauterine system in women with endometriosis) is appropriately mentioned under heading II.2.b.4. The data related to LNG-IUS mainly result from studies comparing the treatment with GnRHa. For GnRHa, there are studies comparing GnRHa with LNG-IUS, but also to placebo and other treatments.

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
233	Department of Fertility and Gynecology, UMC Utrecht		49	1554	Line 1554 "Surgical technique": it might be worthwhile to mention the systematic review and meta-analysis by Younis et al. Human Reproduction Update 2019: both unilateral and bilateral cystectomy associated with lower AMH with a greater effect of bilateral cystectomy; no difference in pre-operative levels	We have added a sentence to include the main conclusion of this article.
234	Department of Fertility and Gynecology, UMC Utrecht		53	1730	is the word 'hysterectomy' supposed to be 'laparotomy' (as the laparoscopic approach also consisted of a hysterectomy)? And if so, consider specifying why that would be considered as the primary treatment if laparoscopy appears to be non-inferior? If you want to say that hysterectomy is not advised to perform routinely, please specify more clearly in the text, or make a GPP stating that hysterectomy is not always necessary?	The word 'hysterectomy' does not imply laparotomy, it may be both laparoscopic or open.
235	Department of Fertility and Gynecology, UMC Utrecht		55	1824	reference is not cited	Thank you for alerting us that indeed the reference was missing. We added it to the text (Bendifallah, 2020 - Recurrence after Surgery for Colorectal Endometriosis: A Systematic Review and Meta-analysis)
236	Department of Fertility and Gynecology, UMC Utrecht		89		Regarding indications for fertility treatments: what is the GPP regarding starting fertility treatment because of invalidating symptoms (i.e. dysmenorrhea) with the purpose of reducing time till pregnancy even though there is no actual subfertility.	We have considered this comment, but we did include this topic as a question and hence it was not formulated as a GPP
237	Department of Fertility and Gynecology, UMC Utrecht		109	4066	'or as repeat rise of the marker CA-125 after surgery'. Should we state that here? There is another recommendation that we should not use biomarkers for the diagnosis of endometriosis. (rec 5)	In this sentence, we are simply referring to the published literature which uses different descriptions of recurrence. We are not recommending CA125 to detect recurrence.
238	Department of Fertility and Gynecology, UMC Utrecht		P117	4393	please add that primary dysmenorrhea is very common in adolescents (up to 90% in several studies); it is difficult to differentiate with endometriosis. Maybe this is part of the delay?	We have added a sentence in the introduction addressing this comment
239	Department of Fertility and Gynecology, UMC Utrecht		P121	4556-4561	please write down the numbers/ prevalence of different stages of endometriosis from the Janssen study (2013) here: this systematic review has more patients (880) in contrast with the retrospective study of 38 and 62 patients now described. Also, in the systematic review, it is more clear that a total of 67% of all adolescents have mild endometriosis (which explains why imaging is more often negative) and only a small portion have stage III and IV endometriosis which is suggested in line 4564.	We have checked this section and made some further clarifications on the studies included.
240	Department of Fertility and Gynecology, UMC Utrecht		P122	4594	this section is not of value for this PICO question and can be removed	We have considered this comment, but decided to leave the information in the guideline because it gives an indication about the prevalence of different symptoms and different ASRM stages, which is important in diagnostics

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
241	Department of Fertility and Gynecology, UMC Utrecht	Chapter diagnosis			You can read in the text: diagnosis of certain 335 presentations of endometriosis for example by ultrasound or MRI (see below) can be considered without laparoscopy with histologic confirmation. As this is different compared to old guidelines, where laparoscopy with histology was the golden standard, shouldn't there be a recommendation or GPP about this?	We have considered this comment, but felt the message in already clear from the recommendation and justification. We made no amendments.
242	Department of Fertility and Gynecology, UMC Utrecht	Chapter pain			Regarding the studies on GnRH agonist treatment with add back therapy, are there studies available comparing the effect to oral contraceptives alone? Do we know what the value is of adding agonists?	To our knowledge, there are no studies comparing to COC.
243	Department of Fertility and Gynecology, UMC Utrecht	Chapter infertility			In the last guideline a size of >3 cm was mentioned in the recommendations about surgery for endometriomas.	We have added a sentence to the text with regards to the size of the cyst, reading "nor studies exploring the indication for surgery depending on the size of the cyst. "
244	Department of Fertility and Gynecology, UMC Utrecht	general			Thank you for all the hard work that has been done!!	Thank you for this kind comment
245	Ellen Klinkert		112	4211	"There" contraceptive properties should be "the"	We have corrected this error in the text.
246	Ellen Klinkert		112	4211	"risks" should be added next to side effects (e.g. the risk of thrombosis)	We have added "risks" to the sentence
247	Ellen Klinkert		115	4291	Right parenthesis should be removed after dienogest	We have corrected this error in the text.
248	Ellen Klinkert		115	4292	Treatments (“s” is missing)	We have corrected this error in the text.
249	Ellen Klinkert		115	4295	Were these therapies effective in treating the pelvic pain? This should me mentioned as well. Did de VAS decrease?	We have added this information from the paper
250	Ellen Klinkert		127	4777	IV.2.c should be V.2.c	We have corrected this error in the text. Thank you for alerting us.
251	Ellen Klinkert		131	4915	"Wo" should be "who"	We have corrected this error in the text.
252	Ellen Klinkert		137	5124 and 5131	Tibolone is associated with a higher risk of endometrial carcinoma than continuous combined therapy, this should be mentioned in the recommendations (Tibolone and risk of gynecological hormone sensitive cancer.Løkkegaard ECL, Mørch LS. Int J Cancer. 2018 Jun 15;142(12):2435-2440; Hormone replacement therapy and the risk of endometrial cancer: A systematic review. Sjögren LL, Mørch LS, Løkkegaard E. Maturitas. 2016 Sep;91:25-35. doi: 10.1016)	We have added the study of Lokkegaard to the text, and removed Tibolone from the recommendation

Nr	Reviewer	Rec	Page	Line	Comment	Action / Reply
253	Julie Prilling	general			Here is the ESHRE Endometriosis Guidelines reviewed by World Health Organization ICD11 - patient diagnosis and medical records guidelines. There are major concerns that the medical field does NOT understand endometriosis, endo-cancer or the global patient medical record process. You should be educating on ICD11. I flagged the Endometriosis Organizations in March for not understanding that ICD classification and not following medical license protocol. ICD is the UNIVERSAL SYSTEM and STAGE. - Endometriosis classification and staging systems: the road to a 1 universally accepted and implemented system. REJECTED. - 2018 ICD11 proposal - REJECTED Now I'm reviewing yet another document showing a medical field that does not understanding an illness for 200 million. Please see notes but anyone who is advising patients should know WHO, ICD-O. https://apps.who.int/iris/bitstream/handle/10665/96612/9789241548496_eng.pdf I will be testing the endometriosis experts for the UN Meeting in September on imaging skills and pathology diagnosis. I hope you can find experts to match protocol. Here is thoracic protocol: https://youtu.be/jo__0EOuX-4 Here is my ICD11 Guideline proposal that has been submitted to the ICD team and is being updated now. Please review as the new STAGE needs to be set. The software doesn't currently work because our medical field does not understand endometriosis by science.	We have read and checked this comment. This guideline is aimed to guide management of endometriosis in clinical practice. While we are aware of the ICD classification, it is outside the scope of the current guideline to discuss the ICD classification or make further comments regarding ICD.