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ESHRE Pages

ESHRE good practice recommendations on recurrent implantation failure†

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ABSTRACT

STUDY QUESTION: How should recurrent implantation failure (RIF) in patients undergoing ART be defined and managed?

SUMMARY ANSWER: This is the first ESHRE good practice recommendations paper providing a definition for RIF together with recommendations on how to investigate causes and contributing factors, and how to improve the chances of a pregnancy.

WHAT IS KNOWN ALREADY: RIF is a challenge in the ART clinic, with a multitude of investigations and interventions offered and applied in clinical practice, often without biological rationale or with unequivocal evidence of benefit.

STUDY DESIGN, SIZE, DURATION: This document was developed according to a predefined methodology for ESHRE good practice recommendations. Recommendations are supported by data from the literature, if available, and the results of a previously published survey on clinical practice in RIF and the expertise of the working group. A literature search was performed in PubMed and Cochrane focussing on 'recurrent reproductive failure', 'recurrent implantation failure', and 'repeated implantation failure'.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The ESHRE Working Group on Recurrent Implantation Failure included eight members representing the ESHRE Special Interest Groups for Implantation and Early Pregnancy, Reproductive Endocrinology, and Embryology, with an independent chair and an expert in statistics. The recommendations for clinical practice were formulated based on the expert opinion of the working group, while taking into consideration the published data and results of the survey on uptake in clinical practice. The draft document was then open to ESHRE members for online peer review and was revised in light of the comments received.

MAIN RESULTS AND THE ROLE OF CHANCE: The working group recommends considering RIF as a secondary phenomenon of ART, as it can only be observed in patients undergoing IVF, and that the following description of RIF be adopted: 'RIF describes the scenario in which the transfer of embryos considered to be viable has failed to result in a positive pregnancy test sufficiently often in a specific patient to warrant consideration of further investigations and/or interventions'. It was agreed that the recommended threshold for the cumulative predicted chance of implantation to identify RIF for the purposes of initiating further investigation is 60%. When a couple have not had a successful implantation by a certain number of embryo transfers and the cumulative predicted chance of implantation associated with that number is greater than 60%, then they should be counselled on further investigation and/or treatment options. This term defines clinical RIF for which further actions should be considered. Nineteen recommendations were formulated on investigations when RIF is suspected, and 13 on interventions. Recommendations were colour-coded based on whether the investigations/interventions were recommended (green), to be considered (orange), or not recommended, i.e. not to be offered routinely (red).

LIMITATIONS, REASONS FOR CAUTION: While awaiting the results of further studies and trials, the ESHRE Working Group on Recurrent Implantation Failure recommends identifying RIF based on the chance of successful implantation for the individual patient or couple and to restrict investigations and treatments to those supported by a clear rationale and data indicating their likely benefit.

WIDER IMPLICATIONS OF THE FINDINGS: This article provides not only good practice advice but also highlights the investigations and interventions that need further research. This research, when well-conducted, will be key to making progress in the clinical management of RIF.

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Keywords: implantation failure / good practice / ART / ESHRE / guidelines / IVF failure / embryo transfer / recurrent implantation failure

WHAT DOES THIS MEAN FOR PATIENTS?

The fertility treatment journey, from the fertility workup to the actual treatments and pregnancy, is a challenge for patients, especially if several transfers of good-quality embryos do not result in a pregnancy. When more than two embryo transfers fail to result in a pregnancy, the term 'recurrent implantation failure' (or RIF) is often used. Much is still unknown regarding the causes of implantation failure, and whether these causes are linked to the mother, the father, the embryo, or all three. With so many unknowns, healthcare professionals may offer several tests and treatments to patients diagnosed with RIF, often without clear evidence from studies that the tests or treatments are helpful to achieve a pregnancy in a next attempt.

This article challenges the concept of RIF as currently accepted and provides a means of individualizing its recognition to each specific patient context. Evidence supporting the different tests and treatments available is summarized with a recommendation on which tests/treatment could be recommended for use in ART clinics, which can be considered, and those which are not recommended until further research in high-quality studies verifies their usefulness and safety. These recommendations aim to support the management of RIF in clinical practice and stimulate research on the topic.

Introduction

ART provides treatment options for heterosexual couples having difficulties conceiving naturally, single people, and same-sex couples. Despite advances in treatment approaches and laboratory technologies, many people fail to conceive with these technologies. When failure arises after serial attempts at IVF, the term 'recurrent implantation failure' (RIF) is often used. However, while this broadly descriptive term is often employed to focus discussions of clinical therapeutic options, it is evident that providing a name to unexplained IVF failure has not led to significant advances in its effective management. In contrast, RIF has become associated with accusations of poor and even exploitative practices, that have coloured the ongoing 'add-ons' debate. However, apparently unexplained repeated failure of IVF treatment is a frequently encountered, distressing, and difficult-to-manage clinical problem.

Implantation failure is a term commonly used to describe the situation in which a good-quality embryo has been transferred into the uterine cavity but has failed to establish a pregnancy evidenced by ultrasound visualization of an intrauterine gestational sac (Zegers-Hochschild *et al.*, 2017). Since this may happen more than once in a woman, the word 'recurrent' has been appended, leading to the emergence of a term akin to that used for women who experience more than one miscarriage. As with recurrent pregnancy loss (RPL), there is a lack of consistency in the clinical definition of RIF. Most definitions currently in use are based on the number of embryos transferred with no pregnancy. However, with changing practices in embryo transfer (ET), namely, from multiple to single embryos, from cleavage to blastocyst stage, and from untested to chromosomally tested embryos, the implications of a single failed ET procedure have changed. A recent comprehensive survey of the definitions in use that employ this paradigm has suggested that a consensus is emerging that regards RIF as the failure to achieve a clinical pregnancy after two to three transfers with good-quality embryos and that maternal age should also be taken into account (Cimadomo *et al.*, 2021). However, several problems arise with such a fixed and precise definition of RIF. Firstly, it does not take into account variables that affect the individual prognosis for successful treatment based on both patient and ART clinic-related factors. Secondly, the concept of RIF as a syndrome or disease that can be diagnosed and treated is open to challenge. This is illustrated by the

difficulties faced by those seeking to provide clinical guidelines in this area since the evidence base available does not permit robust conclusions to be drawn.

The ESHRE Working Group on Recurrent Implantation Failure recognized that there is a need to look afresh at how RIF should be identified, defined, and managed. While there is an evidence base to scrutinize, it is the view of the RIF working group (WG) that the available literature has not generated clinical data of sufficient quality around an agreed and consistent definition of RIF to permit a didactic guideline to be distilled. However, there is still a need for an evidence-supported document describing what represents 'Good Practice' in this challenging area of reproductive medicine. This document aims to meet that need through a systematic search for and synthesis of published studies on the topic, a survey among professionals on current clinical practice in RIF and considering the practical expertise of selected clinicians and embryologists.

Materials and methods

The current good practice recommendation for RIF terminology, investigations, and treatments have been developed according to the manual for the development of ESHRE good practice recommendations (Vermeulen *et al.*, 2019).

A WG tasked with drafting a document for review was composed of representatives of the relevant ESHRE Special Interest Groups (SIGs), notably the SIGs Implantation and Early Pregnancy, Reproductive Endocrinology, and Embryology, and further completed with an independent chair (N.M.), an expert in statistics (D.J.M.) and support for literature searches and project management. In the first meetings, the ESHRE Working Group on Recurrent Implantation Failure discussed the topics to be covered and divided to work in subgroups with defined tasks. Progress with the different tasks and issues arising was discussed in regular online meetings.

A literature search through PUBMED and Cochrane databases was performed using the key terms 'recurrent reproductive failure' OR 'recurrent implantation failure' OR 'repeated implantation failure'. Studies were included from inception to August 2022, with addition of more recent references where available. All titles and abstracts were screened to identify relevant studies, for which full-text papers were collected and summarized. While the literature search was focused on specific studies in RIF patients (defined as such by the authors) and the main outcomes live birth rate (LBR), pregnancy rate (PR), and side effects, in the absence of studies specifically addressing cases of RIF, the impact on implantation after ART, in general, was considered.

