RPL

Recurrent pregnancy loss Guideline (update 2022).

ESHRE Recurrent Pregnancy Loss Guideline Development Group

European Society of Human Reproduction and Embryology

ANNEX 8: REVIEW REPORT

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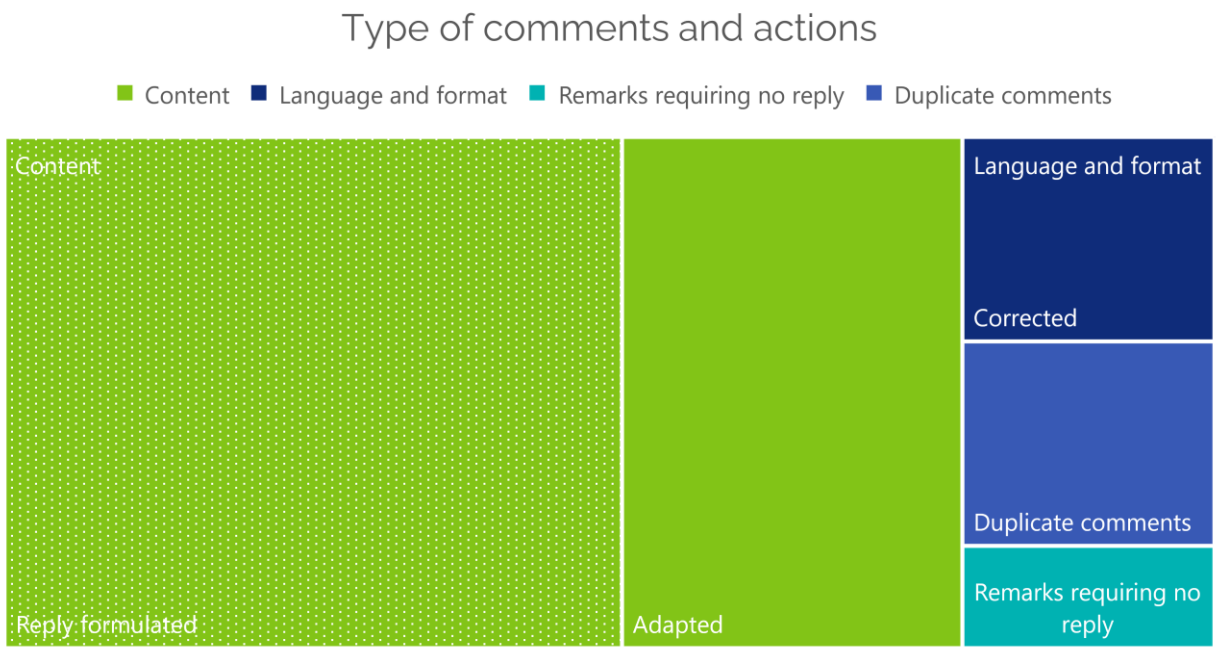
The draft of the guideline "Recurrent pregnancy loss (update 2022)" was published for public review for 6 weeks, between 28 March and 9 May 2022.

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

During the stakeholder review, a total of 96 comments (including 9 duplicates) were received from 13 reviewers. Reviewers included professionals and a representative of an IVF clinic.

The comments were focussed on the content of the guideline (76 comments), language and style (8 comments), or were remarks that did not require a reply (4 comments). All comments to the language and format were checked and corrected where relevant.

The comments to the content of the paper (n= 76) were assessed by the working group and where relevant, adaptations were made in the paper (n= 27; 35.5 %). Adaptations included revisions and/or clarifications of the text, and amendments to the recommendations. Only one comment was considered outside the scope of the guideline.



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
West Coast IVFClinic, Inc.	USA	Michale Massoud Kamrava

Individual experts

Reviewer	Country
Roy Farquharson	UK
Abeer Issa	Saudi Arabia
Tansu Kucuk	Turkey
Mitranovici Melinda Ildiko	Romania
Asher Bashiri	Israel
Catherine Rongiers	France
Shehnaaz Jivraj	UK
Zeev Shoham	Israel
Elena Kostova	The Netherlands
Lisa Lashley	The Netherlands
Nicolas Garrido	Spain
Peter Bisschop	The Netherlands

Reviewer comments and replies

Reviewer	Section	Nr	Comment	Action / Reply
Michael Massoud Kamrava	Section 15.1	1	Could not find a reference to T-Shaped uteri; Using a resectoscope to incise the top lateral walls of the uterus at the junctions of the current internal os and extending down into the elongated cervical canal resulting in an expanded and normal looking cavity, one can prevent pregnancy losses and expect a normal pregnancy outcome. Of course, prior accurate ultrasound/MRI of the uterus must be made.	A meta-analysis published by Garzon et al on 2021, showed that in women with primary reproductive failure and T-shaped uterus, hysteroscopic metroplasty seems to be effective to improve reproductive outcomes. We have to highlight that "seems to be" effective. There are many scientific limitations in this topic leading the GDG to not formulate a recommendation regarding the treatment of RPL in women with T-shaped uterus, including: •A causal relationship between T-shaped uterus and reproductive impairment, as well as the reason supporting the possible effectiveness of metroplasty, is still unproven. Many women with T-shaped uterus are able to conceive, which means that it is not an absolute sterility factor; •There are still no universal morphometric criteria to distinguish between the various types of uterine malformations, which in many cases makes their diagnosis subjective and subject to clinical context above everything else (diagnostic done by 3D US and hysteroscopy); •Most of papers include a low number of patients •All the available studies do not include a control group, and this impedes achieving definitive conclusions about the actual effect of the metroplasty on the reproductive outcomes; •Lack of proper definition of "successful repair or intervention". Most of papers don't include a follow up criterion to consider if surgery was successful or not, and in which extend.

