Identify, appraise and individualize: clinical practice and prediction models in recurrent pregnancy loss

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CHAPTER 3

COMPARISON AND APPRAISAL OF (INTER)NATIONAL RECURRENT PREGNANCY LOSS GUIDELINES

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ABSTRACT

Investigations and treatment options of recurrent pregnancy loss (RPL) differ internationally. This manuscript reviews the similarities and differences between international guidelines. The European Society of Human Reproduction and Embryology (ESHRE) guideline (2017), the American Society for Reproductive Medicine (ASRM) Committee Opinion (2013) and the Royal College of Obstetricians and Gynaecologists (RCOG) guideline (2011) were appraised using the AGREE II criteria. The guidelines were checked for definitions, risk factors, investigations and therapeutic options. The guidelines agreed on acquired thrombophilia analysis. All guidelines agreed on a regimen for the treatment of antiphospholipid antibody syndrome consisting of aspirin and heparin, but only the ESHRE guideline specified the order of starting these medications. Treatment of thrombophilia and uterine anomalies was advised against; all guidelines recommended supportive care for unexplained RPL. The guidelines did not agree on the definition of RPL and differed in investigations regarding lifestyle, karyotype analysis of parents and/or pregnancy tissue, and the diagnostic tool for uterine anomalies. All three guidelines indicate an association between lifestyle and RPL; the ESHRE recommends health behaviour changes. Couples suffering from RPL should be informed about possible investigations and treatment options, and whether those are evidence-based. It is important for clinicians to realize that the guidelines differ internationally.

INTRODUCTION

The first literature describing women with recurrent pregnancy loss (RPL) dates back to the early 1930s. Malpas described a population of women in which miscarriage sequences, at that time named 'abortion sequences', could be identified (1). A model was developed which concluded that three consecutive miscarriages was more than just bad luck (1). The first definition of RPL was three or more consecutive early pregnancy losses prior to the 20th week of gestation, which at that time was referred to as 'repeated early spontaneous pregnancy wastage' (2). Over the years, many underlying risk factors and treatment options have been described and criticized. Not only are the risk factors and treatments debatable components of RPL, but also there is no international consensus regarding the definition.

We recently compared the national protocols on RPL of three academic hospitals and four general hospitals in the Netherlands (3). Differences between diagnostic investigations and treatment options were the most common discrepancies between the protocols. Thus, in addition to an internationally varying definition, we have seen that despite the presence of a national guideline (4), local protocols are inconsistent.

In an attempt to understand this variation in clinical practice, this paper will summarize the similarities and differences between international guidelines on RPL. This exercise is also able to detect areas of uncertainty and evidence gaps and provide information as to which studies should be carried out to improve future RPL care.

It is important to be aware of the (inter)national differences in the care of RPL couples. In our own experience, patients frequently ask for a second opinion in another clinic, or even go abroad. These couples most often then undergo more extensive diagnostic testing, and are being offered treatment options that lack scientific rationale. There is an increasing range of tests and therapies offered to women attending RPL clinics. In general, practice variation can be resolved by the implementation of evidence-based guidelines. This paper provides an overview and critical appraisal, and compares the clinical recommendations in three RPL practical guidelines: the evidence-based guideline of the European Society of Human Reproduction and Embryology (ESHRE) of 2017, two consensus-based committee opinions of the American Society for Reproductive Medicine

(ASRM) considering definition and evaluation and treatment of RPL in 2013, and the evidence-based Royal College of Obstetricians and Gynaecologists (RCOG) guideline of 2011 (5-8).

MATERIALS AND METHODS

Three RPL guidelines of professional societies (ESHRE, ASRM and RCOG) were compared. The guidelines were assessed by three authors (AY, NV, MH). Their methodological similarities and differences were documented with the aim of comparing the definitions and clinical recommendations in the three guidelines. Rather than providing a full methodological assessment and comparison of the guidelines, we focused on the criteria most relevant to the aim of the current study. The criteria were selected from the AGREE II tool for assessment of quality and reporting of practice guidelines (9).