Recommendations for clinical practice were stated based on studies collected through the systematic search of the literature, and recommendations in other guidelines (Coughlan *et al.*, 2014a; Shaulov *et al.*, 2020; Mascarenhas *et al.*, 2022; Sociedad Española de Fertilidad; Grupo de Trabajo de Fracaso Reproductivo), a previously performed survey providing details on current clinical practice (Cimadomo *et al.*, 2021), assessment of biological rationale, and the expert opinion of the WG. While the WG was aware that for most investigations or interventions there may be specific patient groups that may be shown to benefit, or indeed the opposite, in order to aid clinical decision-making, the recommendations were colour-coded to indicate three levels of advice: green, recommended for all patients with suspected RIF; orange, can be considered in RIF patients; red, not recommended. When 'not recommended' is the advice given, this implies that the investigation/intervention is not to be routinely offered, but that does not mean that it is recommended not to be used in any circumstances, since in most cases, the evidence base cannot support such a didactic statement.

While key available evidence was summarized for all investigations and interventions, an exclusively evidence-based approach was not considered possible for the current topic, owing to the lack of consistency in the definition of RIF and the sparse direct and high-quality evidence available for most interventions, including those already established in clinical practice. The recommendations are, therefore, derived from expert interpretation of the available data, their biological rationale, and opinion rather than from the data alone. The evidence assessed and other factors considered for drafting each recommendation are tabulated in Supplementary Data S1 (investigations) and Supplementary Data S2 (interventions).

Specifically concerning the definition of RIF and to define a threshold for considering RIF, an exercise was performed among 10 members of the participating SIGs. In the exercise, three RIF cases were presented and the implications of three different thresholds (70%, 60%, and 50%) for the cumulative success of implantation leading to pregnancy were to be considered. Following the feedback from this exercise, the threshold of 60% was proposed and presented as part of the first draft of the recommendations for investigations and interventions in RIF.

The first draft of the recommendations for good practice was sent for review by the 14 ESHRE SIGs. Feedback was collected on the proposed definition of RIF, criteria for identifying it in an individual patient and on the relevance of diagnostic and treatment options. The feedback was discussed in an in-person WG meeting and adopted by agreement into a final draft of the paper, which was published on the ESHRE website between 1 November and 1 December 2022 for stakeholder review among the ESHRE membership. A total of 204 comments were received, considered by the WG, and incorporated by agreement. The report of the stakeholder review is available on www.eshre.eu/guidelines. The list of experts that contributed to the stakeholder review is included in Supplementary Data S3.

The current document adheres to the previously published definitions for ART, IVF, infertility, pregnancy, and live birth (Zegers-Hochschild *et al.*, 2017). Implantation rate is defined as the number of gestational sacs observed divided by the number of embryos transferred (usually expressed as a percentage) and is preferably calculated per ET procedure (Griesinger, 2016). Implantation is taken to describe the attachment and subsequent penetration by a zona-free blastocyst into the endometrium (Zegers-Hochschild *et al.*, 2017). For the purpose of this document, successful implantation is taken to be the achievement of early pregnancy (i.e. detection of beta hCG in serum or urine indicative of a positive pregnancy test (precise levels will vary depending on the test used)) following an ET procedure.

It is acknowledged that many studies investigating RIF and RIF interventions have primarily looked at PR and/or LBR. Since these outcomes depend on many other factors that can arise after successful implantation, the focus of this document is therefore on determinants of implantation, defined as above rather than as manifest in a live birth. For consideration of factors causing RPL, the reader is referred to the ESHRE Guideline on Recurrent Pregnancy Loss (ESHRE Guideline Group on RPL *et al.*, 2023).

In this document, in line with published research, the terminology and discussion focusses on men and women. The ESHRE Working Group on Recurrent Implantation Failure recognizes that there are individuals confronted with RIF who do not identify with the terms used in the literature. The terminology used in

this document is not intended to isolate, exclude, or diminish any individual's experience or to discriminate against any group.

Defining RIF in ART: from population to individual

The ESHRE Working Group on Recurrent Implantation Failure recommends considering RIF as a secondary phenomenon of ART as it can only be observed in patients undergoing IVF. To address ambiguities in the definition to date, it is recommended that the following description of RIF be adopted:

> **RIF describes the scenario in which the transfer of embryos considered to be viable has failed to result in a positive pregnancy test sufficiently often in a specific patient to warrant consideration of further investigations and/or interventions.**

Considering RIF as a distinct scenario confined to ICSI/IVF patients of heterogeneous cause and prognosis asks for an individualized approach that is not dependent on a 'one size fits all' criterion (e.g. a fixed number of embryos transferred) but accounts, at least in part, for factors known to impact the individual patient's chance of conception. Key to this concept is the need to identify how many embryos/ETs would be expected to be necessary in a specific patient to provide an 'acceptable' cumulative chance of successful implantation.

The task of defining RIF as a clinical entity is further complicated by the fact that ART patients represent a heterogeneous cohort with respect to the indication for treatment and the individual chances of achieving pregnancy. Treated patients range from subfertile couples who would be expected to conceive without treatment if they continue trying long enough to couples and individuals who will not conceive without ART. Similarly, among those undergoing ART, some might be expected to succeed if sufficient cycles are undertaken while others will fail regardless of the number and types of treatments; in the latter group, an identified pathology or advanced ovarian age may account for the poor prognosis. Focussing on couples that would be able to achieve a pregnancy through ART implies that a standardized range of investigations (the 'fertility workup') will have already been completed before the treatment process starts and that patients are deemed suitable for ART and for carrying a pregnancy. The recommended components of the fertility workup have been previously described by ESHRE (Vlaisavljevic *et al.*, 2021) (Fig. 1). The present recommendations for good practice in RIF assume that this baseline fertility workup will already have been carried out before commencing ART, but acknowledge that in different regions and jurisdictions, other and/or additional tests and assessments are recommended (National Institute for Health and Care Excellence, 2013; ACOG, 2019; Toth *et al.*, 2019a,b) (Supplementary Data S4). Furthermore, it is assumed that ART procedures are performed by fully trained and qualified personnel using state-of-the-art technology and procedures.

Defining RIF in the individual couple or patient for clinical purposes

Among ART patients, the chance of successful implantation will differ significantly. To identify RIF indicating further actions in a specific patient, it is necessary to determine what cumulative chance they have had to conceive thus far. If this is greater than an agreed threshold, but no positive pregnancy test has been achieved, then action may be indicated (Fig. 2). Patients whose history indicates that their chance of conceiving thus far has not yet reached the threshold given their specific clinical context should be advised to simply proceed to another ART cycle. However, in patients whose failure to conceive thus far would be recognized as unusual, investigations of underlying contributing factors should be considered.

Two factors are essential for the individual approach for RIF: the model used to estimate the chance of implantation/pregnancy and the level at which the threshold to act is set.

Estimating the chance of implantation

The likelihood of successful implantation after ART is determined by a multitude of factors including, but not limited to, female-related factors such as age, hormonal levels, endometrial and uterine status and underlying conditions, embryo-related factors such as embryonic cleavage speed, euploidy, and previous implantations of sibling embryos, male factors like genetic disorders, and external factors such as the performance of the laboratory and clinic, transfer policies, and legal restrictions.

Ideally, a prediction model including all these factors should be used to provide estimates of the cumulative chance of successful implantation over a number of ETs, but such a model is currently not available. However, published data from observational studies, the European IVF Monitoring Programme (EIM) data collection (European IVF Monitoring Consortium for ESHRE *et al.*, 2022), or the ART centre's own data can be used to derive a model that can provide guidance. Such models should at least consider maternal age, euploidy rate (if screened), and the number of cleavage-stage embryos or blastocysts transferred.

