ESHRE guideline: recurrent pregnancy loss

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Submitted on January 4, 2018; editorial decision on February 7, 2018; accepted on March 5, 2018

STUDY QUESTION: What is the recommended management of women with recurrent pregnancy loss (RPL) based on the best available evidence in the literature?

SUMMARY ANSWER: The guideline development group formulated 77 recommendations answering 18 key questions on investigations and treatments for RPL, and on how care should be organized.

WHAT IS KNOWN ALREADY: A previous guideline for the investigation and medical treatment of recurrent miscarriage was published in 2006 and is in need of an update.

STUDY DESIGN, SIZE, DURATION: The guideline was developed according to the structured methodology for development of ESHRE guidelines. After formulation of key questions by a group of experts, literature searches and assessments were performed. Papers published up to 31 March 2017 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 formulated and discussed until consensus was reached within the guideline group. A stakeholder review was organized after finalization of the draft. The final version was approved by the guideline group and the ESHRE Executive Committee.

MAIN RESULTS AND THE ROLE OF CHANCE: The guideline provides 38 recommendations on risk factors, prevention and investigations in couples with RPL, and 39 recommendations on treatments. These include 60 evidence-based recommendations – of which 31 were formulated as strong recommendations and 29 as conditional – and 17 good practice points. The evidence supporting investigations and treatment of couples with RPL is limited and of moderate quality. Of the evidence-based recommendations, only 10 (16.3%) were supported by moderate quality evidence. The remaining recommendations were supported by low (35 recommendations: 57.4%), or very low quality evidence (16 recommendations: 26.2%). There were no recommendations based on high quality evidence. 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.
**Introduction**

Recurrent pregnancy loss (RPL) is defined as the loss of two or more pregnancies. The exact prevalence of RPL is difficult to estimate, but most studies report that RPL affects 1–2% of women.

An evidence-based guideline for the investigation and medical treatment of recurrent miscarriage was published in 2006 on behalf of the ESHRE Special Interest Group (SIG) Early Pregnancy and Implantation (Jauiaux et al., 2006). Since this guideline needed updating, the SIG Early Pregnancy initiated the development of the ESHRE guideline on the management of RPL.

This guideline offers best practice advice on the care of couples confronted with RPL. Furthermore, the guideline provides an overview of the treatments for RPL that are currently offered to couples, and which of those are recommended. Recommendations are also formulated on the investigations that could be helpful to identify the origin of the pregnancy losses and to select patients for possible therapeutic targets.

**Materials and Methods**

The guideline was developed according to a well-documented methodology that is universal to ESHRE guidelines (Vermeulen, 2014).

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**WHAT DOES THIS MEAN FOR PATIENTS?**

This European guideline looks at how best to care for people who have experienced recurrent pregnancy loss based on the evidence currently available.

Recurrent pregnancy loss 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 that there is a need for more research looking at the impact on men.

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 recurrent pregnancy loss.

The guideline explains that age is a key factor in recurrent pregnancy loss, 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. A patient leaflet based on the Guideline is available on the ESHRE website [https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Recurrent-pregnancy-loss.aspx](https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Recurrent-pregnancy-loss.aspx).
Table I Interpretation of strong versus conditional recommendations in the GRADE approach.*

| Implications for          | Strong recommendation                                                                 | Conditional recommendation                                                                 |
|--------------------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Patients                 | Most individuals in this situation would want the recommended course of action, and only a small proportion would not. | The majority of individuals in this situation would want the suggested course of action, but many would not. |
| Clinicians               | Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. | Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. |
| Policy makers            | The recommendation can be adopted as policy in most situations.                        | Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences. |

*Andrews et al. (2013).

Results

Key questions and recommendations

The current document summarizes all the key questions and the recommendations from the guideline ‘Management of Recurrent Pregnancy Loss’. Further background information and the supporting evidence for each recommendation can be found in the full version of the guideline available at http://www.eshre.eu/Guidelines-and-Legal/Guidelines.

