Human Reproduction Open, pp. 1–12, 2018
doi:10.1093/hropen/hoy004

human reproduction open

ESHRE PAGES

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.

LIMITATIONS, REASONS FOR CAUTION: Several investigations and treatments are offered to couples with RPL, but most of them are not well studied. For most of these investigations and treatments, a recommendation against the intervention or treatment was formulated based on insufficient evidence. Future studies may require these recommendations to be revised.

WIDER IMPLICATIONS OF THE FINDINGS: The guideline provides clinicians with clear advice on best practice in RPL, based on the best evidence available. In addition, a list of research recommendations is provided to stimulate further studies in RPL. One of the most important consequences of the limited evidence is the absence of evidence for a definition of RPL.

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. 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 Daiichi Sankyo. S.Q. reports speaker's fees from Ferring. The other authors report no conflicts of interest.

ESHRE Pages are not externally peer reviewed. This article has been approved by the Executive Committee of ESHRE.

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

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

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 (Jauniaux *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).

In short, 18 key questions were formulated by the Guideline Development Group (GDG), with input from patient organizations (Fertility Europe, Miscarriage Association UK), and structured in PICO format (Patient, Intervention, Comparison, Outcome). For each question, databases (PUBMED/MEDLINE and the Cochrane library) were searched from inception to 31 March 2017, with a limitation to studies written in English. From the literature searches, studies were selected based on the PICO questions, assessed for quality and summarized in evidence tables and summary of findings tables (for interventions with at least two studies per outcome). Cumulative live birth rate, live birth rate and pregnancy loss rate (or miscarriage rate) were considered the critical outcomes. GDG meetings were organized where the evidence and draft recommendations were presented by the assigned GDG member, and discussed until consensus was reached within the group.

Each recommendation was labelled as strong or conditional and a grade was assigned based on the strength of the supporting evidence (High ⊕⊕⊕⊕ – Moderate ⊕⊕⊕◯ Low ⊕⊕◯◯ – Very low ⊕◯◯◯). In the absence of evidence, the GDG formulated no recommendation or a good practice points (GPP) based on clinical expertise (Table I).

The guideline draft and an invitation to participate in the stakeholder review was published on the ESHRE website. In addition, all relevant stakeholders received a personal invitation to review by e-mail. We received 307 comments from 23 reviewers, representing 15 countries, two national societies (Royal College of Obstetricians and Gynaecologists, and Italian Society of Gynecology and Obstetrics Sigo – L'Associazione degli Ostetrici e Ginecologi Ospedalieri

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. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	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. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy makers	The recommendation can be adopted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

*Andrews *et al.* (2013).

Italiani – Associazione Ginecologi Universitari Italiani) and one international research group (ESHRE/European Society for Gynaecological Endoscopy [ESGE] CONgenital UTerine Anomalies Group). All comments were processed by the GDG, either by adapting the content of the guideline and/or by replying to the reviewer. The review process was summarized in the review report which is published on the ESHRE website (www.eshre.eu/guidelines).

This guideline will be considered for update 4 years after publication, with an intermediate assessment of the need for updating 2 years after publication.

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).

Organization 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).	Strong ⊕⊕◯◯
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).	Strong ⊕⊕◯◯
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).	Strong ⊕◯◯◯

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.	GPP
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 (Lashen *et al.*, 2004; Zhang *et al.*, 2010; Boots and Stephenson, 2011; Lo *et al.*, 2012; Boots *et al.*, 2014).	Strong ⊕⊕◯◯
Striving for a healthy normal range BMI is recommended.	GPP
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 problems (foetal alcohol syndrome) (Maconochie *et al.*, 2007; Andersen *et al.*, 2012; Avalos *et al.*, 2014).	Strong ⊕⊕◯◯
Couples with RPL should be advised to limit alcohol consumption.	GPP

There was insufficient evidence for recommendations on other lifestyle factors, including exercise (Schlussel *et al.*, 2008; Hegaard *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.	GPP
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).	Strong ⊕⊕⊕◯

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).	Conditional ⊕⊕◯◯
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).	Strong ⊕⊕◯◯
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.*, 2005; Sugiura-Ogasawara *et al.*, 2008; Flynn *et al.*, 2014).	Conditional ⊕⊕◯◯

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).	Conditional ⊕⊕⊕◯
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).	Strong ⊕⊕◯◯