Another approach is to use existing prediction models developed to predict the chance of live birth following the first fresh ET (Ratna *et al.*, 2020; Ata *et al.*, 2021; Rozen *et al.*, 2021). Typically, such models use a validated set of factors shown to impact the chance of live birth and consider the weight or importance of the distinct factors. Such prediction models can provide more precise and personalized estimates of success. Examples include the 'Dhillon Model', which accounts for female age, BMI, cause of infertility, ethnicity, previous live birth, previous miscarriage, antral-follicle count, and duration of infertility (Dhillon *et al.*, 2016) and the 'IVFpredict' tool derived from female age, duration of infertility, own versus donor oocytes, cause of infertility, previous IVF attempts, pregnancy history, medication, and IVF/ICSI (Nelson and Lawlor, 2011). The IVFpredict tool has been subject to external validation, with varying success (Te Velde *et al.*, 2014; Saha *et al.*, 2015; Smith *et al.*, 2015).

For RIF, the chosen model would be used to estimate the chance of pregnancy after each subsequent ET, which implies that a different calculation would be required. However, to limit complexity, the likelihood of achieving a positive pregnancy test following a defined number of cumulative ETs (n) can be approximated by the following formula: $[\text{likelihood of implantation}]_n = 1-[(1-\text{PR})]^n$, where PR is pregnancy rate. If not a reported outcome, PR can be reasonably estimated by multiplying the live birth rate by 1.16 (Arce *et al.*, 2005; Kolibianakis *et al.*, 2006).

Setting a threshold for the cumulative chance of successful implantation to signal action

Irrespective of the model used, a threshold needs to be defined to determine at what point failure to achieve successful implantation indicates an 'issue' rather than simply 'an event by chance'. The threshold will guide the clinical decision on whether the patient should simply proceed to a further ET or whether investigations for factors contributing to RIF should be explored (Fig. 2).

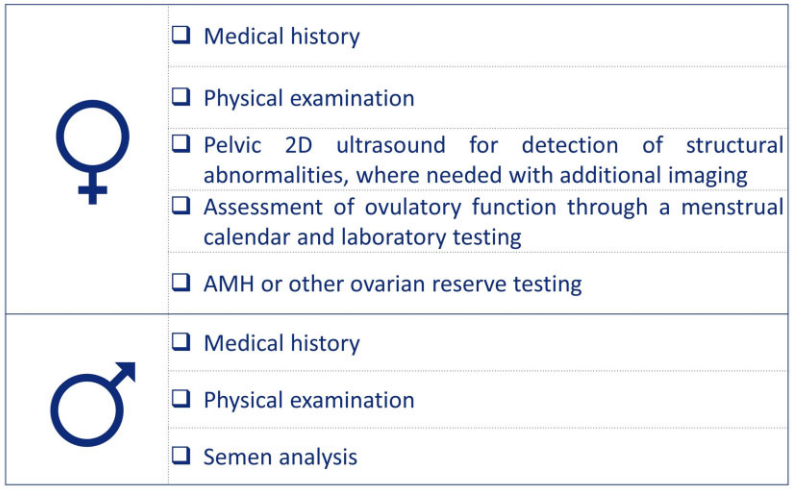

Figure 1. Standard fertility workup in female and male patients. The recommended components of the fertility workup shown here have been described previously by ESHRE (Vlaisavljevic *et al.*, 2021). AMH, anti-Müllerian hormone.

36-year-old woman who has been trying to conceive for 3 years, has damaged tubes, never been pregnant and never had IVF before. She uses her own eggs.

Estimation based on the IVFPredict calculator

With the use of the IVFPredict calculator from the Nelson and Lawlor model (ivfpredict.com), the following calculations can be made for this specific patient:

Her chance of live birth per IVF attempt is 23.8%	according to the IVFPredict tool
Her chance of pregnancy per IVF attempt is 27,6%	calculated by multiplying the LBR by 1.16 to obtain chance of pregnancy i.e., 23.8 X 1.16 = 27.6%
The chance of pregnancy is	calculated by $NP_n = (1\text{-}PR)^n$
• **47% over the course of 2 ET attempts**	1- [(1-0.276) X (1-0.276)] = 0.47
• **62% over the course of 3 ET attempts**	1- $[(1\text{-}0.276)^3]$ = 0.62
• **72% over the course of 4 ET attempts**	1- $[(1\text{-}0.276)^4]$ = 0.72
• **80% over the course of 5 ET attempts**	1- $[(1\text{-}0.276)^5]$ = 0.80

According to the threshold for RIF of >60%,
if the woman is not pregnant after 3 ETs we intervene.

Crude estimation based on the clinic's pregnancy rates

It is recognized that carrying our individual calculations per patients may not always be feasible. An alternative approach could be to make an estimation, based on the clinic's pregnancy rate for specific patient groups. For the example presented in the table, published pregnancy data were used.
While there will be some women who might be expected to have a 60 % chance of implantation after just embryo transfer, the minimum number for identifying implantation failure to be 'recurrent' should be two'.

	Maternal age	Implantation rate / pregnancy rate[1]	Cumulative likelihood of implantation for each embryo transfer (embryos of unknown euploidy) FIRST ET (n=1)	SECOND ET (n=2)	THIRD ET (n=3)	FOURTH ET (n=4)	FIFTH ET (n=5)	SIXTH ET (n=6)	RIF THRESHOLD of >60%
Embryos of unknown euploidy	<35	31,5	31,5	53,1	67,9	78,0	84,9	89,7	Intervene after 3 ETs
	35-39	25,9	25,9	45,1	59,3	69,9	77,7	83,4	Intervene after 4 ETs
	≥40	15	15,0	27,8	38,6	47,8	55,6	62,3	Intervene after 6 ETs
Euploid embryos	<35	68,4	68,4	90,0	96,8	99,0	99,7	99,9	Intervene after 2 ETs
	35-40	64,1	64,1	87,1	95,4	98,3	99,4	99,8	Intervene after 2 ETs
	>40	58,0	58,0	82,4	92,6	96,9	98,7	99,5	Intervene after 2 ETs

Figure 2. Applying the recommended definition of RIF in clinical practice: an example. [1]For embryos of unknown euploidy, pregnancy rates per embryo transfer (ET) for patients using their own oocytes were used from the European IVF Monitoring Programme data (Wyns C *et al.*, 2021); for euploid embryos, pregnancy rates were used from published data (Reig *et al.*, 2020). For the sake of simplicity and because of a lack of positive hCG incidence data in the existing studies/registries, implantation and pregnancy were used interchangeably. RIF, recurrent implantation failure.

While some authors have proposed that this be set at 95% (Ata *et al.*, 2021), it is evident that very few patients will accrue such a high chance of conceiving from IVF and that such a threshold would therefore be of limited utility in the clinical context to which these recommendations for good practice apply. It may be that applying such a rigorous threshold would be useful for

research purposes as it would enrich the study group with patients who have failed to conceive despite an excellent prognosis. While this would indeed be the case, it would require the study group to have had serial transfers of known euploid embryos. Since the purpose of these recommendations for good practice is to provide advice on the management of RIF, we aimed to establish a threshold that can be applied to most clinical situations. It was agreed that a threshold of 60% is the most useful to guide clinical practice. The justification for selecting this threshold is provided in the Materials and Methods section.

The recommended threshold for the cumulative predicted chance of implantation to identify RIF for the purposes of initiating further investigation is 60%. When a couple have not had a successful implantation by a certain number of embryo transfers and the cumulative predicted chance of implantation associated with that number is greater than 60%, then they should be counselled on further investigation and/or treatment options. This term defines *clinical* recurrent implantation failure for which further actions should be considered.

Figure 3 summarizes how the individualized definition of RIF should be integrated into clinical pathways.

Investigations for RIF

While the management of RIF is often empirical and interventions are tried without any attempt to identify the underlying cause, many different investigations for RIF have been proposed. Recognizing the limitations imposed by the current evidence base, this section aims to provide a framework to assist clinicians and couples in decision-making regarding RIF investigations.

In the context of RIF, investigations aim to identify contributing or causative factors. As previously stated, it is assumed that a complete pre-ART fertility workup has already been carried out and that the results are available for consideration. Similarly, the patient's age and past medical history and treatment (e.g. for malignant disease) are assumed to have been accounted for before embarking on ART.

To place each investigation (and associated intervention) into context, data are provided (where available) both on the reported prevalence of their use in clinical practice and the biological rationale underpinning their use.

