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ESHRE PAGES

ESHRE guideline: recurrent pregnancy loss: an update in 2022†

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STUDY QUESTION: What are the updates for the recommended management of women with recurrent pregnancy loss (RPL) based on the best available evidence in the literature from 2017 to 2022?

SUMMARY ANSWER: The guideline development group (GDG) updated 11 existing recommendations on investigations and treatments for RPL, and how care should be organized, and added one new recommendation on adenomyosis investigation in women with RPL.

WHAT IS KNOWN ALREADY: A previous ESHRE guideline on RPL was published in 2017 and needs to be updated.

STUDY DESIGN, SIZE, DURATION: The guideline was developed and updated according to the structured methodology for development and update of ESHRE guidelines. The literature searches were updated, and assessments of relevant new evidence were performed. Relevant papers published between 31 March 2017 and 28 February 2022 and written in English were included. Cumulative live birth rate, live birth rate, and pregnancy loss rate (or miscarriage rate) were considered the critical outcomes.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Based on the collected evidence, recommendations were updated and discussed until consensus was reached within the GDG. A stakeholder review was organized after the updated draft was finalized. The final version was approved by the GDG and the ESHRE Executive Committee.

MAIN RESULTS AND THE ROLE OF CHANCE: The new version of the guideline provides 39 recommendations on risk factors, prevention, and investigation in couples with RPL, and 38 recommendations on treatments. These includes 62 evidence-based recommendations—of which 33 were formulated as strong recommendations and 29 as conditional—and 15 good practice points. Of the evidence-based recommendations, 12 (19.4%) were supported by moderate-quality evidence. The remaining recommendations were supported by low (34 recommendations; 54.8%), or very low-quality evidence (16 recommendations; 25.8%). Owing to the lack of evidence-based investigations and treatments in RPL care, the guideline also clearly mentions those investigations and treatments that should not be used for couples with RPL.

LIMITATIONS, REASONS FOR CAUTION: The guidelines have been updated; however, several investigations and treatments currently offered to couples with RPL have not been well studied; for most of these investigations and treatments, a recommendation against using the intervention or treatment was formulated based on insufficient evidence. Future studies may require these recommendations to be revised.

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WIDER IMPLICATIONS OF THE FINDINGS: The guideline provides clinicians with clear advice on best practice in RPL, based on the best and most recent evidence available. In addition, a list of research recommendations is provided to stimulate further studies in RPL. Still, the absence of a unified definition of RPL is one of the most critical consequences of the limited scientific evidence in the field.

STUDY FUNDING/COMPETING INTEREST(S): The guideline was developed and funded by ESHRE, covering expenses associated with the guideline meetings, with the literature searches and with the dissemination of the guideline. The guideline group members did not receive payment.

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Key words: recurrent pregnancy loss / ESHRE / guideline / evidence-based / recurrent miscarriage / treatment / diagnosis / GRADE

WHAT DOES THIS MEAN FOR PATIENTS?

This European updated guideline looks at how best to care for people who have experienced recurrent pregnancy loss (RPL) based on the recent evidence available.

RPL is defined as the loss of two or more pregnancies, and it affects around 1–2% of couples. The guideline states that the emotional impact needs to be considered, and the preferences in terms of the need of supportive care may differ in men and women.

The guidance explains that providing people with information is essential, and that a specialist outpatient clinic should offer investigations, support and, if possible, treatment. Staff should be experienced and should have appropriate listening skills. The guidance stresses that it should be made clear from the start that there may not always be relevant treatments for RPL.

The guideline explains that age is a key factor in RPL, which is more common in women who are over 40 years old. It gives the lifestyle advice that should be provided to men and women and explains that there is no evidence that stress is a direct cause of pregnancy loss. It details the investigations and interventions, which should—and should not—be carried out, and gives some recommendations for research, making it clear that in many areas there is limited evidence and an urgent need for further studies. An updated patient leaflet based on the guideline is available on the ESHRE website (https://www.eshre.eu/Guidelines-and-Legal).

Introduction

What is the recommended management of women with recurrent pregnancy loss (RPL) based on the best available evidence in the literature? This question was addressed in the ESHRE guideline on RPL, published in 2017, providing 77 recommendations answering 18 key questions on investigations and treatments for RPL, and on how care should be organized (The ESHRE Guideline Group on RPL, 2018) . The need for this guideline is evident from the 365 citations of the document recorded at the time of writing.