Definition and terminology

A pregnancy loss is defined as the spontaneous demise of a pregnancy before the foetus reaches viability. The term therefore includes all pregnancy losses from the time of conception until 24 weeks of gestation.

There has been significant debate in the literature and in the GDG on the definition of RPL and, more specifically, the extent to which this definition needs to be extended or constricted based on the number of losses and whether these are consecutive or not.

The GDG concluded that a diagnosis of RPL could be considered after the loss of two or more pregnancies.

This definition includes pregnancy losses both after spontaneous conception and ART, but excludes ectopic and molar pregnancies (if identified as such) and implantation failure.

The GDG would like to stress the importance of the issue and the need for further scientific research (including epidemiological studies on the effect of various RPL definitions on diagnosis, prognosis and treatment).

Regarding terminology, the GDG concludes to use the term Recurrent Pregnancy Loss and to reserve ‘recurrent miscarriage’ to describe cases where all pregnancy losses have been confirmed as intrauterine miscarriages. The terms spontaneous abortion, chemical pregnancy and blighted ovum are ambiguous and should be avoided (Kolte et al., 2015a).

Organisation of care

Pregnancy loss is a significant negative life event and the repetitive nature of RPL may intensify the grief experienced. Studies have mostly focused on women, and there is a need for studies on the emotional impact of RPL on men. Clinicians and clinics should take the psychosocial needs of couples faced with RPL into account when offering and organizing care for these couples.

How should care for RPL patients be organized?

A dedicated RPL clinic is an outpatient clinic that offers specialist investigations, support and (if possible) treatment of couples with RPL. Information provision is one of the important aims of a RPL clinic. Investigations do not necessarily lead to treatment options and this should be clear from the beginning. The elements required in a RPL clinic are experienced staff members with appropriate listening skills and appropriate imaging facilities.

The first visit at the clinic should allow time for the clinician to review the patient’s history, to answer questions and to propose a plan for investigations and, perhaps, treatment. The first visit is the opportunity to provide general information about RPL incidence, causes and investigations, and to link it to the patient’s history. Staff should be aware that many women with RPL will already have information from a variety of sources, and some explanation and re-education may be needed.

There should be individual evaluation of the investigations appropriate to each woman or couple, based on age, fertility/sub-fertility, pregnancy history, family history, previous investigations and/or treatments. In addition, care should be tailored to the psychological needs of the couples (Musters et al., 2013).

Risk factors and health behaviour modifications

What are the known risk factors of RPL?

Women should be sensitively informed that the risk of pregnancy loss is lowest in women aged 20 to 35 years (Cauchi et al., 1991; Lund et al., 2012). Women should be sensitively informed that the risk of pregnancy loss rapidly increases after the age of 40 years (Grande et al., 2012; Lund et al., 2012).

Stress is associated with RPL, but couples should be informed that there is no evidence that stress is a direct cause of pregnancy loss (Nelson et al., 2003; Nepomnaschy et al., 2006; Li et al., 2012; Kolte et al., 2015b; Plana-Ripoll et al., 2016).
Are health behaviour modifications relevant for reducing the risk of pregnancy loss in women with a history of RPL?

Couples with RPL should be informed that smoking could have a negative impact on their chances of a live birth, and therefore cessation of smoking is recommended.

Couples with RPL should be informed that maternal obesity or being significantly underweight is associated with obstetric complications and could have a negative impact on their chances of a live birth and on their general health (Lashes et al., 2004; Zhang et al., 2010; Boots and Stephenson, 2011; Lo et al., 2012; Boots et al., 2014).

Striving for a healthy normal range BMI is recommended.

Couples with RPL should be informed that excessive alcohol consumption is a possible risk factor for pregnancy loss and a proven risk factor for foetal alcohol syndrome (Maconochie et al., 2007; Andersen et al., 2012; Avalos et al., 2014).

Couples with RPL should be advised to limit alcohol consumption.