A summary of all investigations and whether they are recommended, to be considered or not recommended is provided in Fig. 4. Details on the justification for the

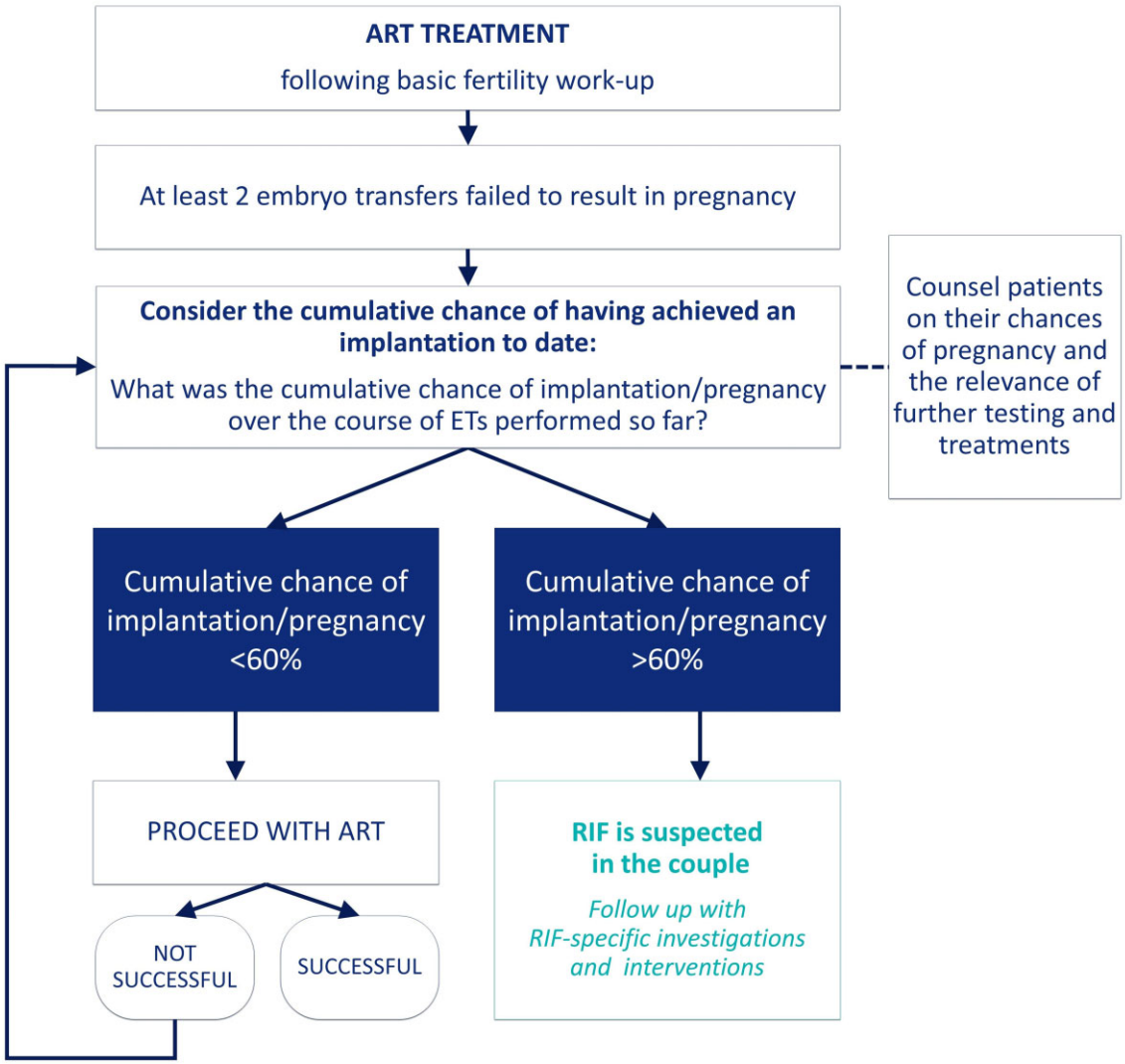

Figure 3. Summary: applying an individualized definition of RIF in clinical practice. This flow diagram follows the *a priori* condition that the patient/couple would be able to achieve a pregnancy through ART, and that ART procedures are performed by fully trained and qualified personnel using state-of-the-art technology and procedures. ET, embryo transfer; RIF, recurrent implantation failure.

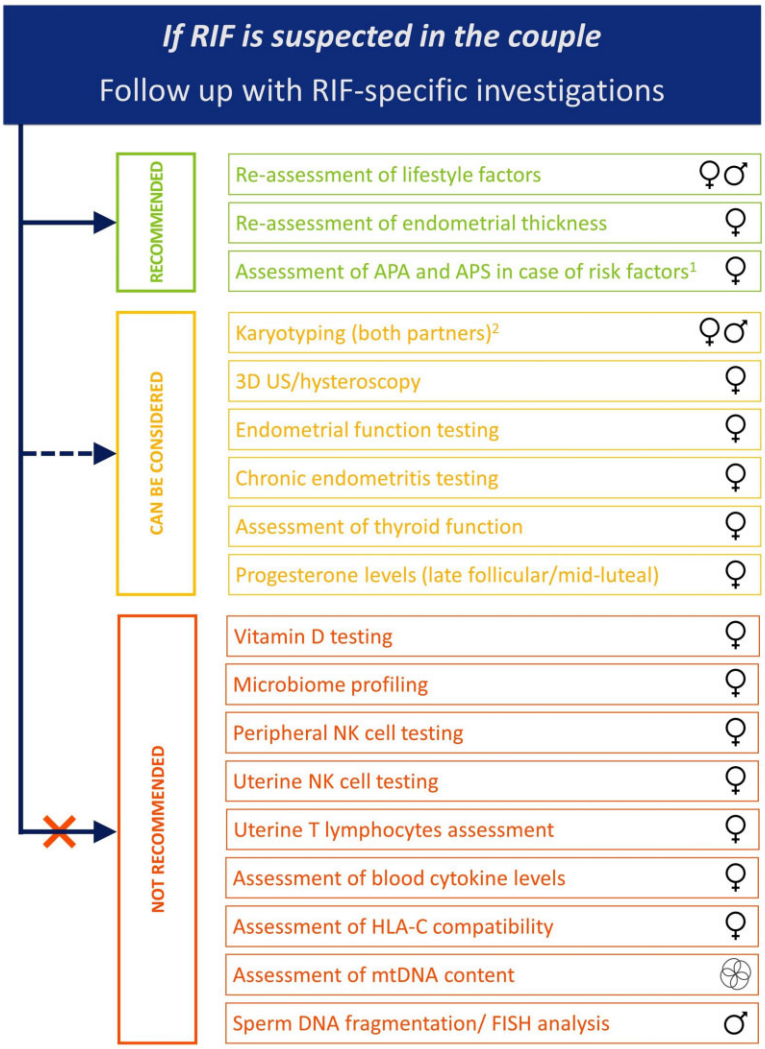

Figure 4. Summary of investigations that are recommended, can be considered, or are not recommended if RIF is suspected in the couple. [1]In the absence of risk factors, assessment of APA and APS can be considered; [2]to confirm the absence of a chromosomal abnormality. APA, antiphospholipid antibodies; APS, antiphospholipid antibody syndrome; mtDNA, mitochondrial DNA; NK, natural killer; RIF, recurrent implantation failure; US, ultrasound.

recommendations are included below and summarized in Supplementary Data S1.

Investigating female factors

Lifestyle factors

In a large survey among 735 clinicians and 300 embryologists, more than two-thirds of clinicians reported taking female lifestyle factors into account, mainly drugs, smoking, and BMI, when managing RIF (Cimadomo *et al.*, 2021). Diet, stress, and caffeine intake were evaluated by about 50% of responding clinicians (Cimadomo *et al.*, 2021). Certain lifestyle behaviours, such as cigarette smoking, alcohol consumption or caffeine, have been associated with lower ART success rates (Kinney *et al.*, 2007; Hornstein, 2016; Ozbakir and Tulay, 2021). However, while association studies abound, evidence from well-designed intervention studies demonstrating an improvement in ART outcomes following short and/or long-term lifestyle changes remains scarce (Freour *et al.*, 2018; Kermack *et al.*, 2020; Wang *et al.*, 2021).