Between 31 March 2017 and 28 February 2022, 1419 papers were added to PUBMED/MEDLINE referring to 'recurrent pregnancy loss' or 'recurrent miscarriage'. Considering the importance of up-to-date clinical guidance, an investigation was carried out on whether these 1419 papers showed data or provide insights that would require a revision of the recommendations included in the 2017 version of the ESHRE guideline on RPL.

This document outlines the amendments to the recommendations formulated in 2017, based on emerging data.

A full list of the current recommendations for management of women with RPL, including the 2017 recommendations that were not modified, is available in Supplementary Table SI. A pictorial summary can be found in Supplementary Fig. S1. The full version of the ESHRE guideline on RPL, including up-to-date data and recommendations, is available on the ESHRE website (https://www.eshre.eu/Guidelines-and-Legal).

The overall aim of the guideline on RPL was, and is, to supply healthcare providers with the best available evidence for investigation and treatment of women with RPL. RPL is defined as the loss of two or more pregnancies. It excludes ectopic pregnancy and molar pregnancy. The guideline provides an overview of suggested treatments for RPL, and which of those are recommended. Furthermore, recommendations are made on the investigations that could be helpful to identify the origin of the pregnancy losses and possible therapeutic targets. In addition, recommendations are written regarding the organization of care for couples faced with RPL.

Materials and methods

In line with standard procedures, ESHRE guidelines are revised at predefined intervals and updated where needed. Four years after publication of the ESHRE Guideline on RPL, the literature searches in PUBMED/MEDLINE and the Cochrane library were repeated, limiting the search results to papers published after the previous inclusion deadline (31 March 2017) up to February 2022.

The guideline development group (GDG) members revised the collected references and papers, and assessed whether they were a relevant addition to the guideline, keeping in mind the hierarchy of evidence.

For each of the topics and key questions, new data were inserted in the guideline text and, where relevant, also in the summary of findings tables. Modifications were labelled to highlight changes. The updated guideline was published for stakeholder review between 28 March and 9 May 2022. Comments were evaluated and addressed where relevant.

Results

Based on the papers and data retrieved from the literature search, there was no need to revise the definition of RPL or the proposed terminology, nor the recommendations for the organization of care, and risk factors and health behaviour modifications.

Investigations in RPL

Recommendations for investigation in RPL that have been modified in line with recent data are summarized in Table I.

In the recommendations on immunological screening, a small amendment was made to the recommendation on HLA determination. While HLA is not recommended, consistent with the 2017 recommendation, the specific alleles that could be tested in very specific and defined circumstances were extended to include HLA-DRB1*07, based on the study of Thomsen *et al.* (2021).

Based on recent data showing that adenomyosis seems to be associated with higher rates of pregnancy loss, even if not RPL (Younes and Tulandi, 2017; Stanekova *et al.*, 2018), the GDG considered it relevant to emphasize this and added a recommendation for 2D ultrasound to rule out adenomyosis. There were no further amendments to the recommendations on anatomical investigations in the diagnosis of RPL.

While the 2017 guideline referred to a lack of research into the contribution of male factors in RPL, the update of the literature revealed several new publications, including a few important reviews and meta-analyses (Du Fossé *et al.*, 2020; Pu *et al.*, 2020; Li *et al.*, 2021; West *et al.*, 2022), even if not all specifically investigating RPL but focusing on miscarriage. Based on the new evidence (Du Fossé *et al.*, 2022), the suggestion to assess lifestyle factors as a good practice point (GPP) was rephrased to an evidence-based recommendation for assessing lifestyle in the male factor and including his age. Sperm DNA fragmentation, previously suggested for explanatory purposes based on indirect evidence, it is now to be considered for diagnostic purposes. A complicating factor in sperm DNA fragmentation testing is that many different methods and protocols exists, and it has not been established which test is most informative in which clinical scenario. The data supporting this update were provided by the Hyaluronic Acid Binding Sperm Selection (HABSelect) trial (Miller *et al.*, 2019; West *et al.*, 2022).