The following data were extracted from the three guidelines: definition of RPL, risk factors, diagnostic investigations and therapeutic options. For each aspect, the clinical recommendations were tabulated and an assessment made about whether there was agreement between the three guidelines. In cases of disagreement, we attempted to provide an explanation. The discrepancies and similarities between the guidelines, and the lack of evidence, are summarized later in this paper.

RESULTS

EXISTING GUIDELINES ON RPL

The included guidelines were developed by international (ESHRE, ASRM) and national (RCOG) professional organizations. The guidelines were published between 2011 and 2017. The methodological similarities and differences between the three guidelines are summarized in **Table 1**.

Two of the guidelines were supported by a literature search for evidence and a strict methodology for formulating recommendations (ESHRE, RCOG), while the other was mainly consensus-based. Most guideline development groups were composed of gynaecologists, with only one guideline (ESHRE) including experts from other domains (internal medicine, endocrinology, genetics, andrology and a patient representative). Conflicts of interest were documented in all three guidelines (ESHRE, ASRM and RCOG). All three

guidelines were externally reviewed by stakeholders before finalization and publication, but approaches to stakeholder involvement differed. All three societies are independent and are not externally financed.

Table 1 | Comparison of the most relevant AGREE II tools for the assessment of quality of the RPL practice guidelines

	ESHRE 2017	ASRM 2013	RCOG 2011
Multidisciplinary group (AGREE 4)	YES	NO	NO
Patient input (AGREE 5)	YES	NO	NO
Evidence search (AGREE 7)	YES	NO	YES
Methods for formulation of recommendations (AGREE 10)	YES	NO	YES
External review (AGREE 13)	YES	YES	YES
Tools for practice (AGREE 19)	YES[1]	NO	YES[1]
Resource implication (AGREE 20)	NO	NO	NO
Monitoring criteria (AGREE 21)	NO	NO	NO
COIs documented (AGREE 23)	YES	YES	YES

[1] These guidelines were supplemented with a patient version of the guidelines.

With regard to implementation, none of the guidelines included information on resource implications (i.e., which resources would be needed to implement the guidelines), or criteria for monitoring the uptake of the guidelines. Two of the guidelines (ESHRE, RCOG) were supplemented with a patient version, which can be considered a tool for clinical practice, contributing to the implementation of the guideline. One of the guidelines (ESHRE) is supplemented by a summary paper which may serve as a format for local protocols (5). None of the guidelines were supplemented by other tools such as decision aids, pathways or risk of pregnancy loss calculators.

DEFINITION OF RPL

There are four main components in the definition of RPL: defining pregnancy (biochemical, visualized, intrauterine), defining up to how many weeks the loss of pregnancy is considered a pregnancy loss, defining recurrence and deciding whether those recurring pregnancy losses have to be consecutive. The definitions of the guidelines are summarized in **Table 2**. The ASRM Committee Opinions advise confirming a pregnancy by ultrasonography or histopathology. The ESHRE guideline discusses the location of pregnancies and concludes that ectopic and molar pregnancies should not be included in the definition. The ESHRE and RCOG guidelines both mention that a miscarriage includes all pregnancy losses before the foetus reaches viability, i.e., up to 24 weeks of gestation. The ASRM guideline does not mention a time limit. The ESHRE and ASRM guidelines consider two pregnancy losses sufficient to meet the definition of RPL and consider diagnostic investigations. However, the ESHRE guideline states that not all guideline group members agreed to this definition. The RCOG guideline considers three pregnancy losses to meet the definition of recurrence. The last component of the definition is whether the recurring losses are obliged to be consecutive or not. The ESHRE guideline discusses the probability of including non-consecutive pregnancy losses, while the other guidelines only include consecutive pregnancy losses (**Table 2**).