BMI is considered to be a relevant risk factor for ART failure (Moragianni *et al.*, 2012). Although most studies indicate that obesity does not significantly affect embryo quality (Bellver *et al.*, 2021), the role of BMI on oocyte quality cannot be completely ruled out (Bellver *et al.*, 2010; Comstock *et al.*, 2015).

While vitamin D assessment and supplementation are widely offered (Cimadomo *et al.*, 2021), its role in ART remains controversial: some studies found an association of serum and intrafollicular levels of vitamin D with pregnancy rates (Ozkan *et al.*, 2010; Baldini *et al.*, 2021) while others did not (Franasiak *et al.*, 2015). Recent data question the accuracy of vitamin D measurement (Franasiak *et al.*, 2021) and, consequently, the ability to determine vitamin D deficiency and potentially the susceptibility to poor ART outcomes. Despite that, vitamin D measurement and supplementation is considered a relevant RIF intervention by published guidelines and is widely applied in clinical practice (Cimadomo *et al.*, 2021).

Based on the probable relevance of lifestyle factors on ART success rates, the WG considered re-evaluating these factors appropriately. For vitamin D, the value of measuring blood levels is not clear.

While lifestyle factors have been investigated during the fertility workup, patient behaviours can change so it is recommended to review these and their optimization when RIF is encountered.

There are insufficient data to recommend the routine measurement of vitamin D levels or treatment of vitamin D deficiency.

Screening for genetic factors: karyotyping of the female and male partner

In a survey of clinical practice, 67% of clinicians reported considering chromosomal disorders as a potential risk factor for RIF and most clinicians assess both the female and male karyotypes (Cimadomo *et al.*, 2021). Embryonic chromosomal disorders represent the major cause of (early) pregnancy loss in humans (Papas and Kutteh, 2021). Aneuploid blastocysts have a significantly reduced developmental capacity during the preimplantation stage (Rubio *et al.*, 2007; Martín *et al.*, 2021) and negligible implantation potential (Grati *et al.*, 2018; Capalbo *et al.*, 2022). However, most embryonic chromosomal aneuploidies are of maternal meiotic origin.

In line with these observations, case–control studies have shown that karyotype anomalies are more frequent in patients with RIF, even if the absolute prevalence (2.1%) is low (Stern *et al.*, 1999; Raziel *et al.*, 2002; De Sutter *et al.*, 2012). These figures are within the prevalence range of chromosomal abnormalities described in infertile couples undergoing ART, ranging from 2.8% to 12% in males and from 3.0% to 15% in females (Meschede *et al.*, 1998). With regards to the type of karyotype abnormalities in couples with RIF (8 females and 5 males), autosomal abnormalities, sex chromosome aberrations, and chromosomal mosaicism were found in 6, 2, and 1 females and 4, 0, and 1 males, respectively (De Sutter *et al.*, 2012).

The contribution of abnormal parental karyotype to predispose to chromosomal embryonic errors is plausible (Insogna *et al.*, 2021; Yuan *et al.*, 2021).

Despite the low prevalence, karyotyping can be considered to confirm the absence of a chromosomal abnormality in parents.

If a chromosomal abnormality is detected, genetic counselling and, where relevant, preimplantation genetic testing (PGT), is recommended.

Anatomical investigations

Eighty-five per cent of clinicians have been reported to take anatomical and gynaecological investigations into account in diagnosing the cause of RIF (Cimadomo *et al.*, 2021). Asherman's syndrome, hydrosalpinx, endometriosis/adenomyosis, uterine malformations, endometrial atrophy, as well as uterine fibroids, are widely considered relevant. Ovarian cysts were considered relevant by 23% of clinicians. Hysteroscopy is the most widely used technique for anatomical investigations, followed by 3D and 2D transvaginal ultrasound (Cimadomo *et al.*, 2021).

Assessment of the uterine cavity

Transvaginal ultrasound is considered to be performed as part of the fertility workup.

Given the general diagnostic accuracy attributed to 3D transvaginal ultrasound, it has been proposed as an alternative non-invasive procedure for the diagnosis of uterine anomalies and a good practice approach (Grimbizis *et al.*, 2016). Currently, there are no studies evaluating whether 3D transvaginal ultrasound improves the outcomes in patients with RIF. Given the limited cost and non-invasiveness, it can be considered a routine diagnostic tool during fertility workup, when available. If not performed at the start of the ART treatment, it may be of benefit when assessing the patient presenting with RIF.

If 3D ultrasound has not been performed at fertility workup, it can be considered.

While assessment of the presence of adenomyosis, endometriosis, and submucosal fibroids should be carried out before ART, if there is renewed suspicion owing to emerging clinical signs or ultrasound features noted after RIF, then further investigations including MRI or diagnostic laparoscopy should be considered.

The use of hysteroscopy is often proposed when uterine pathology has been detected by transvaginal ultrasound and further diagnostics are indicated (e.g. submucous fibroids, uterine adhesions). A meta-analysis focussing on patients with RIF reported a significantly higher LBR after hysteroscopy compared to those that did not have hysteroscopy (Risk Ratio (RR) 1.29; 95% CI 1.03–1.62; 4 studies; $n = 2247$; $P = 0.046$) (Cao *et al.*, 2018). The analysis by Cao *et al.* included a large randomized controlled trial (RCT) (the TROPHY study) that reported a similar LBR after ART in patients with RIF (two to four failed IVF cycles) without a previously recognized pathology ($n = 702$) when comparing those undergoing hysteroscopy versus those proceeding to ART without hysteroscopy (29% versus 29%, RR 1.0; 95% CI 0.79–1.25; $P = 0.96$) (El-Toukhy *et al.*, 2016). Sonohysterography is another technique to diagnose uterine pathologies, but it is less well studied in RIF (Negm *et al.*, 2012; Reda *et al.*, 2016).

Other uterine cavity anomalies can be treated by established interventions including endometrial polypectomy, surgical removal of submucous fibroids, uterine septum resection, or removal of intrauterine adhesions. While the interventions are established for the treatment of symptoms, their impact on pregnancy or LBRs has, to our knowledge, not been evaluated in patients with RIF. Similarly, the effect of treatment of adenomyosis on pregnancy or LBR in women with RIF has not been evaluated.

Hysteroscopy can be considered, especially when there is a suspicion of a uterine anomaly visualized on transvaginal ultrasound.

There is a lack of studies evaluating hysterosalpingography (HSG) in the context of RIF, but HSG or other means of imaging of the fallopian tubes can be considered if there is a doubt about hydrosalpinx after ultrasound.

Endometrial function and receptivity tests

During anatomical and gynaecological investigations to explore possible causes of RIF, 59% of clinicians reported considering the window of implantation (WOI) (endometrial biopsy) (Cimadomo *et al.*, 2021).

However, this assesses just one element and the mechanisms underlying human endometrium receptivity are complex. Given the numerous endometrial functions that can collectively be considered to represent 'receptivity', it is unlikely that a single test

would provide sufficient insight for clinical use. However, tests have emerged that focus on specific aspects of endometrial function. One such test entails the analysis of a panel of genes associated with endometrial receptivity from an endometrial biopsy taken during the putative WOI. Transcription of these genes is quantified and interpreted to report the endometrium as either pre-receptive, receptive, or post-receptive. Information relating to the response of the endometrium to progesterone exposure can be provided by histological assessment of Noyes' criteria, but this has been shown to be too subjective for clinical use. Since then, several other endometrial receptivity tests similarly focussing on measuring maturation have been marketed. Recently, a comprehensive in-depth analysis of all the transcriptomic panels investigated for their association with impaired endometrial receptivity has supported the hypothesis that RIF might be due to both displacement and disruption of the WOI (Koot *et al.*, 2016). This implies that a test aimed at assessing only one aspect will be of limited utility (Sebastian-Leon *et al.*, 2018).