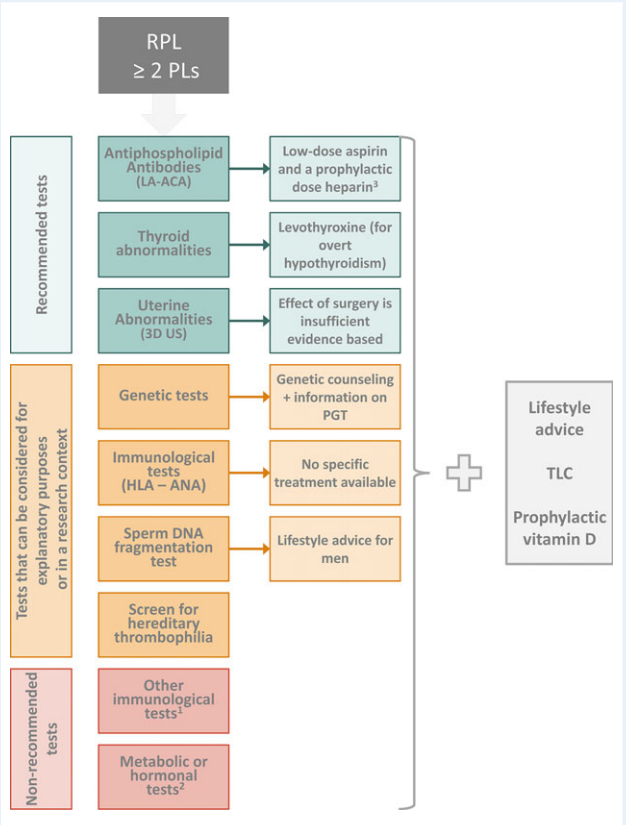

Figure 1 Pictorial summary of the recommendations for investigations and treatments of couples with recurrent pregnancy loss.

1: Including anti-HY antibodies, Natural Killer (NK) cell testing, anti-HLA antibodies.
2: Including cytokine testing/polymorphisms, assessment of polycystic ovary syndrome (PCOS), fasting insulin and fasting glucose, prolactin testing, ovarian reserve testing, luteal phase insufficiency testing, androgen testing, LHtesting, homocysteine plasma levels.
3: Low-dose aspirin and heparin are recommended after three or more pregnancy losses, or in the context of a clinical trial.

RPL: recurrent pregnancy loss. LA: lupus anticoagulant. ACA: anticardiolipin antibodies. 3D US: 3D ultrasound. PGT: preimplantation genetic testing. ANA: antinuclear antibody. TLC: tender loving care.

For women with RPL, screening for β2 glycoprotein I antibodies (aβ2GPI) can be considered after two pregnancy losses.	GPP

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).	Conditional ⊕⊕◯◯
Measurement of anti-HY antibodies in women with RPL is not recommended in clinical practice (Nielsen *et al.*, 2010).	Conditional ⊕⊕◯◯

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).	Strong ⊕⊕◯◯
Cytokine polymorphisms should not be tested in women with RPL (Choi and Kwak-Kim, 2008; Medica *et al.*, 2009).	Strong ⊕⊕⊕◯
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; Giasuddin *et al.*, 2010; Ticconi *et al.*, 2010; Cavalcante *et al.*, 2014; Molazadeh *et al.*, 2014; Hefler-Frischmuth *et al.*, 2017).	Conditional ⊕⊕◯◯
There is insufficient evidence to recommend natural 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).	Strong ⊕◯◯◯
Testing anti-HLA antibodies in women with RPL is not recommended (Lashley *et al.*, 2013).	Strong ⊕⊕⊕◯

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).	Strong ⊕⊕⊕◯
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).	Strong ⊕⊕⊕◯
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; Ispasoiu *et al.*, 2013; Kazerooni *et al.*, 2013).	Strong ⊕⊕◯◯
Prolactin testing is not recommended in women with RPL in the absence of clinical symptoms of hyperprolactinemia (oligo/amenorrhoea) (Bussen *et al.*, 1999) (Triggianese *et al.*, 2015) (Li *et al.*, 2013).	Conditional ⊕⊕◯◯
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).	Strong ⊕⊕◯◯
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 Westpfal, 2000; Li *et al.*, 2000).	Strong ⊕⊕◯◯
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; Cocksedge *et al.*, 2008; Kazerooni *et al.*, 2013).	Strong ⊕⊕◯◯
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).	Strong ⊕◯◯◯
Measurement of homocysteine plasma levels is not routinely recommended in women with RPL (Nelen *et al.*, 2000; Alonso *et al.*, 2002; Zammiti *et al.*, 2008; Creus *et al.*, 2013; Puri *et al.*, 2013; Lee *et al.*, 2016).	Strong ⊕◯◯◯