Roy Farquharson	General	2	Overall, a comprehensive update and welcome addition to a complex area. More evidence has been accumulated and thoroughly peer reviewed. The flags for 2022 updating is especially welcomed. Chapter structure and style provides a systematic and objective approach for the non-expert in RPL. Perhaps a list of Chapter headings (n=18) at the beginning of the GDL would be useful for the trainee and non-expert to aid assimilation and focus?? Furthermore, it would improve focus and allow the reader to orientate themselves in a necessarily long GDL (lots of evidence)	A table of content will be added in the published version
	Section 4.1	3	Please consider inserting 'failed' before pregnancy tissue, just to be clear (as opposed to live pregnancy so as to avoid confusion and validate genetic analysis recommendation)	This was adapted in the guideline as following: pregnancy tissue following pregnancy loss
	Part A	4	Effect of RPL on male partner is grossly neglected and ESHRE should consider funding preliminary research in this area – there are only a few who know how to start this, and one name in particular comes to mind	Thank you for this comment. We will consider this for a future project
	Part A	5	Definition of RPL is clear and inclusive while acknowledging differing national definitions globally	Thank you for this comment
	General	6	No typos noted! Failing eyesight of reader?	Thank you for this comment
Abeer Issa	Section 12.1	7	Management of further pregnancy by low dose Aspirin & thromboprophylaxis	The evidence available in the literature (based on a systematic Cochrane review combining 9 RCTs (De Jong et al. 2014) showed that there is no significant effect of treatment with aspirin, LMWH and LMWH + aspirin compared to placebo in women with RPL with or without hereditary thrombophilia
	Section 5.2	8	Recurrent pregnancy is the loss of 2 or more pregnancies before 24 weeks pregnancy. The most common causes are chromosomal genetic, anatomical, antiphospholipid syndrome congenital or acquired. Diagnosis in such case is antiphospholipid syndrome	Thank you for this comment and suggestion. We consider this point covered by Recommendation 15.

Tansu Kucuk	Section 1.1 9	I agree that when the risk of RPL is at the lowest (age 20-35) 2 events are enough to establish the diagnosis of RPL. But when it starts to increase (>35 years of age) the time is not on patient's side. For the ladies with diminished ovarian reserve even 1 loss is enough to diagnose and to start evaluation.	The GDG recommends to sensitively inform women that the risk of pregnancy loss is rapidly increased after the age of 40. However, in the definition of "Recurrent pregnancy loss", the GDG did not define a specific age range. In general, RPL is defined as the loss of 2 or more pregnancies, and this should be the start of investigations and treatments. The current guideline does not deal with non-recurrent miscarriage, and therefore does not define specific patient groups that need investigations after 1 loss.
	Section 4.1 10	I am practising for 36 years and saw many patients who wasted precious time (and eggs) waiting for spontaneous successful pregnancy. I believe genetic analysis of a pregnancy tissue should be routinely done, in order to be able to diagnose 2 consecutive genetic loss which directly pushes you towards ART + PGS. Genetic study of the couple cannot say anything about the germ line meiosis, while the analysis of abort material can... So, genetic analysis of the material is not explanatory only.	Thank you for this comment. It was stated in the guideline that "Genetic analysis of pregnancy losses is not routinely recommended by the GDG but could be considered for explanatory purposes". This was formulated as a conditional recommendation because the role of genetic analysis of pregnancy tissue needs to be clarified with prognostic modelling to clarify its effect on subsequent live birth".
	Section 7.4 11	Ovarian reserve testing should be offered to the patients particularly after a certain age and to the ones with high risk for premature menopause. It is not only to explain the pregnancy loss but also for scheduling the fertile time ahead.	The available data suggest a correlation between diminished ovarian reserve and RPL, but there is no data on the prognostic value of ovarian reserve testing, and hence Ovarian reserve testing is not routinely recommended in women with RPL.
	Section 15.1 12	There is increasing number of publications related to hysteroscopy for T shape uterus. I strongly agree that T shape uterus does not require an intervention. And in fact, there is no T shape "uterus", but there is T shape endometrial cavity (Kucuk and Ata. Infantile or hypoplastic uterus? A proposal for a modification to the ESHRE/ESGE classification of female genital tract congenital abnormalities. FVV Ob Gyn2022, 14(1):49-50)	Thank you for this comment and stating your agreement with the recommendation. With regards to the terminology, we have kept T-shaped uterus, as this is consistent with other published ESHRE recommendations, namely the ESHRE/ESGE classification of female genital tract congenital abnormalities.

Mitranovici Melinda Ildiko	General	13	A simple Table with algorithm of tests that should be performed by the couple in RPL situation is needed, based on the conclusions presented, starting from the evidence-based medicine. It could be added as Annex or supplementary data. It could also contain the recommendation for each pathology.	The summary is updated in parallel with the guideline and the updated recommendations
	General	14	Thank you very much for allowing me to review this excellent guide.	Thank you for this comment
	Definitio n of RPL	15	I strongly agree with the definition of RPL and reconsider that two pregnancy loss is enough for a couple, even psychologically, it should be patient-sensitive	Thank you for this comment.
	Section 1.5	16	An excellent presentation but unfortunately cannot be used in clinical practice, so more study are needed	Thank you for this comment. A recommendation for future research was added in the guideline: study the endometrial decidualization and senescence.
	Section 15.1	17	Metroplasty in bicornuate uterus should be find in Table of recommendation bellow, 3976	A recommendation on the use of metroplasty in bicornuate uterus has been formulated in the guideline: Rec 57: " Metroplasty is not recommended for bicorporeal uterus with normal cervix (former AFS bicornuate uterus) and RPL"
Asher Bashiri	Section 17.6	18	I believe that the focus of the guideline is incorrect, with references to threatened miscarriage (PRISM) and no reference to meta-analyses Haas et al., 2019 or others. The reference to Coomarasamy et al., 2019 is irrelevant because this is a randomized trial that was designed and powered to investigate women with threatened miscarriage. The reference to Coomarasamy et al., 2020 is an expert review with data that reiterates the PROMISE and PRISM studies. The authors state that they have restricted their analysis to progesterone; however, the publications of Kumar 2014 and El-Zibdeh 2005 are included in Figure 7	The PRISM trial included women with previous miscarriages at <24 weeks of gestation and the meta-analysis performed by Coomarasamy et al in 2020 combining the PROMISE trial of 836 women with RPL and the PRISM trial of 4153 women (with a subgroup with RPL) with bleeding in early pregnancy is a high-quality meta-analysis and the updated recommendation is based on this evidence. There was a significant difference for the women with three or more previous losses and some less difference or improvement in women having 2 losses or one previous loss. Thus, it was stated that the treatment with "vaginal progesterone may improve LBR in women with 3 or more pregnancy losses and vaginal blood loss"