There was insufficient evidence for recommendations on other lifestyle factors, including exercise (Schulss et al., 2008; Hegard et al., 2016) and caffeine intake (Maconochie et al., 2007; Stefanidou et al., 2011).

Investigations in RPL

A summary of all recommended investigations and treatments is available in Fig. 1.

Medical and family history could be used to tailor diagnostic investigations in RPL.

The guideline development group (GDG) recommends to base prognosis on the number of preceding pregnancy losses and female age (Brigham et al., 1999; Lund et al., 2012; Kaandorp et al., 2014; Egerup et al., 2016).

What is the value of screening for genetic factors in the diagnosis of RPL?

Genetic analysis of pregnancy tissue is not routinely recommended but it could be performed for explanatory purposes (Hogge et al., 2003; Bernardi et al., 2012; Foyouzi et al., 2012; van den Berg et al., 2012).

For genetic analysis of the pregnancy tissue, array-based comparative genomic hybridization (array-CGH) is recommended based on a reduced maternal contamination effect (Robberecht et al., 2009).

Parental karyotyping is not routinely recommended in couples with RPL. It could be carried out after individual assessment of risk (Franssen et al., 2006; Barber et al., 2010) (Franssen et al., 2003; Sugura-Ogasawara et al., 2008; Flynn et al., 2014).

What is the value of thrombophilia screening in women with RPL?

For women with RPL, we suggest not to screen for hereditary thrombophilia unless in the context of research, or in women with additional risk factors for thrombophilia (Bradley et al., 2012).

For women with RPL, we recommend screening for antiphospholipid antibodies (lupus anticoagulant [LA], and anticardiolipin antibodies [ACA IgG and IgM], after two pregnancy losses (Miyakis et al., 2006; Opatrny et al., 2006).

For women with RPL, we recommend screening for anti-β2-glycoprotein I antibodies (β2GPI) can be considered after two pregnancy losses.

What is the value of immunological screening in the diagnosis of RPL?

HLA determination in women with RPL is not recommended in clinical practice. Only HLA class II determination (HLA-DRB1*15:01 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 (Nielsen et al., 2009).

Measurement of anti-HY antibodies in women with RPL is not recommended in clinical practice (Nielsen et al., 2010).
Cytokine testing should not be used in women with RPL in clinical practice (Mueller-Eckhardt et al., 1994; Calleja-Agius et al., 2012; Lee et al., 2013). Cytokine polymorphisms should not be tested in women with RPL (Choi and Kwak-Kim, 2008; Medica et al., 2009).

Antinuclear antibodies (ANA) testing could be considered for explanatory purposes (Christiansen, 1996; Ogasawara et al., 1996; Stern et al., 1998; Kaider et al., 1999; Matsubayashi et al., 2001; Bustos et al., 2006; Gasuddin et al., 2010; Tieconi et al., 2010; Cavalcante et al., 2014; Molazadeh et al., 2014; Heller-Frischmuth et al., 2017).

There is insufficient evidence to recommend normal killer (NK) cell testing of either peripheral blood or endometrial tissue in women with RPL (Chao et al., 1995; Souza et al., 2002; Shakhar et al., 2006; Hadinedoushan et al., 2007; Karami et al., 2012; Lee et al., 2013).

Testing anti-HLA antibodies in women with RPL is not recommended (Lashley et al., 2013).

What is the value of screening for metabolic/endocrinological abnormalities in the diagnosis of RPL?

Thyroid screening (thyroid-stimulating hormone [TSH] and thyroid peroxidase [TPO]-antibodies) is recommended in women with RPL (Rao et al., 2008; van den Boogaard et al., 2011).

Abnormal thyroid-stimulating hormone (TSH) and thyroid peroxidase [TPO]-antibody levels should be followed up by thyroxine (T4) testing in women with RPL (van den Boogaard et al., 2011; Lazarus et al., 2014).