A meta-analysis from 2022 included 11 studies and reported that the prevalence of displaced WOI, as detected through endometrial receptivity tests, was 34% (95% CI 24–43%) in RIF/poor prognosis patients (Liu *et al.*, 2022b). In patients with RIF, comparable ongoing pregnancy rates (OPR)/LBR were found between those with diagnosed non-receptive endometrium undergoing personalized ET (p-ET) and those with receptive endometrium undergoing routine ET (40.7% versus 49.6%; odds ratio (OR) 0.94; 95% CI 0.70–1.26; 6 studies; $n = 2552$) (Liu *et al.*, 2022b). In a more recent multicentre cohort study in patients with a single previous failed transfer, LBR and cumulative LBR were reported to be higher after unguided ET compared to p-ET, for both autologous and donor transfers (Cozzolino *et al.*, 2022).

A propensity score-matching approach adopted to limit the effect of putative confounders showed no significant improvement in clinical outcomes after using an endometrial receptivity test for p-ET (Bergin *et al.*, 2021). A recent 5-year multicentre RCT comparing p-ET after endometrial receptivity testing to fresh and frozen ET without the test showed comparable outcomes per transfer. Only in a per-protocol analysis, were higher cumulative LBRs in the p-ET reported (Simón *et al.*, 2020).

There is insufficient evidence to support the routine use of the currently available endometrial receptivity testing in ART and more studies are required to discern its value in identifying and enabling the treatment of endometrial maturation defects in women presenting with RIF. It is possible that, in the future, a more comprehensive assessment of endometrial receptivity through a combination of tests may be of benefit in the context of RIF (Hernández-Vargas *et al.*, 2020). Tests of endometrial receptivity increasingly assess other aspects. One example is a test for 'uterine immunological activation' based on RT–PCR analysis of a range of factors considered to be involved in differentiation of the secretory endometrium to the receptive state (Lédée *et al.*, 2017). While this test remains to be subject to assessment in RCTs, cohort studies (Lédée *et al.*, 2020) have suggested that it may have a role in the diagnostic workup of the endometrium in RIF, as indeed may other emerging tests. Moreover, increasing evidence is emerging for the role of decidualized endometrium acting as a gatekeeper to implantation after the epithelial layer is breached. Novel markers of this function are being developed (Muter *et al.*, 2021).

While there are insufficient data to recommend the routine use of any commercially available test of endometrial receptivity to diagnose the cause of RIF, assessment of specific aspects of endometrial function by testing can be considered.

Investigating chronic endometritis

Chronic endometritis (CE) has been described in patients with RIF with bacterial colonization, but also in women without clinical signs of infection and can lower the pregnancy rate (Johnston-MacAnanny *et al.*, 2010; Kitaya *et al.*, 2014, 2019; Cicinelli *et al.*, 2015; Bouet *et al.*, 2016; Kushnir *et al.*, 2016; Song *et al.*, 2018; Li *et al.*, 2020; Saxtorph *et al.*, 2020; Zargar *et al.*, 2020). It can be diagnosed by hysteroscopy, haematoxylin and eosin staining, and CD138-labelling (Kitaya *et al.*, 2014, 2019). Other diagnostic tests for endometritis include chromohysteroscopy (methylene blue dying of endometrium during hysteroscopy), bacterial culture, and molecular techniques such as PCR, RT–PCR, and next-generation sequencing (NGS) (Küçük and Safali, 2008; Moreno *et al.*, 2018). Nowadays, CE (and vaginal infection) seems to be routinely investigated in clinical practice (85% of clinicians) (Cimadomo *et al.*, 2021), even if there are limitations to histology in general, a lack of standardization of the concentration of plasma cells that should be regarded as a threshold (e.g. >1 or >5 plasma cells per high power field), and available studies often include only small numbers of patients or lack controls.

Antibiotics can be considered for the treatment of CE. Recent reviews on the topic, with different inclusion criteria and overlap in the studies included, reported conflicting results. Based on data from four studies, one systematic review reported significantly higher LBR/OPR (OR 5.33; 95% CI 2.41–11.79; $I^2 = 0\%$) in patients with cured CE (treated with antibiotics) compared to those with persistent CE (Vitagliano *et al.*, 2022). Another review calculated the LBR/OPR was not significantly higher in RIF patients with cured CE (after oral antibiotics) compared to those with persistent CE (OR 2.90; 95% CI 0.65–12.98; $I^2 = 77\%$; 4 studies) (Cheng *et al.*, 2022). The reviewers did report higher CPR in cured compared to persistent CE. A third review concluded oral antibiotic treatment for CE did not improve PR or LBR (Kato *et al.*, 2022).

At present, conclusions regarding the value of the diagnosis and treatment of endometritis are significantly hampered by the lack of standardization. However, the investigation and treatment of CE can be considered in RIF. Revision of this recommendation may be indicated should studies using more standardized diagnostic techniques, including the emerging DNA-based tests, reveal a clearer benefit.

Assessment for chronic endometritis (CE) can be considered. If CE is diagnosed, treatment with antibiotics can be considered.

Re-assessment of endometrial thickness

In clinical practice, 90% of clinicians considered the evaluation of endometrial thickness (EMT) relevant in RIF investigations (Cimadomo *et al.*, 2021). This reflects, in part, the ease of assessing this parameter.

A recent systematic review and meta-analysis investigating the association between endometrial thickness and LBR in fresh cycles reported that women with a thin endometrium (EMT < 7 mm) had a significantly lower LBR compared to women

with EMT >7 mm (OR 0.47; 95% CI 0.37–0.61) (Liao *et al.*, 2021). Significant heterogeneity was observed in the results, but sensitivity analysis did not change the direction of the effect. An association between EMT and clinical outcomes has also been reported in frozen ETs and stimulated cycles (Nishihara *et al.*, 2020; Shalom-Paz *et al.*, 2021). In a univariate aggregated data meta-analysis, the probability of clinical pregnancy in the next cycle in women with thin endometrium was found to be significantly lower compared to those with EMT >7 mm, with a positive and negative predictive value of 77% and 48%, respectively (Kasius *et al.*, 2014). However, after controlling for confounders, the potential independent association of EMT with ART treatment outcome has been reported as weak (Yuan *et al.*, 2016; Griesinger *et al.*, 2018). A recent large retrospective study concluded that EMT at the time of ET does not seem to predict the chance of implantation in case of euploid frozen blastocyst transfer (Ata *et al.*, 2023). However, EMT may still be a contributor in the context of RIF, but it may be particularly relevant for non-euploid embryos.

If EMT is assessed and thin endometrium documented, ensuring sufficient exposure to estradiol by augmenting oral therapy with patches or vaginal treatment remains the mainstay of management (Vartanyan *et al.*, 2020). Intrauterine platelet-rich plasma (PRP) infusion has been investigated as a therapy to increase EMT, and some studies have suggested it can be effective in improving endometrial proliferation (Mouanness *et al.*, 2021). However, to date, few studies have been conducted to evaluate its relevance for RIF patients with thin endometrium. Similarly, intrauterine granulocyte colony-stimulating factor (G-CSF) infusion for ART patients with thin endometrium has been proposed, and the limited published studies show conflicting results (Rocha *et al.*, 2020). Further studies should elucidate the value of these and other interventions following the detection of thin endometrium in patients with RIF.

If the endometrium remains thin despite adjustment of the endometrial preparation regimen, hysteroscopy can be considered to rule out adhesions or Asherman's syndrome.

Re-assessment of endometrial thickness is recommended. A review of the estradiol treatment regimen is recommended if the endometrium is noted to remain thin. Hysteroscopy to rule out Asherman's syndrome can be considered.

Microbiome profiling

In recent years, the Human Microbiome Project has highlighted the importance of micro-organisms and their genomes in human health and disease (Human Microbiome Project Consortium, 2012). Almost 10% of the bacterial population present in the body resides in the female genital tract and *Lactobacillus* species are part of the physiologic flora (Moreno and Simon, 2019). Whether microbial dysbiosis is among the determining factors of implantation failure remains under study, but in clinical practice, 47% of clinicians consider this a relevant factor (Cimadomo *et al.*, 2021). Microbiome testing in the context of fertility treatment is attracting much attention and has been indicated to offer promise as a potentially treatable factor in embryo implantation. A small study failed to demonstrate a correlation between the presence of *Lactobacillus* strains and ongoing pregnancy after analyzing the embryo catheter tips (Franasiak *et al.*, 2016). However, a recent meta-analysis of six cohort studies, including a total of 1095 women, and several other studies have reported an association between dysbiotic microbiota and impaired reproductive outcomes (Moreno *et al.*, 2016, 2022; Koedooder *et al.*, 2019; Kyono *et al.*, 2019; Singer *et al.*, 2019). In RIF, a case–control study comparing the vaginal and endometrial microbial configuration through 16S rRNA gene sequencing in 145 women with RIF and 21 healthy women with male factor infertility showed lower levels of *Lactobacillus* in vaginal samples but not in the endometrium of patients with RIF (Ichiyama *et al.*, 2021).