	Section 17.6	19	In general, the recommendation is not reflected in the literature. The PROMISE trial (Coomarasamy et al., 2016) showed no significant difference: the live birth rate in the progesterone group was 65.8% (262/398) and in the placebo group it was 63.3% (271/428), giving a relative risk of 1.04 (95% confidence interval 0.94 to 1.15; p = 0.45). And the conclusion was clear: There is no evidence that first-trimester progesterone therapy improves outcomes in women with a history of unexplained RM. The limitation of the study was that it did not explore the effect of treatment with other progesterone preparations or treatment during the luteal phase of the menstrual cycle.	A meta-analysis of Coomarasamy et al 2015 and 2019 showed that the treatment with progesterone in women with 3 or more pregnancy losses and vaginal blood loss may improve live birth (RR = 1.28, 95% CI 1.08-1.51; rate difference 15%) and this was clearly stated in the recommendation and the justification. See recommendation 74: Vaginal progesterone may improve live birth rate in women with 3 or more pregnancy losses and vaginal blood loss in a subsequent pregnancy
	Prognosis	20	Allow me to call your attention to Bashiri et al., 2020 "A proposed prognostic prediction tool for a live birth among women with recurrent pregnancy loss". This should be considered, along with Lund, Brigham, Kolte and Westergaard.	The GDG have included Bashiri study in the evidence description, but decided not to recommend using this prediction model, given that this model, as well as the Lund and Brigham models, has limited sample size and do not discriminate between explained and unexplained RPL. A recommendation for future research was added to highlight the need for new validated and dynamic prediction models including more risk factors to predict a next pregnancy chance.
	Section 17.6	21	Section 17.6 is titled PROGESTERONE; however, the section also refers to oral dydrogesterone which an oral progestogen. This section should be titled PROGESTOGEN	Progesterone was replaced by Progestogen where appropriate

	Other Guidelines	22	I am surprised to see how this guideline is not in line with other (national) guidelines recommendations: OEGGG 2018, Saudi 2020, Malaysia 2020, Israel 2021, China 2021, Taiwan 2022	The ESHRE guideline is an evidence-based guideline based on the data published up to February 2022. While we did not perform a through comparison with other RPL guidelines, evidence in RPL is scarce, leaving room for interpretation in developing recommendations. We suspect any discrepancy with the mentioned guidelines is the result of such expert interpretation and/or the fact that new scientific evidence became available. In the context of care section, the ESHRE guideline is largely related to the European setting.
	Section 10.2	23	There should be reference made to Bashiri et al.,2020 "A proposed prognostic prediction tool for a live birth among women with recurrent pregnancy loss".(Asher Bashiri, Mila Giliutin,Hanna Ziedenberg, Ygal Plakht, Yael Baumfeld. J Matern Fetal Neonatal Med. 2020. Nov 1;1-7). This should be considered, along with Lund, Brigham, Kolte and Westergaard.	Please see comment 20.
	Section 17.6	24	It should be noted that dydrogesterone is a progestogen, and not a progesterone. The guideline states that there is "a benefit of progestogen in reducing a subsequent risk of miscarriage compared with placebo", and I wonder why there is no clear recommendation in line 4546 regarding dydrogesterone. "The risk of occurrence of miscarriage after 3 abortions was 2.4 times higher in the placebo group vs. the treatment group (risk ratio = 2.4, 95% CI = 1.3–5.9)"	The GDG considered that more trials are needed to formulate a recommendation supporting the use of dydrogesterone is effective.

	Section 17.6	25	In Kumar et al., women with live pregnancy were enrolled at 4–8 weeks of gestation. I disagree that the gestational age of 6.5 weeks is considered "late stage of first trimester". The immunomodulatory effect of progesterone at the trophoblastic decidual interface is presumed to be the mechanism for preventing recurrent miscarriage which is the reason that the PROMISE study recruited at gestational week 4 to 6; however, there is evidence that progestogen treatment can be beneficial even at gestational age of 6 weeks (Kumar).	This was adapted in the text
	Section 17.6	26	this is incorrect. The women were randomized from a time after a positive urinary pregnancy test (up until 6 weeks) and not randomized up through 12 weeks of gestation	"up" was removed
	Section 17.6	27	Again, this should state "progestogen" instead of progesterone.	Please see comment 21