Assessment of polycystic ovary syndrome (PCOS), fasting insulin and fasting glucose is not recommended in women with RPL to improve next pregnancy prognosis (Rai et al., 2000; Craig et al., 2002; Wang et al., 2011; Maryam et al., 2012; Chakraborty et al., 2013; Ipsasou et al., 2013; Kazerooni et al., 2013).

Prolactin testing is not recommended in women with RPL in the absence of clinical symptoms of hyperprolactinemia (oligo/amenorrhoea) (Bussen et al., 1999) (Tiggesanese et al., 2015) (Li et al., 2013).

Ovarian reserve testing is not routinely recommended in women with RPL (Bussen et al., 1999; Hofmann et al., 2000; Prakash et al., 2006; Atasever et al., 2016).

Luteal phase insufficiency testing is not recommended in women with RPL (Balasch et al., 1986; Jordan et al., 1994; Stephenson, 1996; Ogasawara et al., 1997; Badawy and Westphal, 2000; Li et al., 2000).

Androgen testing is not recommended in women with RPL (Watson et al., 1993; Okon et al., 1998; Rai et al., 2000; Nardo et al., 2002; Cockesedge et al., 2008; Kazerooni et al., 2013).

LH testing is not routinely recommended in women with RPL (Sagle et al., 1988; Regan et al., 1990; Carp et al., 1995; Rai et al., 2000; Prakash et al., 2006; Kazerooni et al., 2013).

Measurement of homocysteine plasma levels is not routinely recommended in women with RPL (Nelen et al., 2000; Alonso et al., 2002; Zammit et al., 2008; Creus et al., 2013; Puri et al., 2013; Lee et al., 2016).

Even though one study showed a significant prevalence of vitamin D deficiency in women with RPL, there are no indications that vitamin D status is a contributing factor for RPL (Ota et al., 2014). Moreover, there is no report of an association between vitamin D status and miscarriage, and hence testing of vitamin D status is not recommended for women with RPL. Irrespective of RPL, vitamin D supplementation is nowadays frequently prescribed in pregnant women.

What is the value of anatomical investigations in the diagnosis of RPL?

All women with RPL should have an assessment of the uterine anatomy (Saravelos et al., 2008; Chan et al., 2011a, b; Venetis et al., 2014; Grimbizis et al., 2016).

The preferred technique to evaluate the uterus is transvaginal 3D ultrasound (3D US), which has a high sensitivity and specificity, and can distinguish between septate uterus and bicornoreal uterus with normal cervix (former American Fertility Society classification (AFS) bicornuate uterus) (Saravelos et al., 2008; Ghi et al., 2009; Caliskan et al., 2010).

Sonohysterography (SHG) is more accurate than hysterosalpingography (HSG) in diagnosing uterine malformations. It can be used to evaluate uterine morphology when 3D ultrasound (3D US) is not available, or when tubal patency has to be investigated (Saravelos et al., 2008).

If a Mullerian uterine malformation is diagnosed, further investigation (including investigation of the kidneys and urinary tract) should be considered (Oppelt et al., 2007; Ramanathan et al., 2016).

MRI is not recommended as first line option for the assessment of uterine malformations in women with RPL, but can be used where 3D ultrasound (3D US) is not available (Oppelt et al., 2007; Saravelos et al., 2008; Chan et al., 2011b).

Does the quality of the male gametes contribute to RPL?

In the male partner, it is suggested to assess life style factors (smoking, alcohol consumption, exercise pattern, and body weight).

Assessing sperm DNA fragmentation in couples with RPL can be considered for explanatory purposes, based on indirect evidence (Robinson et al., 2012).

Prognosis and treatment

What is the value of information on medical and family history in establishing the prognosis of RPL?

The guideline development group (GDG) recommends to base prognosis on the number of preceding pregnancy losses and female age (Bingham et al., 1999; Lund et al., 2012; Kaandorp et al., 2014; Egerup et al., 2016).

Prognostic tools (Lund et al., 2012) (Bingham et al., 1999) can be used to provide an estimate of subsequent chance of live birth in couples with unexplained RPL.