While published data were assessed and summarized for the topics on screening for genetic factors, thrombophilia screening, and screening for metabolic/endocrinological abnormalities, they did not require any amendments to the recommendations previously published.

Prognosis and treatment

The eight recommendations for prognosis and treatment in RPL that were updated in 2022 as compared to 2017 are provided in Table II.

Assessing the individual prognosis in couples with RPL in a next pregnancy and in the long term is an essential part of the management of couples and allows them to decide for or against further pregnancy attempts. In a difficult research area, a new prognostic tool to predict a live birth in the next pregnancy has been developed and validated internally using the large Denmark national database (Kolte *et al.*, 2021). While this model still has to be externally validated, it is considered to be the better tool, and the recommendation was adapted accordingly.

Furthermore, this register-based study showed that a woman's age and the exact and complete pregnancy history are important in estimating the chance of live birth in the next pregnancy, much more than the total number of pregnancy losses and live births (Kolte *et al.*, 2021). Therefore, it was recommended to base a prognosis on the woman's age and her complete pregnancy history, including number of previous pregnancy losses, live births, and their sequence.

With regards to therapeutic interventions, the most recent data supported or strengthened the 2017 recommendations, with only few published data requiring a change in clinical management.

While the value of levothyroxine therapy in euthyroid women with thyroid peroxidase antibodies was still under investigation in 2017, two trials, the Thyroid Antibodies and Levothyroxine (TABLET) trial (Dhillon-Smith *et al.*, 2019) and the T4life trial (Van Dijk *et al.*, 2022) showed no increase in live birth rates (LBR) in

Table I Overview of the recommendations for investigation in RPL that have been updated in 2022 as compared to 2017.

Recommendation in 2017	Recommendation in 2022
Human Leukocyte Antigen (HLA) determination in women with RPL is not recommended in clinical practice. Only HLA class II determination (HLA-DRB1*15:01 and HLADQB1*05:01/05:2) could be considered in Scandinavian women with secondary RPL after the birth of a boy, for prognostic purposes. (Conditional; ⊕⊕◯◯)	**Human Leukocyte Antigen (HLA) determination in women with RPL is not recommended in clinical practice. Only HLA class II determination (HLA-DRB1*15:01, HLA-DRB1*07, and HLA-DQB1*05:01/05:2) could be considered in Scandinavian women with secondary RPL after the birth of a boy, for prognostic purposes. (Conditional; ⊕⊕◯◯)**
None	**All women with RPL could have 2D ultrasound to rule out adenomyosis. (Conditional; ⊕⊕◯◯)**
In the male partner, it is suggested to assess lifestyle factors (smoking, alcohol consumption, exercise pattern, and body weight). (GPP)	**In couples with RPL, it is recommended to assess lifestyle in the male partner (paternal age, smoking, alcohol consumption, exercise pattern, and body weight). (Strong; ⊕⊕◯◯)**
Assessing sperm DNA fragmentation in couples with RPL can be considered for explanatory purposes, based on indirect evidence. (Conditional; ⊕⊕◯◯)	**Assessing sperm DNA fragmentation in couples with RPL could be considered for diagnostic purposes. (Conditional; ⊕⊕⊕◯)**

RPL, recurrent pregnancy loss.

Table II Overview of the recommendations for prognosis and treatment in RPL that have been updated in 2022 as compared to 2017.