	Section 17.6 28	The reference to Saccone et al., 2017 Figure 1 in Saccone et al., 2017 includes different progestogens, and it is noteworthy that the only two publications (El-Zibdeh 2005 and Kumar 2014) that favor progestogens involved dydrogesterone.	The El-Zibdeh study does not meet the standard criteria for a valid RCT study: the patients were randomised to oral dydrogestone (82 patients), intramuscular Profasi (50 patients) or no treatment (48 patients) according to the day of the week the women attended the clinic. This is in no way a random allocation: the physician can decide who is going get either "treatment" when he/she is planning the working programme for the week, so this introduces a severe selection bias. Furthermore, the treatments were not blinded: no placebo was given. This will introduce performance bias. The main problem in the Kumar et al. RCT is the late inclusion. Patients were included only after detection of foetal heart activity by ultrasound and the mean gestational age at recruitment was as high as 6.5 weeks and inclusion could be as late as week 8 or later. At this time of gestation, the majority of embryos that will be lost in patients with RPL have already died or are in the stage of dying. Testing a treatment after most of the "at risk" period has passed is not good methodology and will increase the risk of flawed results. The very low miscarriage rates of 6.9% and 16.8% in both allocation groups stresses this. Almost all other RCTs with RPL patients have reported miscarriage rates of at least 30% in the placebo group. The meta-analysis by Howard Carp is just a combined analysis of the El-Zibdeh study and the Kumar study with the addition of a very small non-randomized study by Freedman. It is thus not surprising that this meta-analysis finds dydrogesterone effective and it adds nothing to the literature.

	Section 17.6	29	the reference to Coomarasamy et al., 2019 is irrelevant because this is a randomized trial that was designed and powered to investigate women with threatened miscarriage. The reference to Coomarasamy et al., 2020 is an expert review with data that reiterates the PROMISE and PRISM studies. The authors state that they have restricted their analysis to progesterone; however, the publications of Kumar 2014 and El-Zibdeh 2005 are included in Figure 7	Please see comment 18
	Section 17.6	30	The claim that the meta-analysis by Saccone 2017 is flawed is not justified, and I wonder why there was no reference to Haas et al., 2019	6 of the 10 RCTs included in the Saccone metanalysis were from before 1972 and do not meet the criteria for valid research today. e.g., the start of progestogens was in most studies between week 10 and 16 and the methods for diagnosing miscarriage at that time without availability of ultrasound were poor. The inclusion of that many poor studies renders the Saccone et al. meta-analysis invalid. Haas et al. 2019 is included in the guideline (Section 17.6)
	Section 17.6	31	I fail to see how the recommendation for vaginal progesterone was updated from conditional to strong based on Coomarasamy et al., 2015 and Coomoarasamy et al., 2019 as the results showed no significant difference between the treatment group and the placebo group; plus, the fact that the latter trial was designed and powered for threatened miscarriage	The data from the very large and high-quality PRISM RCT were evaluated by an international expert group, which found that the criteria for a credible and prespecified subgroup analysis of patients with 1, 2, or 3 or more previous miscarriages were met. And this analysis showed that in patients with 3 or more previous miscarriages and current vaginal bleeding, vaginal progesterone increased the live birth rate with 15%, which was highly significant. The strength of the recommendation was adapted and the recommendation to use the vaginal progesterone treatment in this subgroup is now conditional.

	Section 17.6	32	Mix-up in terminology – oral progesterone vs oral dydrogesterone. See Schindler et al., 2003. Oral progesterone has poor bioavailability, Stanczyk et al., 2013. The molecular structure of dydrogesterone, a retroprogesterone, allows for an oral formulation with a higher bioavailability as compared to oral progesterone. See Schindler et al., 2009 and Unfer et al., 2006	Please see comment 21
Catherine Rongieres	Definition of RPL	33	First of all, the definition is too large. Before 24 weeks include pregnancy loss before 12 weeks and between 12 and 24 weeks. Between 12 and 24 weeks, miscarriages are much rarer, and pathologies are more easily identified. Second, if cause and effect relationships are recognized in the case of translocation in one of the parents and more than likely in the case of uterine abnormality. On the other hand, the cause-and-effect relationship of thrombophilia or autoimmune pathology is more debatable. In any case, many pregnancies evolve with this type of anomaly without any obstetrical consequences. In studies, there is never an exhaustive follow-up of miscarriages in a population compared to a control population without miscarriages for which the same pathologies would have been sought. Perhaps defining RPL with 3 or more embryo losses before 12 weeks and at least one fetal loss after 12 weeks would make everyone agree	We understand there is disagreement with the proposed definition, and we have added in the text that details on whether investigations should be performed after 2 pregnancy losses, or whether they can be postponed. Still, the guideline group confirmed the previously published definition, also as there are no data supporting a change.

	Prevalence of RPL	34	It is difficult to talk about prevalence when all RPL up to 24 weeks are considered. We are not in the same risks. How to compare a miscarriage at 7 weeks and an in-utero death at 18 weeks or even at 23 weeks. It seems essential to dissociate these terms of pregnancies because the incidences are not at all the same as well as the psychological consequences (for example to have felt or not, its "baby" moving")	We acknowledge that there is a continuum of existing underlying risk factors contributing to early and late pregnancy losses. It is quite rare, but in clinical care we are sometimes confronted with couples who have both early and one late loss. This guideline applies to them as well.
	Section 1.2	35	The experience of RPL inevitably leads to stress. So it is difficult in my opinion to distinguish between the psychological consequences of several miscarriages and the stress that existed prior to these miscarriages. Cf 486	The guideline reads consistent with the reviewers' comment: "the studies indicate that there is an association between stress and pregnancy loss, but" the studies "provide no information on whether the stress is a result of RPL, or whether stress could be a causal factor in RPL. Ideally, prospective studies should be performed assessing the impact of high stress on the outcome of a subsequent pregnancy". Hence, no adaptations were made in reply to this comment
	General	36	How can you put a strength: "strong" when the quality of evidence is only one cross, and the justification is: "only very low-quality evidence on an association and no evidence for a causal relation"	the level of evidence of the studies indicating that there is an association between stress and PL is low, therefore we grade it with one plus. The labelling "weak" or "strong" is dependent on the phrasing, and whether the GDG considers the recommendation is applicable in all women with RPL, or to a subgroup/under certain conditions. In this case, the GDG considers that all women with RPL should be informed that there is no evidence that stress is a direct cause of pregnancy loss.
	Section 4.1	37	How can we talk about embryoscopy in 2022 when we have a high-performance obstetrical ultrasound? Nobody uses embryoscopy	The technique was described in an introduction as background information, but was not evaluated nor addressed as a technique to be used in clinical practice