Which therapeutic interventions should be offered to couples with RPL due to genetic/chromosomal causes to increase live birth rate?

All couples with results of an abnormal foetal or parental karyotype should receive genetic counselling.

All couples with results of an abnormal foetal or parental karyotype may be informed about the possible treatment options available including their advantages and disadvantages.
The limited evidence for preimplantation genetic testing in couples with RPL shows no clear benefit of treatment (Franssen et al., 2011; Musters et al., 2011; Ikuma et al., 2015).

**Which therapeutic interventions should be offered to couples with RPL and thrombophilia to increase the chance of a live birth?**

For women with hereditary thrombophilia and a history of RPL, we suggest not to use antithrombotic prophylaxis unless in the context of research, or if indicated for venous thromboembolism (VTE) prevention (Skeith et al., 2016).

For women who fulfill the laboratory criteria of antiphospholipid syndrome (APS) and have a history of three or more pregnancy losses, we suggest administration with low dose aspirin (75–100 mg/day), starting before conception, and a prophylactic dose heparin (unfractionated heparin [UFH] or low molecular weight heparin [LMWH]) starting at date of a positive pregnancy test, over no treatment (Empson et al., 2005; Mak et al., 2010; Ziakas et al., 2010).

The guideline development group (GDG) suggests offering anticoagulant treatment for women with two pregnancy losses and antiphospholipid syndrome (APS), only in the context of clinical research.

**Which therapeutic interventions should be offered to couples with RPL with suspicion of immunological background to increase live birth rate?**

No immunological biomarker, except for high-titre antiphospholipid antibodies, can be used for selecting couples with RPL for specific immunological treatments.

**Which therapeutic interventions should be offered to couples with RPL AND metabolic or hormonal abnormalities to increase live birth rate?**

Overt hypothyroidism arising before conception or during early gestation should be treated with levothyroxine in women with RPL (Stagnaro-Green et al., 2011; Khan et al., 2017).

There is conflicting evidence regarding treatment effect of levothyroxine for women with subclinical hypothyroidism and RPL. Treatment of women with subclinical hypothyroidism (SCH) may reduce the risk of miscarriage, but the potential benefit of treatment should be balanced against the risks (Negro et al., 2010; Bernardi et al., 2013).

If women with subclinical hypothyroidism and RPL are pregnant again, thyroid-stimulating hormone (TSH) level should be checked in early gestation (7–9 weeks AD), and hypothyroidism should be treated with levothyroxine.

If women with thyroid autoimmunity and RPL are pregnant again, thyroid-stimulating hormone (TSH) level should be checked in early gestation (7–9 weeks gestational age), and hypothyroidism should be treated with levothyroxine.

There is insufficient evidence to support treatment with levothyroxine in euthyroid women with thyroid antibodies and RPL outside a clinical trial (Visseren et al., 2012).

There is insufficient evidence to recommend the use of progesterone to improve live birth rate in women with RPL and luteal phase insufficiency (Coomarasamy et al., 2015).

There is insufficient evidence to recommend the use of hCG to improve live birth rate in women with RPL and luteal phase insufficiency (Morley et al., 2013).

There is insufficient evidence to recommend metformin supplementation in pregnancy to prevent pregnancy loss in women with RPL and glucose metabolism defects (Zolghadri et al., 2008).

Bromocriptine treatment can be considered in women with RPL and hyperprolactinemia to increase live birth rate (Hirahara et al., 1998).

Preconception counselling in women with RPL could include the general advice to consider prophylactic vitamin D supplementation.

Controlled ovarian stimulation by human menopausal gonadotrophins could be beneficial for decreasing the chance of a next pregnancy loss in women with RPL diagnosed with luteal phase insufficiency (Li et al., 2001), but the GDG decided that the evidence was too limited to support recommending controlled ovarian stimulation in women with RPL but without polycystic ovary syndrome (PCOS).