Recommendation in 2017	Recommendation in 2022
The Guideline Development Group (GDG) recommends to base prognosis on the number of preceding pregnancy losses and female age. (Strong; ⊕⊕⊕◯)	**The Guideline Development Group (GDG) recommends to base prognosis on woman's age and her complete pregnancy history, including number of previous pregnancy losses, live births, and their sequence. (Strong; ⊕⊕⊕◯)**
Prognostic tools (Lund, Brigham) can be used to provide an estimate of subsequent chance of live birth in couples with unexplained RPL. (GPP)	**Prognostic tools (Kolte & Westergaard) can be used to provide an estimate of subsequent chance of live birth in couples with RPL. (GPP)**
There is insufficient evidence to support treatment with levothyroxine in euthyroid women with thyroid antibodies and RPL outside a clinical trial. (Conditional; ⊕⊕◯◯)	**Euthyroid women with thyroid antibodies and RPL should not be treated with levothyroxine. (Strong; ⊕⊕⊕◯)**
Whether hysteroscopic septum resection has beneficial effects (improving live birth rates, and decreasing miscarriage rates, without doing harm), should be evaluated in the context of surgical trials in women with RPL and septate uterus. (Conditional; ⊕◯◯◯)	**Only one small RCT showed no benefit of using hysteroscopic septum resection to reduce the rate of pregnancy loss. (Conditional; ⊕◯◯◯)**
Sperm selection is not recommended as a treatment in couples with RPL (GPP)	**There is no evidence to support sperm selection by physiological intracytoplasmic sperm injection (PICSI) in couples with RPL. (Conditional; ⊕◯◯◯)**
Intravenous immunoglobulin (IvIg) is not recommended as a treatment of RPL. (Strong; ⊕⊕◯◯)	**The use of repeated and high doses of IvIg very early in pregnancy may improve live birth rate in women with four or more unexplained RPL. (Conditional; ⊕⊕◯◯)**
Vaginal progesterone does not improve live birth rates in women with unexplained RPL. (Conditional; ⊕⊕⊕◯)	**Vaginal progesterone may improve live birth rate in women with three or more pregnancy losses and vaginal blood loss in a subsequent pregnancy (Conditional; ⊕⊕⊕◯)**
There is insufficient evidence to recommended G-CSF in women with unexplained RPL. (Conditional; ⊕⊕◯◯)	**There is no evidence to recommended G-CSF in women with unexplained RPL. (Strong; ⊕⊕⊕◯)**

RPL, recurrent pregnancy loss.

euthyroid women with thyroid antibodies and RPL using the treatment as compared to placebo, and hence the recommendation was amended accordingly.

In relation to hysteroscopic septum resection in the context of RPL, the call in 2017 for more data and trials resulted in a single small randomized controlled trial (RCT) showing no benefit of using

hysteroscopic septum resection to reduce the rate of pregnancy loss (Rikken *et al.*, 2021). It was considered relevant to update the recommendation, but impossible to recommend for or against hysteroscopic septum resection based on the limited data, and hence a very transparent recommendation was formulated allowing for consideration and relevant patient counselling.

Previous data showing that ICSI with hyaluronan-selected sperm (so-called physiological ICSI or PICSI) decreased the incidence of pregnancy loss were confirmed by the recent HABSelect trial (Miller *et al.*, 2019; West *et al.*, 2022), specifically in women above 35 years old. Sperm selection was not recommended in 2017 and, while the results of the HABSelect trial could not be ignored, there was a consensus that more evidence is needed to recommend this treatment for couples with RPL but also to reformulate the recommendation, stating that there is no evidence in support of the treatment rather than stating it is not recommended.

Recently, a high-quality RCT found that intravenous immunoglobulin given in repeated doses (400 mg/kg) for five consecutive days very early in pregnancy to women with four or more unexplained pregnancy losses increased the LBR significantly (OR 2.60; 95%CI 1.15–5.86) (Yamada *et al.*, 2022). This study was found sufficiently relevant to adapt the recommendation and suggesting intravenous immunoglobulin for a specific RPL group, mirroring the study population.

While the data by Coomarasamy *et al.* (2015) from the Progesterone in Recurrent Miscarriages (PROMISE) trial supported the recommendation against vaginal progesterone in 2017, the study group published additional data on the topic, i.e. the Progesterone In Spontaneous Miscarriage (PRISM) study (Coomarasamy *et al.*, 2019) and a meta-analysis of the PROMISE trial and the PRISM study (Coomarasamy *et al.*, 2020), and concluded that the risk ratio (RR) for subsequent live birth in progestogen-treated women with a minimum of three previous pregnancy losses and current bleeding was significantly increased (RR = 1.28, 95% CI 1.08–1.51; rate difference 15%). The recommendation was adapted accordingly.

Discussion

The new version of the ESHRE guideline on RPL aims to supply healthcare providers with the data of recently published evidence for the investigation and treatment of women with RPL.