	Section 4.2	38	I absolutely do not agree. Even if the number of carrier patients is low and even if the risk of a live birth of a child with a deficiency is low, the search for a chromosomal anomaly in the parents is justified +++. On the one hand, it answers questions about the cause of RPL, and on the other hand, it may allow other solutions to be proposed, ranging from gamete donation to PGD. Finally, there is a real relationship of cause and effect of	The recommendation has been modified and reads now as following: "Parental karyotyping could be carried out after individual assessment of risk for diagnostic purposes". Treatment options including PGT, gamete donation, adoption or other alternatives were added in the justification section.
	Section 4.2	39	Yes there is a treatment: at least PGD otherwise gamete donation.	Please see comment 38
	Section 4.2	40	In case of *de novo* translocation, there will never be a family history. And if it is not *de novo*, patients are not always aware of miscarriages in the family because women do not talk about their miscarriage.	Please see comment 38
	Section 4.2	41	In any case, it is a simple test to do (just a blood test) and it eliminates a cause with very strong implications.	Please see comment 38
	Section 4.2	42	What I have underlined above is all the more true since you evoked that "paternal and maternal chromosomal causes excluded.	Please see comment 38
	Section 5.2	43	the RPL is sometimes the symptom that allows the diagnosis of an APL disease	The GDG recommends screening for APL in women with RPL (strong recommendation with moderate-quality evidence), Indeed, RPL is one of the criteria for a diagnosis of APL syndrome
	Section 11.2	44	One cannot put in the same risk an anomaly of the embryo *de novo* and an anomaly of the karyotype carried by one of the parents. the risk is not at all the same. In case of anomaly in one of the parents the PGD can be proposed	The limited evidence for preimplantation genetic testing in couples with RPL shows no clear benefit of treatment. The overall quality of the evidence is very low. Therefore, the GDG strongly recommends all couples with abnormal genetic results from pregnancy tissue testing or parental karyotypes should be offered genetic counselling to discuss likely prognosis and further diagnostic options.

	Section 12.2	45	I do not understand this recommendation. If we consider that the definition of RPL considers 2 or more miscarriages, then why if a APS was found in a woman who had only two miscarriages would we not treat the patient even outside of a clinical research? In addition, there is a risk of obstetrical complications related to APS which requires preventive treatment.	We understand that this is counterintuitive, however the prognosis of recurrent pregnancy loss after two losses in APS is better than after three losses. There is no evidence showing that the use of an anticoagulant treatment for women with APS and with two or more pregnancy losses improves LBR; The existing evidence is only for women with APS and 3 or more pregnancy losses; we agree that women with APS likely benefit from aspirin for late obstetrical complications but the PICO is focused on recurrent pregnancy loss.
	Section 14.1	46	And not only in any woman who wishes to become pregnant at least to avoid neurological consequences in the child	This comment is out of the topic.
	Section 14.2	47	Recommendation of College national des Gynécologues Obstétriciens Français (CnGOF) 2014: "Progesterone supplementation in the first trimester decreases the risk of recurrence of miscarriage in patients with RPL (NP2). No conclusions can be drawn regarding the molecules, route of administration the optimal doses, to establish a recommendation given the heterogeneity of the studies" Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Cochrane Database Syst Rev 2008	We acknowledge the review of Haas 2008, which states that "In a subgroup analysis of four trials involving women who had recurrent miscarriages (three or more consecutive miscarriages; four trials, 225 women), progestogen treatment showed a statistically significant decrease in miscarriage rate compared to placebo or no treatment (Peto OR 0.39; 95% CI 0.21 to 0.72). However, these four trials were of poorer methodological quality." Given the poor quality of the data, there is no unequivocal opinion based on evidence only. We assume the French society made other considerations in formulating a recommendation, but the ESHRE GDG confirms its statement that there is insufficient evidence to recommend the use of progesterone to improve LBR in women with RPL and luteal phase insufficiency.
	Section 17.6	48	this recommendation is in contradiction with the one above?	The two recommendations are for two different groups. Vaginal progesterone may improve live birth rate in women with 3 or more pregnancy losses and vaginal blood loss in a subsequent pregnancy. Therefore, it is only advised in a subsequent pregnancy with blood loss, after 3 or more miscarriages in women with unexplained pregnancy loss.

Shehnaaz Jivraj	Section 17.6 49	Since the publication of the PRISM trial, in my RPL clinic, many women are choosing to start vaginal progesterone before any vaginal bleeding has occurred rather than waiting for any vaginal bleeding before being started on vaginal progesterone. This practice is becoming more common. The guideline has addressed the use of vaginal progesterone in the presence of vaginal bleeding. However, clinicians across the UK and Europe will benefit from ESHRE's standpoint on this. I believe this should be clarified that there is no evidence to suggest that starting vaginal progesterone before any bleeding improves pregnancy outcome (PROMISE trial) but starting vaginal progesterone once bleeding has started, has been shown to improve pregnancy outcome in a large RCT (PRISM trial)	This was clearly stated in the recommendation, that vaginal progesterone may improve live birth in women with 3 or more pregnancy losses and vaginal blood loss based on the PRSIM and PROMISE trial