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).	Strong ⊕⊕◯◯
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 bicorporeal uterus with normal cervix (former American Fertility Society classification (AFS) bicornuate uterus) (Saravelos *et al.*, 2008; Ghi *et al.*, 2009; Caliskan *et al.*, 2010).	Conditional ⊕⊕◯◯
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).	Conditional ⊕⊕◯◯
If a Müllerian 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).	Conditional ⊕⊕◯◯
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).	Conditional ⊕⊕◯◯

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

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 (Brigham *et al.*, 1999; Lund *et al.*, 2012; Kaandorp *et al.*, 2014; Egerup *et al.*, 2016).	Strong ⊕⊕⊕◯
Prognostic tools (Lund *et al.*, 2012) (Brigham *et al.*, 1999) can be used to provide an estimate of subsequent chance of live birth in couples with unexplained RPL.	GPP

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.	GPP
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.	GPP

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).	Conditional ⊕⊕OO
For women who fulfil 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).	Conditional ⊕OOO
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.	GPP

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).	Strong ⊕⊕OO
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).	Conditional ⊕⊕OO
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.	GPP
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.	GPP
There is insufficient evidence to support treatment with levothyroxine in euthyroid women with thyroid antibodies and RPL outside a clinical trial (Vissenberg *et al.*, 2012).	Conditional ⊕⊕OO
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).	Conditional ⊕⊕⊕O
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).	Conditional ⊕⊕OO
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).	Conditional ⊕OOO
Bromocriptine treatment can be considered in women with RPL and hyperprolactinemia to increase live birth rate (Hirahara *et al.*, 1998).	Conditional ⊕OOO
Preconception counselling in women with RPL could include the general advice to consider prophylactic vitamin D supplementation	GPP

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).	Conditional ⊕OOO
Metroplasty is not recommended for bicorporeal uterus with normal cervix (former American Fertility Society classification (AFS) bicornuate uterus) and RPL (Bailey *et al.*, 2015; Sugiura-Ogasawara *et al.*, 2015).	Strong ⊕OOO
Uterine reconstruction is not recommended for hemi-uterus (former American Fertility Society classification (AFS) unicornuate uterus) and RPL (Jaslow, 2014).	Strong ⊕OOO
There is insufficient evidence in favour of metroplasty in women with bicorporeal uterus and double cervix (former American Fertility Society classification (AFS) didelphic uterus) and RPL (Bailey *et al.*, 2015).	Conditional ⊕OOO
There is insufficient evidence supporting hysteroscopic removal of submucosal fibroids or endometrial polyps in women with RPL (Pritts *et al.*, 2009; Lieng *et al.*, 2010; Salim *et al.*, 2011; Jaslow, 2014).	Conditional ⊕OOO
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 (Pritts *et al.*, 2009; Jaslow, 2014).	Conditional ⊕OOO
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).	Conditional ⊕OOO
Women with a history of second-trimester pregnancy losses and suspected cervical weakness should be offered serial cervical sonographic surveillance.	Strong ⊕⊕OO

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.	Conditional ⊕⊕◯◯

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.	GPP
Sperm selection is not recommended as a treatment in couples with RPL.	GPP
Antioxidants for men have not been shown to improve the chance of a live birth (Showell *et al.*, 2014).	Conditional ⊕◯◯◯

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).	Strong ⊕⊕◯◯
Intravenous immunoglobulin (Ivlg) is not recommended as a treatment of RPL (Egerup *et al.*, 2015).	Strong ⊕⊕◯◯
Glucocorticoids are not recommended as a treatment of unexplained RPL or RPL with selected immunological biomarkers (Tang *et al.*, 2013; Gomaa *et al.*, 2014).	Strong ⊕⊕◯◯
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).	Strong ⊕⊕⊕◯
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.	Strong ⊕⊕◯◯
Vaginal progesterone does not improve live birth rates in women with unexplained RPL (Coomarasamy *et al.*, 2015) (Saccone *et al.*, 2017).	Conditional ⊕⊕⊕◯
There is insufficient evidence to recommend intralipid therapy for improving live birth rate in women with unexplained RPL.	Strong ⊕◯◯◯
There is insufficient evidence to recommended granulocyte-colony stimulating factor (G-CSF) in women with unexplained RPL (Scarpellini and Sbracia, 2009).	Conditional ⊕⊕◯◯
There is no evidence to recommended endometrial scratching in women with unexplained RPL.	GPP

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.	GPP

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 the absence of 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 leucocyte 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 Bisschop 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 Daiichi Sankyo. S.Q. reports speaker's fees from Ferring. The other authors reported no conflicts of interest.