**Which therapeutic interventions should be offered to women with RPL and uterine abnormalities to increase live birth rates?**

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 (Rikken et al., 2017).

Metroplasty is not recommended for bicornual uterus with normal cervix (former American Fertility Society classification (AFS) bicornuate uterus) and RPL (Bailey et al., 2015; Sugura-Ogasawara et al., 2015).

Uterine reconstruction is not recommended for hemi-uterus (former American Fertility Society classification (AFS) unicornuate uterus) and RPL (Jaslow, 2014).

There is insufficient evidence in favour of metroplasty in women with bicornual uterus and double cervix (former American Fertility Society classification (AFS) didelphic uterus) and RPL (Bailey et al., 2015).

There is insufficient evidence supporting hysteroscopic removal of submucosal fibroids or endometrial polyps in women with RPL (Pritt et al., 2009; Lieng et al., 2010; Salim et al., 2011; Jaslow, 2014).

Surgical removal of intramural fibroids is not recommended in women with RPL. There is insufficient evidence to recommend removing fibroids that distort the uterine cavity (Pritt et al., 2009; Jaslow, 2014).

There is insufficient evidence of benefit for surgical removal of intrauterine adhesions for pregnancy outcome. After hysteroscopic removal of intrauterine adhesions in women with RPL, precautions have to be taken to prevent recurrence of adhesions (Kodaman and Arici, 2007; Jaslow, 2014).

Women with a history of second-trimester pregnancy losses and suspected cervical weakness should be offered serial cervical sonographic surveillance.
In women with a singleton pregnancy and a history of recurrent second-trimester pregnancy loss attributable to cervical weakness, a cerclage could be considered. There is no evidence that this treatment increases perinatal survival.

**Which therapeutic interventions should be offered to couples with RPL due to male factor to increase live birth rate?**

Couples with RPL should be informed that smoking, alcohol consumption, obesity and excessive exercise could have a negative impact on their chances of a live birth, and therefore cessation of smoking, a normal body weight, limited alcohol consumption and a normal exercise pattern is recommended.

Sperm selection is not recommended as a treatment in couples with RPL.

Antioxidants for men have not been shown to improve the chance of a live birth (Showell et al., 2014).

**Which therapeutic interventions should be offered to couples with unexplained RPL to increase live birth rate?**

Lymphocyte immunization therapy should not be used as treatment for unexplained RPL as it has no significant effect and there may be serious adverse effects (Wong et al., 2014).

Intravenous immunoglobulin (ivlg) is not recommended as a treatment of RPL (Egerup et al., 2015).

Glucocorticoids are not recommended as a treatment of unexplained RPL or RPL with selected immunological biomarkers (Tang et al., 2013; Gomaa et al., 2014).

Heparin or low dose aspirin are not recommended, as there is evidence that they do not improve live birth rate in women with unexplained RPL (de Jong et al., 2014).

Low dose folic acid is routinely started preconceptionally to prevent neural tube defects, but it has not been shown to prevent pregnancy loss in women with unexplained RPL.

Vaginal progesterone does not improve live birth rates in women with unexplained RPL (Coomarasamy et al., 2015) (Saccone et al., 2017).

There is insufficient evidence to recommend intralipid therapy for improving live birth rate in women with unexplained RPL.

There is insufficient evidence to recommended granulocyte-colony stimulating factor (G-CSF) in women with unexplained RPL (Scarpellini and Sbracia, 2009).

There is no evidence to recommended endometrial scratching in women with unexplained RPL.

**Which therapeutic interventions could be offered to all couples with RPL, irrespective of a cause, to increase live birth rates?**

If women with RPL ask about using multivitamin supplements, they should be advised on multivitamin supplements that are safe in pregnancy.

**Discussion**

This ESHRE guideline on the management of RPL aims to supply healthcare providers with the best available evidence for the investigation and treatment of women with RPL.