Zeev Shoham	Section 17.6 50	I would like to suggest that ESHRE RPL guideline would be updated to giving Dydrogesterone a strong recommendation based on the followings: El-Zebdeh 2005 paper which was not mentioned. This is a randomized controlled study. Dydrogesterone had a significantly lower miscarriage rate compared with the control (no treatment) group (13.4% vs 29%; p=0.028) El-Zibdeh MY. Dydrogesterone in the reduction of recurrent spontaneous abortion. Steroid Biochem Mol Biol 2005;97(5):431–434. There are two meta-analyses that demonstrate the efficacy of Dydrogesterone in reducing the risk of RPL. These were not mentioned in the guidelines. 1. Carp H. Gynecol Endocrinol 2015;31(6):422–430. • There was a significant reduction in the miscarriage rate with dydrogesterone 2. Haas DM, et al. Cochrane Database Syst Rev 2019;(11):CD003511. • There was a numerical decrease in the miscarriage rate with progestogen treatment (not significant); however, the two studies showing a clear reduction were those with treatment with Dydrogesterone (El-Zibdeh 2005 and Kumar 2014). Finally, patient convenience should be taken into consideration. Oral dydrogesterone (convenient, easier to administer)	Please See comment 28:

		versus vaginal application (discharge and irritation, bleeding, interference with intercourse).	
Elena Kostova	General 51	Thank you very much for the opportunity to review this updated guideline. I would like to congratulate the Early Pregnancy Guideline Development Group for this very important and comprehensive work. Well done!	Thank you for this comment
	General 52	Throughout the document the word "recent" is often used referring to studies that are not recent anymore, so this should be adjusted (a couple of examples are provided below).	Thank you for this comment; the word recent was removed
	Chapter 16 53	An update of the Cochrane review on antioxidants for male subfertility, Smits et al 2019 has just been published: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007411.pub5/full The guideline refers to the review several times, so these sections should be checked and adjusted accordingly. An example is provided below.	Thank you for this comment. The updated reference was added in the guideline
	Section 7.2 54	Is there really nothing in the literature about insulin insensitivity and diabetes as risk factors for RPL?	According to the literature search update, no relevant studies about insulin resistance and diabetes as risk factors for RPL were found
	Section 10.2 55	Is it common to include prognostic tools as a "treatment option" in guidelines?	We consider that prognostic tools are a complementary strategy to improve care for patients, therefore we add them in the treatment section.
	Section 12.2 56	Why recommend treatment for APS RPL with 3 or more RPL (when it is recommended to test for APS with 2 or more RPL)?	We understand that this is counterintuitive, however, the prognosis of recurrent miscarriage after two losses in APS is better than after three losses. There is no evidence showing that the use of an anticoagulant treatment for women with APS and with two or more pregnancy losses improves LBR; The existing evidence is only for women with APS and 3 or more pregnancy losses;

	Part B	57	This is a great summary of how care should be organized. Is there data on how many such clinics exists in practice (in Europe)? Unfortunately, most patients will never receive this level of care. Most countries don't offer specialized tailored care for women/couples with RPL.	Thank you for your comments. Unfortunately, we don't have information about the number of dedicated RPL clinics across Europe or the quality of service that is currently provided. This guideline presents a set of recommendations, but we recognise that they may not always be achievable.
	Section 1.2	58	The statement "stress is associated with RPL", as mentioned, is based on (small) studies with many limitations. Perhaps the wording should be less strong (ie might be, may be associated etc)	The strong recommendation is for informing, reassuring couples, not for the effect of stress. We have stated that the association between stress and RPL is weak and there is no evidence to state that stress causes RPL, hence we decided to leave wording as it is.
	Chapter 3	59	This sentence is somewhat confusing: "complete pregnancy history (i.e. the number of previous pregnancy losses, live births and their sequence) is more informative than only the total number of preceding pregnancy losses and live births". Both sounds very similar so probably it needs some clarification.	The statement "woman's exact pregnancy history and female age " is replaced by "woman's age and her complete pregnancy history, including number of previous pregnancy losses, live births and their sequence".
		60	There is a full stop missing after "could be considered".	Thank you for this comment
	Chapter 11	61	You could mention the Cochrane review by Cornelisse et al "Preimplantation genetic testing for aneuploidies (abnormal number of chromosomes) in in vitro fertilisation" (https://doi.org/10.1002/14651858.CD005291.pub3)	This Cochrane systematic review does not include women with RPL. The only study with women with RPL mentioned in this review is not yet published (Effects of PGS in Infertile Female Patients With RPL).
		62	. after "Evidence" should be deleted	Thank you for this comment
	Section 5.2 and 12.2	63	It is recommended that women are screened for APS after two losses, while treatment is recommended after 3 losses (due to lack of published evidence). In practice this recommendation will be ambiguous. If a woman is screened for APS after two losses and the tests confirm she fulfils the criteria for APS, GDG recommends no treatment? Why not give a conditional recommendation to offer treatment for APS after 2 RPL?	We understand that this is counterintuitive, however, the prognosis of recurrent miscarriage after two losses in APS is better than after three losses. There is no evidence showing that the use of an anticoagulant treatment for women with APS and with two or more pregnancy losses improves LBR; The existing evidence is only for women with APS and 3 or more pregnancy losses.