This is a dynamic area of research, and several questions remain to be addressed before the proper place of microbiome testing in the context of RIF can be ascertained. These include the optimal means of evaluating the microbiome (Sola-Leyva *et al.*, 2021), the stability and rate of spontaneous resolution of an unfavourable microbiome, changes that can occur during the menstrual cycle and IVF treatment, and the efficacy of interventions aimed at improving the microbiome. Finally, it remains unclear whether a suboptimal microbiome can itself disrupt implantation, or whether it is a marker for some other causative factor.

Based on the currently available data, and considering there are several unanswered questions on the relevance of microbiome testing in the context of RIF, uterine and vaginal microbiome profiling is not currently recommended.

Uterine and vaginal microbiome profiling is not recommended.

Metabolic and endocrinologic factors

In a survey of clinical practice, endocrine aspects were considered relevant in RIF by 82% of clinicians, with the focus being mostly on thyroid function (98%), hyperprolactinemia (84%), diabetes (82%), and PCOS (30–60%) (Cimadomo *et al.*, 2021).

Thyroid function

Whereas thyroid function may be considered as a diagnostic test, other endocrine factors such as thyroid autoimmunity, prolactin, free androgen levels or diabetes (HBA1C) are either not addressed or considered not to be relevant in RIF by other guidelines. However, as can be seen from the survey, the use of thyroid function in the diagnosis of RIF is well-established in clinical practice (Cimadomo *et al.*, 2021). Recent guidance from the European Thyroid Association suggested that in the context of ART, serum thyroid stimulating hormone levels >4 mIU/l (subclinical hypothyroidism) or <0.4 mIU/l (subclinical hyperthyroidism) may be considered thyroid dysfunction and require further follow-up and treatment (Biondi *et al.*, 2015; Poppe *et al.*, 2021). Assessment of thyroid function can be considered during the ART fertility workup or when RIF is detected, but as no specific association with implantation failure has been reported, assessment is not generally recommended as an investigation for RIF.

Assessment of thyroid function can be considered.

Progesterone

In recent years, there has been growing interest in the reported association between premature progesterone rises, measured around the time of triggering oocyte maturation, and clinical outcomes after fresh ET (Venetis *et al.*, 2013). While still a topic of

debate, there is a widespread view that this can lead to endometrial/embryo asynchrony, meriting delaying ET to a subsequent freeze-thaw cycle (Bosch *et al.*, 2010; Venetis *et al.*, 2013). Deferred ET in cases of premature progesterone elevation has been shown to restore implantation rates in a cohort study (Lawrenz *et al.*, 2018).

Another topic is the assessment of mid-luteal progesterone levels to evaluate exogenous progesterone therapy. A Cochrane meta-analysis reported a higher LBR/OPR with progesterone compared to placebo/no treatment for luteal phase support in women undergoing ART (OR 1.77; 95% CI 1.09–2.86; $I^2 = 5\%$; 5 RCTs; $n = 642$) (van der Linden *et al.*, 2015). Consistent with the possibility that absorption from the vagina may be variable between women, there is increasing evidence linking low blood progesterone levels on the day of ET to poorer outcomes after fresh ET (Thomsen *et al.*, 2018) and after frozen ET (Alsbjerg *et al.*, 2018; Lawrenz *et al.*, 2018; Labarta *et al.*, 2021). A recent matched cohort study showed low mid-luteal progesterone levels to be more prevalent in women with a history of RIF versus controls (Saxtorph *et al.*, 2020). Individualized progesterone administration has been shown to restore implantation rates in cohort studies (Álvarez *et al.*, 2021; Labarta *et al.*, 2021).

With regards to both late follicular and mid-luteal progesterone level assessment, questions remain about the validity of published cut-off levels for individual centres as assays can vary. Local validation of cut-off progesterone levels is recommended.

Assessment of late follicular and mid-luteal progesterone levels can be considered.

Immunological screening

The notion that an excessive maternal immune response to the implanting embryo is disruptive to implantation has become widely accepted. In a survey of clinical practices for managing RIF, immunological screening of some kind was applied by 69% of clinicians. The most frequently employed tests included antithyroid antibodies (80%) and anti-nuclear autoantibodies (ANA) (>60%) (Cimadomo *et al.*, 2021). There is a lack of evidence on the impact of ANA on pregnancy outcomes in infertile women undergoing IVF/ICSI treatment and, as such, for ANA screening in RIF (Zeng *et al.*, 2019).

A full assessment of the biological basis of immunological screening in RIF is beyond the scope of this article, but the more commonly employed approaches used are addressed below.

Uterine and peripheral natural killer cells

Uterine natural killer cells (uNK cells) are known to be key players at the feto-maternal interface, where they represent around 70% of immune cells (Lédée-Bataille *et al.*, 2004; Tuckerman *et al.*, 2010; Lash and Bulmer, 2011; Moffett and Colucci, 2014; Seshadri and Sunkara, 2014; Vomstein *et al.*, 2020). However, compared to peripheral NK cells (pNK cells), uNK cells are not cytotoxic. Both NK cell types act as immunomodulators but demonstrate a different profile of secreted cytokines and receptor/gene expression (Tang *et al.*, 2011; Seshadri and Sunkara, 2014; Vomstein *et al.*, 2020). Besides functional differences, measured numbers of pNK and uNK cells do not correlate in an individual and therefore should be regarded as two individual markers (Kuon *et al.*, 2017a; Woon *et al.*, 2022). uNK cell concentrations undergo tremendous changes during the menstrual cycle, showing hormone-dependent changes in phenotype and high levels in the luteal phase, underlining the need for defining strict criteria when analyzing uNK cell counts and functions (Fraser and Zenclussen, 2022). Some studies have reported that finding higher than normal uNK cell counts is associated with a less favourable implantation milieu (Chen *et al.*, 2017; Kuon *et al.*, 2017b; Odendaal and Quenby, 2021) and in a recent systematic review, including eight studies with patients with RIF, a significant difference in total CD56+ uNK cells was shown in women with RIF compared with controls (standardized mean difference 0.49; 95% CI −0.01–0.98; $P = 0.046$; 604 women) (Woon *et al.*, 2022). However, other studies have not shown an association of either uNK cells (Donoghue *et al.*, 2019) or pNK cells with RIF (Seshadri and Sunkara, 2014; Salazar *et al.*, 2022).

This may, in part, reflect the lack of consensus regarding the most reliable means of quantifying or assessing the distribution of uNK cells (e.g. with immunohistochemistry or FACS analysis) and reference ranges vary substantially between studies (Lash *et al.*, 2016; Chen *et al.*, 2017; Kuon *et al.*, 2017b; Vomstein *et al.*, 2020; Woon *et al.*, 2022). It is also uncertain to what degree simply assessing the numbers of uNK cells reflects their function in the endometrium. Functional tests, including the constitution of receptors (e.g. killer immunoglobulin-like receptors: KIRs), may have more clinical value (Woon *et al.*, 2022).

Recent studies have further elucidated the roles of uNK cells in the endometrium, including that in the biosensor function of the decidualized endometrium (Kong *et al.*, 2021). It has also been proposed that inadequate activation of uNK cells might be a cause of RIF (Donoghue *et al.*, 2019; Alecsandru *et al.*, 2020) and the same is true for pNK cells in RIF (Seshadri and Sunkara, 2014; Salazar *et al.*, 2022).