Table 2 | Comparison of the elements of RPL definitions in three (inter)national guidelines

	ESHRE 2017	ASRM 2013	RCOG 2011
Pregnancy	Serum or urine hCG; ectopic and molar pregnancies not to be included in the definition	Clinical pregnancy documented by ultrasonography or histopathological examination	All pregnancy losses not further defined
Weeks of Gestation	Up to 24 weeks	Only mentions that majority is lost prior to 10th week	Up to 24 weeks
Recurrence	2	2	3
Consecutive	Consecutive or non- consecutive	Consecutive	Consecutive

INVESTIGATIONS

Investigations carried out in couples with RPL aim to detect underlying risk factors contributing to the losses, and can include assessment of lifestyle, genetic analysis, thrombophilia, immunologic and metabolic testing, assessment of uterine anatomy, and assessment of male factor contribution. The similarities and differences between the investigational advice in the guidelines are summarized in **Table 3**, and the differences highlighted. All three guidelines indicate an association between lifestyle (body mass index, smoking status, use of alcohol) and RPL, and two of the three guidelines (ESHRE and ASRM) mention that lifestyle should be investigated.

Genetic analyses can be divided into two main categories: parental genetic analysis and pregnancy tissue genetic analysis. Parental analysis can be performed to detect chromosomal abnormalities, which could increase the chances of a couple experiencing RPL. Analysis of the pregnancy tissue, however, may provide a reason for the particular pregnancy loss, but does not necessarily explain RPL in that couple. All three guidelines focus on the parental analysis, of which the ESHRE guideline determines that it should not be performed on a routine basis, but it could be carried out after individual assessment of risk. One guideline (RCOG) recommends starting with analysis of the pregnancy tissue on the third and subsequent consecutive pregnancy loss, and performing parental karyotyping only in case an unbalanced structural chromosome abnormality is found.

Thrombophilia can either be acquired or inherited. Acquired thrombophilia or antiphospholipid syndrome (APS) is an autoimmune syndrome caused by antibodies directed against phospholipids, leading to a hypercoagulable state. APS is characterized by thrombosis and/or pregnancy morbidity, including RPL. All guidelines recommend screening for anticardiolipin antibodies (ACA) and lupus anticoagulant (LAC). Furthermore, the ASRM guideline recommends screening for anti-β2-glycoprotein I, another antibody associated with APS. Regarding screening for inherited thrombophilia, the evidence is less clear, and screening is limited to cases with additional risk factors in all guidelines. The ESHRE does advise against measuring homocysteine levels because of inconsistent evidence regarding an association with RPL and possible pregnancy complications, and regarding the impact of several lifestyle factors on plasma homocysteine levels.

Table 3 | Comparison of investigations and therapeutic options of the RPL guidelines.

	ESHRE	ASRM	RCOG
Year of publication	2017	2012, 2013	2011
Risk factors			
	Age (female), anatomical factors, APS, embryonic factors, endocrine factors, genetic factors, lifestyle factors, preceding pregnancy losses	Anatomical factors, APS, embryonic factors, endocrine disorders, genetic factors, inherited thrombophilia, lifestyle factors	Anatomical factors, APS, embryonic factors, endocrine factors, genetic factors, immune factors, lifestyle factors, maternal age, preceding pregnancy losses, thrombophilia
Investigations			
General	Medical, obstetric and family history	Medical history related to RPL, lifestyle	-
Genetics	Parental karyotyping not on a routine base. Analysis of pregnancy tissue for explanatory purpose, using array-CGH	Parental karyotyping. Karyotyping of the products of conception may be useful in setting of on-going RPL therapy	Cytogenetic analysis on pregnancy tissue on third and subsequent consecutive pregnancy loss(es), parental karyotyping in case of unbalanced structural abnormality
Thrombophilia	No screening unless in context of research or in case of additional risk factors for thrombophilia	No screening unless in context of research or in case of additional risk factors for thrombophilia (FV Leiden, FII, Protein C, Protein S, and AT deficiencies)	FV Leiden, FII and protein S only in women with second trimester pregnancy loss