All recommendations in the guideline were formulated after an assessment of the best available evidence in the literature and discussion within the GDG, taking into account the balance of benefits versus harms, patient preferences, clinicians’ expertise and resource use. The guideline includes 77 recommendations, including 60 evidence-based recommendations – of which 31 were formulated as strong recommendations and 29 as conditional – and 17 good practice points. Evidence supporting investigations and treatment of couples with RPL is limited and of moderate quality. Of the evidence-based recommendations, only 10 (16.3%) were supported by moderate quality evidence. The remaining recommendations were supported by low (35 recommendations (57.4%)) or very low quality evidence (16 recommendations (26.2%)). There were no recommendations based on high quality evidence.

One of the most important consequences of the limited evidence, is that there is evidence for a definition of RPL. An evidence-based definition was not feasible. Furthermore, for most investigations and treatments, there are no data on when investigations and/or treatment should be started, whether it can be postponed until after a next pregnancy loss, and whether the care of couples with primary versus secondary, or consecutive versus non-consecutive losses should be approached differently. For most investigations and treatments, the decision on when to start 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.

A second consequence of the limited evidence is the number of recommendations specifying investigations and treatments to be applied in a research context rather than routine clinical practice. The current guideline contains three recommendations on interventions to be applied in a research context only. In the 2006 guideline, five treatments were listed as requiring more RCTs. Four of these treatments (progesterone, ivlg, folic acid and donor leukocyte immunization) are currently believed not to improve the chance of a live birth in couples with RPL. The fifth, aspirin/heparin, is recommended as treatment for women with APS and three pregnancy losses, but more research is now needed in women with APS and two losses, or women with RPL and hereditary thrombophilia.

Third, the lack of evidence-based investigations and treatments has resulted in a significant research wastage in RPL care. Therefore, the guideline also clearly mentions investigations and treatments that should not be used for couples with RPL (Fig. 1). Some of these treatments are not recommended because they have been shown to be ineffective for increasing the chance of a live born baby in couples with RPL, while others have not been studied in couples with RPL, or were shown to have significant adverse events. Similarly, several investigations are currently being applied to couples with RPL while they have no benefit to the couples.

It is clear that evidence-based practice in RPL is not yet feasible as studies are lacking. The current guideline clearly 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 (Supplementary Fig. S1). While awaiting evidence and evidence-based recommendations, GPPs are provided to support clinicians in routine practice.
Supplementary data

Supplementary data are available at Human Reproduction Open online.

Acknowledgements

The Guideline Development Group would like to thank invited experts Peter Bischoff for providing helpful comments on thyroid abnormalities, and Grigoris Grimbizis for checking the chapters on uterine malformations. The guideline development group also acknowledges the help of many clinicians and patient organizations who refereed the content of the Guideline and submitted helpful comments to the draft version.

Authors’ roles

M.G. chaired the guideline development group and hence fulfilled a leading role in collecting the evidence, writing the manuscript and dealing with reviewer comments. N.V., as methodological expert, performed all literature searches for the guideline, provided methodological support and coordinated the guideline development. R.B.A. represented the patient perspective in the guideline group. All other authors, listed in alphabetical order, as guideline group members, contributed equally to the manuscript, by drafting key questions, synthesizing evidence, writing the different parts of the guideline and discussing recommendations until consensus within the group was reached.

Funding

The study has no external funding; all costs for meetings were covered by ESHRE.

Conflict of interest

J.E. reports position funding from CARE Fertility. S.L. reports position funding from SpermComet Ltd. S.M. reports research grants, consulting and speaker’s fees from GSK, BMS/Pfizer, Sanquin, Aspen, Bayer and Daichi Sankyo. S.Q. reports speaker’s fees from Ferring. The other authors reported no conflicts of interest.

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Supplementary Figure S1  
Research agenda for recurrent pregnancy loss. RPL: recurrent pregnancy loss. APS: antiphospholipid syndrome. NGS: Next Generation Sequencing. PGD-A: PGD of aneuploidy. LMWH: low molecular weight heparin. UFH: unfractionated heparin.