All modified or added recommendations in the guideline were formulated after an assessment of the best and recent available evidence in the literature up to February 2022 and discussion within the GDG, taking into account the balance of benefits versus harms, patients' preferences, clinicians' expertise, and resource use. The updated guideline includes 77 recommendations, comprising 62 evidence-based recommendations—of which 33 were formulated as strong recommendations and 29 as conditional—and 15 GPPs. Of the evidence-based recommendations, 12 (19.4%) were supported by moderate-quality evidence. The remaining recommendations were supported by low (34 recommendations; 55.8%), or very low-quality evidence (16 recommendations; 25.8%). The evidence level of the recommendations has slightly increased compared to the initial guideline in 2017, with more recommendations supported by good-quality evidence, mainly because of more published trials in the field. Still, owing to the lack of evidence-based investigations and treatments in RPL care, the guideline also clearly mentions investigations and treatments that should not be used for couples with RPL.

The update of the literature failed to find evidence for a definition of RPL, and this is one of the most important consequences of the limited evidence. As in 2017, providing an evidence-based definition was not feasible. Furthermore, the update of the literature did not find data on when most of the investigations and/or treatments should be started, whether they can be postponed until after a next pregnancy loss, and whether the care of couples with primary versus secondary, or consecutive losses should be approached differently. For most investigations and treatments, the decision on when to start the investigations or treatment will have to be decided by the doctor and the couple, as the result of shared decision-making, and be compliant with available resources.

Some recommendations (four recommendations) specifying investigations and treatments to be applied in a research context rather than routine clinical practice are still formulated in this updated version of the guideline because of the lack of evidence.

Based on the recent evidence, some investigations and/or treatments have been shown to have no benefit or to be ineffective for increasing the chance of a live born baby in couples with RPL or were shown to have significant adverse events. The updated recommendations clearly mention those investigations and/or treatments that should not be used for couples with RPL to avoid the research wastage in RPL care. For some other recommendations, the quality of evidence is low to very low and future research is still needed.

Some GPPs were amended to formulate evidence-based recommendations. However, an evidence-based practice in RPL is not yet feasible as studies are lacking. The current guideline exposes areas where more research is necessary and a research agenda has been developed, with the aim of stimulating research on RPL and, more specifically, on the questions in urgent need of an answer. While awaiting evidence and evidence-based recommendations, GPPs are still provided to support clinicians in routine practice.

Supplementary data

Supplementary data are available at *Human Reproduction Open* online.

Data availability

The full guideline and supporting data (literature report, evidence tables) are available on https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Recurrent-pregnancy-loss.

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Authors' roles

M.G. chaired the Guideline Development Group and hence fulfilled a leading role in collecting the new evidence, rewriting the updated chapters, and dealing with reviewer comments. N.V. and S.M. as methodological experts, performed all literature searches to update the guideline, provided methodological support, and coordinated the guideline development. All other authors, listed in alphabetical order, as Guideline Group members, contributed equally to the manuscript, by synthesizing the updated evidence, rewriting the updated parts of the guideline, and discussing the amendments of the recommendations until consensus within the group was reached.

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Conflict of interest

O.B.C. reports being a member of the executive board of the European Society for Reproductive Immunology and has received payment for honoraria for giving lectures about RPL in Australia in 2020. M.G. reports unconditional research and educational grant received by the Centre for Reproductive Medicine, Amsterdam UMC from Guerbet, Merck, and Ferring, not related to the presented work. S.L. reports position funding from EXAMENLAB Ltd. and ownership interest by stock or partnership of EXAMENLAB Ltd (C.E.O). S.Q. reports being a deputy director of Tommy's National centre for miscarriage research, with payment received by the institution for research, staff time, and consumables for research. H.S.N. reports grants with payment to institution from Freya Biosciences ApS, Ferring Pharmaceuticals, BioInnovation Institute, the Danish ministry of Education, Novo Nordic Foundation, Augustinus Fonden, Oda og Hans Svenningsens Fond, Demant Fonden, Ole Kirks Fond, and Independent Research Fund Denmark and speakers' fees for lectures from Ferring Pharmaceuticals, Merck A/S, Astra Zeneca, IBSA Nordic, and Cook Medical. She also reports to be an unpaid founder and chairman of a maternity foundation. M.-L.v.d.H. received small honoraria for lectures on RPL care. The other authors have no conflicts of interest to declare.

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