	ESHRE	ASRM	RCOG
Hyperhomocysteinemia	Not routinely recommended	-	-
Immunology/APS	ACA and LAC anti-β_2-glycoprotein I antibodies ((aβ2GPI) could be considered ANA could be considered	ACA, LAC and anti-β_2-glycoprotein I	ACA and LAC on two occasions 12 weeks apart
Endocrinology	Thyroid screening (TSH and TPO) followed up by T4 testing in case of abnormal screening results	Screening for thyroid (TSH) or prolactin abnormalities and test for HbA1c	-
Anatomy	3D ultrasound	Sonohysterogram, HSG and/or hysteroscopy	Pelvic ultrasound uterine anatomy. Suspected anomalies require further investigations using hysteroscopy, laparoscopy or 3D pelvic ultrasound
Male factor	Sperm DNA fragmentation can be considered	Sperm DNA fragmentation not recommended	-
Therapy			
Lifestyle	Health advice on diet, smoking and alcohol	-	-
Balanced chromosome abnormality	Genetic counselling, IVF + PGT optional	Genetic counselling if a structural genetic factor is identified, IVF + PGT optional	Genetic counselling, IVF + PGT optional
Thrombophilia	Insufficient evidence. Only in the context of research	-	Insufficient evidence

	ESHRE	ASRM	RCOG
Immunology/APS	Low dose aspirin (75-100 mg daily) starting before conception and a prophylactic dose heparin (unfractioned or low molecular weight starting at positive pregnancy test	Prophylactic dose of unfractioned heparin and low dose aspirin	Low dose aspirin plus heparin
Hyperhomocysteinemia	-	-	-
Endocrinology	Levothyroxine for hypothyroidism Vitamin D supplementation Bromocriptine treatment for hyperprolactinemia Other treatments not advised	Maternal endocrine disorders (thyroid dysfunction, diabetes and hyperprolactinemia) should be treated Other treatments not advised	Insufficient evidence
Anatomy	Insufficient evidence. Septum resection in context of trial	Consider surgical correction	Insufficient evidence
Unexplained RPL	No therapeutical interventions recommended	TLC. Emphasize chance for future successful pregnancy can exceed 50-60%	Supportive care of a dedicated early pregnancy assessment unit
Success rate subsequent pregnancy	Shown in a figure (17, 18)	Shown in a figure (18)	5% (17, 19)
Follow up	Supportive care	TLC. Psychological counselling and support	-

Several immunological aspects have been investigated and linked to RPL, including antinuclear antibodies (ANA), cytokine polymorphisms, human leukocyte antigen (HLA) typing and screening for HLA antibodies. ANA testing could be considered according to the ESHRE guideline, but there is no current treatment. Other immunological tests are not recommended in either of the guidelines. HLA typing, screening for HLA antibodies, and cytokine polymorphism testing are not recommended by the ESHRE or ASRM.

Metabolic testing in RPL is largely focused on thyroid function. Hypothyroidism is mentioned as a risk factor in every guideline. The ASRM and ESHRE guidelines recommend thyroid function screening; ESHRE suggests measurement of T4 in case of abnormal thyroid-stimulating hormone (TSH) or anti-thyroid peroxidase (anti-TPO) levels. The ASRM guideline advises testing the levels of HbA1c and prolactin for abnormalities.

Uterine examination is recommended by all guidelines. The ASRM guideline recommends examining the uterine cavity using hysterosonography (HSG), hysteroscopy or sonohysteroscopy. The RCOG suggests starting with pelvic ultrasound and applying HSG, hysteroscopy or sonohysteroscopy or 3D ultrasound in case of inconclusive findings, while ESHRE concludes that 3D ultrasound is the preferred technique to evaluate the uterus.

On male factors, the ESHRE guideline states that the assessment of sperm DNA fragmentation can be considered for explanatory purposes; the ASRM guideline, however, concludes that this assessment is not recommended.

THERAPY

Treatment options for RPL are limited and depend on the results of the investigations. The following interventions can be considered: lifestyle advice, IVF plus preimplantation genetic testing (PGT), aspirin and heparin, levothyroxine and surgery for uterine anomalies. Therapeutic advice from the guidelines is summarized in **Table 3** and the differences are discussed here.

The ESHRE guideline provides advice on lifestyle changes, regardless of the underlying cause: weight loss if BMI ≥25, healthy diet, cessation of smoking and reduction in alcohol consumption.