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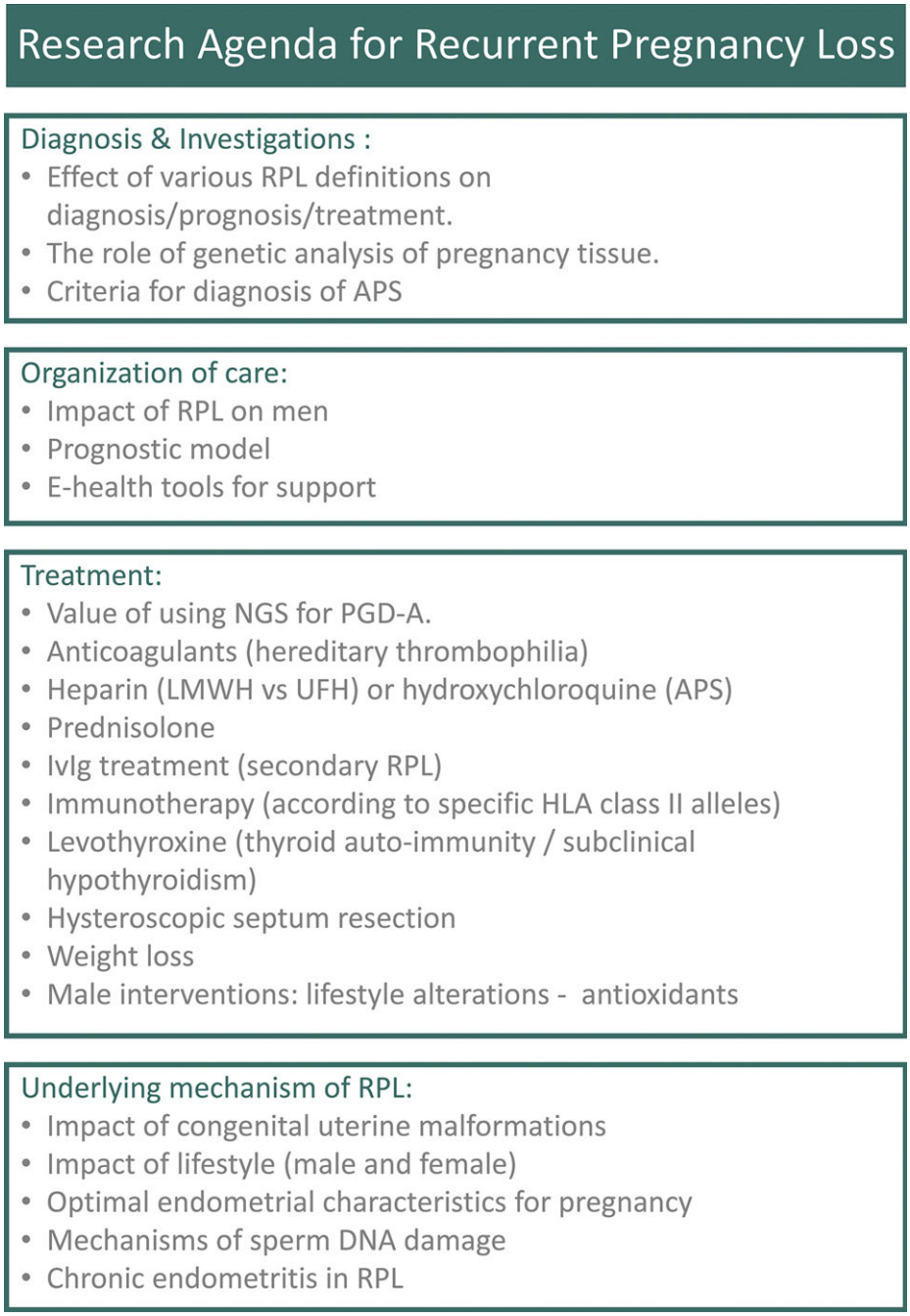
Human Reproduction Open, 2018
doi:10.1093/hropen/hoy004

human reproduction open

SUPPLEMENTARY DATA



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