		64	The word “good” is too informal. Do you mean “good quality”?	This was corrected: "Good quality trials"
	General	65	I would remove “recently” as the review cited was published in 2013	The word recently was removed
	Section 14.2	66	The recommendation states there is insufficient evidence, but the review reports on 5 RCTs and a significant difference. Looking at the review, it is clear that the effect is lost when a sensitivity analysis restricted to good quality trials is performed. Perhaps worth adding this information here to clarify. I see a sentence that touches upon this below (3637).	"but power of the meta-analysis was limited due to the small number of studies and methodological and clinical heterogeneity" was replaced by " but when a sensitivity analysis restricted to good-quality trials was performed and two studies of weaker methodological quality were removed, there was no longer a statistically significant benefit (RR 0.74; 95% CI 0.44 - 1.23, three RCTs)"
	Section 14.4 & 14.5	67	It seems the evidence for some recommendations has not been assessed consistently. For example, here it is recommended that bromocriptine be used based on a trial with 24 subjects, while above (3700) a recommendation was not made due to limited evidence (a trial with 21 subjects which is quite comparable). If there are other reasons (ie risk of bias) this should be mentioned.	We understand the reviewer's point. Since no relevant study was found in the update of literature search, and the GDG decided to keep it as it in the old guideline version and also to remove the recommendation on the use of bromocriptine for RPL associated with hyperprolactinemia given the small sample size.
	Section 15.1	68	In many countries surrogacy is not allowed by law, so “depending on the regulations” etc could be added here	"if permitted by local regulations" is added to the sentence
		69	a more recent study” refers to a study from 2010	removed
	Chapter 16	70	A can see that the text here is taken from the abstract of Mansour Ghanaie et al. 2012. Unfortunately, I don’t understand where the numbers are coming from. I also looked at Table 2 and it is still unclear to me. Also, I would not use the word “developed” a miscarriage.	Thank you for this comment. It was adapted in the text and numbers were corrected
	Chapter 16	71	you could refer to the Cochrane review “Advanced sperm selection techniques for assisted reproduction” https://doi.org/10.1002/14651858.CD010461.pub3 (it includes the Miller study)	Thank you for this comment. The Cochrane review was included in the text

	Chapter 16	72	An update of the Cochrane review on antioxidants for male subfertility has just been published https://doi.org/10.1002/14651858.CD007411.pub5. This section needs to be updated accordingly.	Thank you for alerting us of this update. It was included in the text
	Section 17.6	73	Formulated as such, does the recommendation state that vaginal progesterone should only be offered to women with bleeding and 3 or more RPL? Why is that? NICE recommends vaginal progesterone be offered to anyone with early pregnancy bleeding with at least 1 previous miscarriage https://www.nice.org.uk/guidance/ng126/chapter/Recommendations#managementof-miscarriage Shouldn't the guidelines be aligned with each other on such an important recommendation? Also, Coomarasamy et al. 2019 shows progesterone could be beneficial for 1 or 2 previous miscarriages (subgroup analysis)	This recommendation was made based on the available evidence (Coomarasamy et al 2020) which shows that there is no significant difference after progesterone treatment in women with 1 or 2 previous pregnancy losses. This large RCT by Coomarasamy et al. (PRISM) was published after completion of the NICE guideline which could therefore not include the information from the PRISM trial
	Future research	74	Study endometrial decidualization and senescence	Added in the recommendations for research in RPL section
		75	Study prognostic value of ANA antibodies and potential treatment	Added in the recommendations for research in RPL section
		76	Study potential involvement of insulin resistance in RPL	Added in the recommendations for research in RPL section
		77	Study the effectiveness and safety of metformin for RPL and glucose metabolism defects	Added in the recommendations for research in RPL section
Lisa Lashley	General	78	We would like to thank and compliment the committee for updating this guideline. The document represents a good and complete overview of all recommendations	Thank you for this comment
	Guideline implementation	79	Please mention the suggested method of implementation of the current recommendations in international daily care	Please check the Guideline implementation strategy in the manual for ESHRE guideline development: https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Guideline-development-process.

	Chapter 1	80	Please add: The risk of miscarriage is increasing with advancing paternal age. Significant effects are shown with age> 40yrs [du Fosse et al, Hum Reprod Update 2020]	the following sentence was added to the text: "A meta-analysis investigating the association of advanced paternal age with spontaneous miscarriage during the first trimester of pregnancy showed that there is an increased risk for miscarriage for male age categories 30-34, 35-39 and 40-44 and this risk was higher for the ≥45 age category (du Fossé et al. 2020)."
	Chapter 2	81	Please specify that both the females, as the males are advised to stop smoking, as paternal smoking of >10 cigarettes per day in the preconception period was found to be associated with an increased risk of pregnancy loss, after adjustment for maternal smoking status [du Fosse et al, F&S reviews 2021]	The following sentence was added to the text: "In a meta-analysis of 8 studies, paternal smoking of >10 cigarettes per day in the preconception period was found to be associated with an increased risk of pregnancy loss, after adjustment for maternal smoking status (1–10 cigarettes per day, 1.01; 95% confidence interval [CI], 0.97–1.06; 11–19 cigarettes per day, 1.12; 95% CI, 1.08–1.16; ≥20 cigarettes per day, 1.23; 95% CI, 1.17–1.29) [du Fossé, 2021 #2689]."
	Chapter 3	82	The recommendation 'The GDG recommends to base prognosis on woman's exact pregnancy history and female age' is not clear. Please change into 'The GDG recommends to base prognosis on the woman's age and her complete pregnancy history, including number of previous pregnancy losses, live births and their sequence'	Thank you for this comment. This was adapted in the document.
	Chapter 8.2	83	For several investigations with no or uncertain prognosis or treatment the recommendations in the guideline are presented by 'could be performed for explanatory purposes (e.g. genetic analysis of pregnancy tissue and ANA). We would advise to change new recommendations with this level of uncertainty in equal phrasing. Thus, 2D ultrasound could be performed in women with RPL to rule out adenomyosis and Sperm DNA fragmentation in couples with RPL could be performed for explanatory purposes	We agree that extra phrasing helps for clarity. The implementation strategy (what would/ could etc means) is published as an annex in the final version of this guideline