All guidelines recommend referring couples with detected chromosomal abnormalities to a clinical geneticist to offer a prognosis on future pregnancies. PGT can be a treatment for couples with parental genetic abnormalities, as by genetic testing of a few embryo cells on the presence of a previously diagnosed abnormality it allows for the selection of embryos without the genetic abnormality from the parents. RCOG discusses IVF plus PGT but recommends informing couples that their chances of a live birth through natural conception (50–70%) are higher than general live birth rates after IVF and PGT (about 30%). The ESHRE and the ASRM guidelines also discuss IVF plus PGT as an optional treatment. They conclude that data are limited, but that patients may be informed about the possibility, advantages and disadvantages of IVF plus PGT.

All guidelines advise on treatment for APS in women with RPL with low-dose aspirin plus heparin. ESHRE recommends starting low-dose aspirin (75–100 mg daily) before conception and a prophylactic dose of heparin (unfractionated or low molecular weight) once there is a positive pregnancy test. The other guidelines do not specify the order of aspirin and heparin.

The ASRM guideline only explores the screening of thyroid or prolactin abnormalities while the ESHRE and RCOG guidelines discuss other endocrine problems and treatment options. The ASRM guideline recommends treatment of endocrine disorders (such as diabetes, thyroid dysfunction when TSH levels are abnormal) in the context of RPL. ESHRE recommends treatment of hypothyroidism arising before or during early gestation with levothyroxine. ESHRE also suggests including general advice to consider vitamin D supplementation for all pregnant women, as concerns have been raised over the prevalence of vitamin D deficiency. Furthermore, the ESHRE guideline suggests bromocriptine treatment in case of hyperprolactinemia. The RCOG guideline concludes that there is insufficient evidence for the treatment of these causes. Other treatments such as progesterone supplementation, human chorionic gonadotrophin (HCG) supplementation and suppression of high LH is not advised.

In case of an anatomical uterus abnormality, the ASRM guideline suggests considering resection. However, the RCOG concludes that there is insufficient evidence so far for this treatment. Likewise, the ESHRE guideline concludes that the effect of septum resection should be evaluated in randomized controlled trials and that other uterine reconstructions are not recommended. The TRUST trial (Dutch trial number: NTR 1676) is currently investigating whether hysteroscopic septum resection improves the reproductive outcome in women with a septate uterus (10). Regarding acquired intrauterine malformations, the ESHRE and ASRM conclude that there is insufficient evidence for the removal of fibroids or adhesions (Asherman syndrome).

All guidelines aim to improve success in subsequent pregnancies. Emphasis on the relatively high chances of success focus points of the ASRM Committee Opinions. The RCOG guideline gives information on the psychological aspects and provides patients with support via a specialized care unit, and the ESHRE guideline recommends different interventions based on the current available evidence.

Supportive care is suggested to comfort patients in the ASRM and the ESHRE guideline.

DISCUSSION

This paper describes a methodology assessment (AGREE II), summarizes and compares the recommended definitions, risk factors, investigations and therapies of three guidelines considering RPL. It is clear that discrepancies exist between the three guidelines, which could explain variation in practice. Also notable is that the ESHRE and RCOG guidelines have a similar format, while the ASRM has the style of a review, but discusses the same subjects and makes evidence-based recommendations on those subjects.

Guidelines are living documents, subjected to updates based on recent trial results, and they should inspire clinicians to base their clinical practice on the most recent available data.

To ensure couples with RPL all over the world receive comparable and preferably evidence-based diagnostic investigations and treatment options, only one internationally accepted guideline is in fact needed. When evidence shows what diagnostic methods and what treatments are

beneficial, it is unnecessary to have different guidelines in all countries. Of course, not all the recommendations are applicable to all populations worldwide, but if countries are similar in terms of medical services and populations, guidelines could be unified. The ESHRE guideline, for example, is available for official consideration by any professional society in obstetrics and gynaecology.