	Chapter 9	84	In the justification of the recommendation for sperm DNA testing, we advise to add a consideration on the following: many different assays and protocols exist on sperm DNA fragmentation testing, and it has not been established which test is most informative and most reliable. We believe that at this moment, first a standardized and validated test should be developed, before advising to perform this in daily routine	Thank you for this comment. A statement was added in the justification: It has not been established which test is most informative and most reliable. Therefore, the GDG recommend assessing sperm DNA fragmentation for diagnostic purposes using a validated test in order to screen for male factor in couples with RPL.
	Chapter 3	85	See remark p37 (comment 82)	Thank you for this comment. This was adapted in the document.
	Chapter 10.2	86	We would advise not to refer to the model by Lund et al or Brigham et al. First, the Lund model was not designed for individual risk assessment and the study does not discriminate between unexplained and explained RPL. The model of Brigham et al showed overestimation, too extreme predictions and poor discriminative ability upon external validation [Youssef et al Human Reproduction 2022].	The GDG decided to keep the Lund and Brigham tools in the evidence description text but not to recommend using those two models as prognostic tools. Youssef et al 2022 has been published after our literature search. But their conclusions about the existing Brigham model has been mentioned quite extensively in the justification section of this chapter. The study was included in the guideline and the text was adapted accordingly.
	Section 15.1	87	We do not agree with this recommendation. Yes, there is a difference in the effect of septum resection in observational studies versus the TRUST trial. However, the TRUST is the only study with the highest level of methodological evidence and based on this study septum resection, should NOT be recommended. Moreover, the recent large cohort study by the same authors concluded as well that septum resection is not effective but is associated with increased financial costs and possible higher complication risk.	On one hand, a large meta-analysis of retrospective studies (Krsihnan et al 2021) showed that septum resection has a beneficial effect on the miscarriage rate (but not LBR). On the other hand, only one small RCT shows no benefit from using it. Therefore, the recommendation is changed based on this single small RCT and the GDG recommended to not use the hysteroscopic septum resection to reduce the rate of pregnancy loss. Larger randomized controlled trials are still needed to demonstrate a clear benefit of hysteroscopic septum resection

	General	88	This recommendation should be changed and specified. First, IVF or ICSI is not routinely performed in patients >35yrs. Therefore, the recommendation should state that it is only for patients >35yrs with indication for ICSI treatment. Secondly, sperm selection by PICSI was shown effective for another population, not specifically for the RPL population. Therefore, this recommendation is not correct	In the more recent mechanistic paper from the HabSelect study (West et al, 2022,) a subgroup of patients was investigated with a primary outcome of predicted miscarriage using parsimonious selection to enable the development of models for exploring and explaining data trends. The GPP has been changed as following: "Sperm selection by PICSI may be considered for older women (>35y) who have experienced RPL. "
Nicolas Garrido	Chapter 16	89	It seems that many of the papers /affirmations are on papers studying just miscarriage, not recurrent pregnancy loss. These are different topics. Not every couple with a miscarriage will have a second. It's what one can interpret from reading. I would recommend being careful on this, since can be misleading for those looking for info on RPL.	Most of the studies included in the SoF tables are studies on RPL women. Where it is not the case, the quality of evidence is lowered, and this was clearly stated in the evidence description or the justification. We accept this is a difficulty. Particularly, since there is little evidence for male factors linked to recurrent pregnancy loss, we believe that the area should be extended in this instance to include papers on sporadic pregnancy loss as in the previous 2017 guideline. We have included a proviso in the justification of Chapter 16. Sperm selection, to alert readers to this. Since this emerging area of interest has less evidence than other areas in the guideline, studies focused on sporadic pregnancy loss have also been included

	Chapter 16 90	I stressed out that the paper from Miller et al. was not correctly calculated, and no mention is made. Moreover, this paper is within a bigger Cochrane review (Lepine et al,, 2019), that modulates the effect's size reported, and also evaluated the quality of the evidence. I have not repeated the stats, but miscarriage seems to still remain significant, but less, if you only analyse pregnant patients (sample size is lower). You should not evaluate per intention to treat a secondary outcome that can only happen if a specific previous outcome (pregnancy) is achieved That said, the message from this paper, in any case is 1. Live birth rates are not affected (which is the main endpoint for our patients) 2. In any case, it avoids miscarriage, but nothing is evaluated regarding RPL. This is not studied.	As before in comment 88, in the more recent mechanistic paper from the HabSelect study (West et al, 2022,) a subgroup of patients was investigated with a primary outcome of predicted miscarriage using parsimonious selection to enable the development of models for exploring and explaining data trends. The Cochrane review (Lepine et al. 2019) was included in the text and the GPP has been changed as following: "Sperm selection by PICSI may be considered for older women (>35 y) who have experienced RPL"
Peter Bisschop	Section 7.1 91	Please note that TPOAb are also antibodies against the thyroid gland	This was corrected in the text: "in women with RPL, thyroid peroxidase autoantibodies (TPOAb) are mostly studied, and shown to be more relevant than other antibodies against the thyroid gland (Marai et al., 2004) "
	Section 7.1 92	Does "a more recent.." refer to (Ticoni et al. 2011)? If yes, please consider rephrasing	This was corrected in the text.
	Section 7.1 93	I propose to change 'Abnormal TSH and TPO antibody levels should be followed up by …' to 'Abnormal TSH levels should be followed up by …', because a normal TSH rules out thyroid dysfunction.	This was changed in the text as following: "Abnormal TSH levels should be followed up by T4 testing in women with RPL."
	Section 7.1 94	Does 'No' association in the table imply that it has sufficiently been studied and no association has been shown or can it also mean that it has not sufficiently been studied?	From the known studies included in our guideline, no association has been found. This was clarified in the table

	Section 14.1	95	For the recommendation on trimester specific upper limits for TSH it is my opinion that the recommendation by the ATA 2017 (Alexander et al.) is better supported by the literature than the ETA 2014 recommendation. The ATA 2017 recommendation is also supported by three Dutch cohort studies: 1] Benhadi 2007, 2] Medici 2012 and Korevaar 2017, 3] Pop 2018	ATA 2017 is incorporated in the text, and we refer to the conclusions of this study.
	Section 14.1	96	Please consider rephrasing in view of the recent RCT's mentioned in lines 3585-3590	Thank you for this comment. This was adapted in the text.