One major hurdle in the universal application of one guideline is the inconsistency of the definition criteria of RPL, which appears to be more a discussion based on opinions rather than evidence. If not, internationally consistent it will inherently lead to discrepancies in therapy of RPL. The definition will also have significant resource implications, as it will define when to start performing investigations.

Jaslow et al. (2010) showed that there is no difference in the prevalence of abnormal test results in women with different numbers of RPL. Furthermore, the risk of miscarriage after two consecutive miscarriages is clinically similar to the risk of recurrence among women with three or more consecutive pregnancy losses (11). There is evidence that the risk of APS is not associated with the number of pregnancy losses or with pregnancy losses being consecutive (12). Carrier status of a balanced chromosomal abnormality does not differ between couples with two or three consecutive losses versus woman with two or three non-consecutive losses (13). The ASRM document mentions that for epidemiological studies, a threshold of three or more losses should ideally be used. For the sake of this emotionally stressful situation and based on studies showing that there seems to be no differences in finding a cause between two or three losses, women with two losses should be offered evaluation. Egerup et al. argued that only consecutive pregnancy losses should count in the definition of RPL, showing that a birth in women with secondary RPL eradicates the negative prognostic impact of previous pregnancy losses (14). The ESHRE guideline includes non-consecutive losses in its definition. Furthermore, Kolte et al. states that non-visualized pregnancies should also be included in the definition of RPL, as does the ESHRE guideline (15). This study showed that non-visualized pregnancies are of prognostic importance, although only assessed in women with idiopathic RPL.

Risk factors and investigations are generally similar between the compared guidelines. Discrepancies between the recommendations in the guidelines can be explained partly by their methods of development and the time of their publication, and the lack of strong evidence on some clinical aspects of RPL.

In general, guidelines are believed to stay up to date for 4 years. The three guidelines were published at different time points, ranging from 2011 to 2017, and this explains some of the differences. For example, homocysteine levels and maternal thrombophilia are no longer considered to be associated with RPL. The most recent guideline (ESHRE) therefore no longer advises performing these tests. Another example is the focus toward thyroid function testing in the more recent guidelines (ESHRE, ASRM). Although the format of the ASRM guideline differs from the ESHRE and RCOG, being written in the form of a review, we could not detect significant differences, as the ASRM also reviewed the available literature, as did the ESHRE and RCOG guidelines.

The absence of sufficient evidence could explain the differences regarding the investigation and treatment of uterine malformations, and most of the endocrinological and immunological tests and treatments. For testing hereditary thrombophilic factors and treatment of hereditary thrombophilia, all guidelines agree on the lack of evidence. Currently, the ALIFE II study is investigating whether antithrombotic treatment in patients with RPL would result in higher live birth rates in comparison with placebo (16). The recent ESHRE guideline emphasizes that many recommendations in this field are still based on a low level of evidence also documented in a recent publication (5). The guideline was supplemented with a research agenda outlining aspects of RPL for which studies should be performed to reduce uncertainty, and improve care of couples in the near future.

Finally, one significant difference between the guidelines cannot be clearly attributed to method of development or lack of evidence, which is the difference in genetic investigations between the RCOG and the other guidelines. The RCOG advises selective parental karyotyping when an unbalanced chromosome abnormality is identified in the pregnancy tissue, because of the high costs and the relatively low incidence of unbalanced

chromosome abnormalities. The other guidelines advise parental karyotyping according to the risk table, and do not routinely investigate the pregnancy tissue.

In conclusion, the current paper describes the similarities and differences between clinical recommendations provided in three RPL guidelines, and attempts to explain some of the differences based on the time and method of development, and on the lack of supporting evidence. As a clinician it is important to realize that there are differences in the guidelines considering the treatment of RPL. Nowadays there is an increasing range of tests and therapies offered to women attending recurrent miscarriage clinics. Couples that suffer from RPL should be informed about the possible investigations and treatment options, and whether those are evidence-based.

We advise following the most recent guidelines, being aware of discrepancies and only making use of evidence-based therapies. To answer the questions for which evidence is lacking and improve the future care for RPL couples, new trials could be set up and patients could be asked to participate in an ongoing randomized controlled trial.

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