Treatment approaches have been proposed for patients with elevated uNK cells or evidence of disrupted function including lipid infusions (Lédée *et al.*, 2018) and glucocorticoid administration (Quenby *et al.*, 2005). While some cohort studies have suggested an impact of uNK cells on clinical outcomes, adequately powered RCTs of targeted interventions in RIF are still required. While the emerging role of uNK cells suggests that they remain a potential target for effective interventions, until better-validated tests of uNK cell function and treatment strategies are available, NK cell testing is not recommended.

Peripheral NK cell testing is not recommended.

Uterine NK cell testing is not recommended.

T lymphocytes

Imbalances in CD4+ T-helper lymphocytes, i.e. Th1, Th2, Th17, and regulatory T cells (Treg), have been suggested as contributing to RIF (Ali *et al.*, 2018).

In a small case–control study, patients with RIF showed significant reductions of blood polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs), myeloid-derived suppressor cells, Tregs, and nitrous oxide production by PMN-MDSCs, whereas the expression of ζ chain on CD4+ T-cell receptor and CD8+ T-cell receptor was upregulated (Jiang *et al.*, 2017). Furthermore, a retrospective study reported a reduced blocking efficiency of CD3, CD4, and CD8 in patients with RIF (Gao *et al.*, 2021). Huang *et al.* (2021) compared patients with RIF who conceived with patients who failed to conceive and found higher percentages of CD3+ lymphocytes in the failed group. However, no differences were observed in CD4+ and CD8+ lymphocytes in RIF in the study of Harrity *et al.* (2019). In yet another study, no significant differences in circulating T-lymphocytes were observed, although the

authors reported higher production of Th1 and Th2 cytokines (Lashley *et al.*, 2015).

Uterine T lymphocytes assessment is not recommended.

Peripheral blood cytokine levels

During implantation, cytokines in the peripheral blood have been described as changing from a proinflammatory (Th1 type) to an anti-inflammatory (Th2 type) profile (Zhao *et al.*, 2021). While this may represent an over-simplification, some studies with small study populations showed that a pro-inflammatory state persists in women with RIF, which might disturb implantation (Inagaki *et al.*, 2003; Liang *et al.*, 2015a,b; Marron and Harrity, 2019). However, as the assessment of cytokine levels is time-consuming and expensive, it is not applied in clinical practice.

The assessment of blood cytokine levels is not recommended.

HLA-C compatibility

Owing to their genetic variability and ability to bind to specific HLA class I allotypes, KIRs on uNK cells have been considered good candidates for balancing maternal leukocyte tolerance towards the embryo. It has been postulated that an adequate interaction between maternal KIRs and their ligands, the HLA class I molecules, expressed by the extravillous trophoblast cells is crucial for sustained implantation (Díaz-Hernández *et al.*, 2021).

An increased risk of RIF is observed in women carrying the HLA-C2 allotype and the HLA-G allele with a 14 bp insertion (Lashley *et al.*, 2014). However, the fact that neither human blastocysts at the time of transfer nor the syncytiotrophoblast express HLA-C, and that HLA-C starts to be expressed later during placentation when the endovascular trophoblast starts to replace the spiral arteries (Blaschitz *et al.*, 2001), raises the importance of further research on the role of HLA-C in RIF. Moreover, its analysis is not widely applied in practice.

Assessing HLA-C compatibility is not recommended.

Thrombophilia screening

Thrombophilia represents a pathological predisposition to form blood clots that could induce local vascular impairment that may be detrimental to embryo implantation. They have become widely implicated as a cause of both RIF and RPL. In a survey of clinical practice, haemostatic aspects were considered worthy of investigation in RIF by 74% of clinicians, of whom 96% reported performing investigations for antiphospholipid antibody syndrome (APS) and 75% perform hereditary thrombophilia screening tests (Cimadomo *et al.*, 2021).

Inherited thrombophilia

Inherited thrombophilia comprises conditions in which a genetic mutation affects the amount or the function of a protein in the coagulation pathway. Mutations in several genes have been shown to be involved: G1619A (factor V Leiden), R2 H1299R (factor V Leiden polymorphism), A1298C (methylenetetrahydrofolate reductase (MTHFR) enzyme mutation), C677T (MTHFR polymorphism), V34L (factor XIII polymorphism), G20210A (mutation of the prothrombin gene), a/b L33P (ribosomal polymorphism of MTHFR enzyme), and 4G/5G (plasminogen activator inhibitor-1 (PAI-1)) (Neamţu *et al.*, 2021).

Inherited thrombophilia has been implicated in early pregnancy loss and implantation failure, by impairment of the vascular changes necessary for successful pregnancy (Qublan *et al.*, 2006; Neamţu *et al.*, 2021).

Qublan *et al.* (2006) reported significantly more homozygous mutations in the Factor V Leiden and the MTHR (C677T) gene in women experiencing multiple IVF failures compared to women with a successful first IVF cycle and 25% in healthy fertile controls. Coulam *et al.* (2006) reported a higher prevalence of PAI-1 4G/5G mutations than controls in women with a history of implantation failure after IVF-ET. Azem *et al.* (2004) reported a significantly increased incidence of inherited thrombophilia in women with a history of four or more IVF failures compared to healthy fertile women (44.4% versus 18.2%; OR 3.6; 95% CI 1.25–10.6). However, several studies have reported that the incidences of aforementioned inherited thrombophilia in women with RIF were not different from those in controls (Vaquero *et al.*, 2006; Simur *et al.*, 2009).

Acquired thrombophilia

Acquired thrombophilia includes acquired C protein, S protein, APS, antithrombin III deficiency, and drug-induced thrombophilia. Acquired thrombophilia has been associated with pregnancy morbidity, specifically RPL (Miyakis *et al.*, 2006).

A recent review summarized studies evaluating the prevalence of antiphospholipid antibodies (APA) in women with RIF (Papadimitriou *et al.*, 2022). The RR for the presence of any type of APA was 3.06 (95% CI 1.97–4.77; $I^2 = 15\%$; 5 studies; $n = 864$) in women with RIF compared to women having at least one successful IVF-ET. In women experiencing at least two implantation failures, the presence of anti-cardiolipin antibodies only or lupus anticoagulant was associated with a significant RR of, respectively, 5.06 and 5.81 for impaired implantation. A recent study evaluated the prevalence of APS (meeting all clinical and laboratory criteria) in 185 patients with RIF and showed APS in only 2.88% of patients, with <5% having APA (Vomstein *et al.*, 2020).

While the investigation and management of both inherited and acquired thrombophilia have been the mainstay clinical approach to RIF and RPL, their role in the aetiology of both of these conditions is being increasingly challenged. Consistent with the recent ESHRE guideline on the management of RPL (ESHRE Guideline Group on RPL *et al.*, 2023), the role of testing is likely to be very limited in the context of RIF and should mainly focus on women with a clinical or family history of thromboembolic events. However, given the severe implications that APS can have on both maternal and foetal outcomes, it should be excluded before ART when there is a clinical suspicion (e.g. RPL or a clinical history of arterial or venous thrombosis).

Assessment of APA and APS is recommended in RIF women with additional risk factors for thrombophilia and can be considered in women without such risk factors.

Investigating factors related to the embryo

Mitochondrial DNA content

The mitochondrial DNA (mtDNA) content of human embryos has been proposed as a possible indicator of embryo viability and implantation potential. Several studies have reached contradictory results on mtDNA content—often expressed as the mitochondrial score or the ratio of mitochondrial/nuclear DNA copy number—according to embryo developmental day, embryo quality, maternal age, and implantation capacity. On the clinical significance of mtDNA content or the mitochondrial score for predicting the embryo's ability to implant, the study results are highly conflicting, finding a positive, negative, or no correlation with implantation rate (Tan *et al.*, 2014; Diez-Juan *et al.*, 2015; Fragouli *et al.*, 2015, 2017; Ravichandran *et al.*, 2017; Treff *et al.*, 2017; Victor *et al.*, 2017; de los Santos *et al.*, 2018; Klimczak *et al.*, 2018; Podolak *et al.*, 2022). It could be considered that only extreme values for mtDNA content may be correlated with clinical outcomes (Podolak *et al.*, 2022). Given the experimental nature of the test, the small sample size, and the small number of studies, further studies are required to reach a conclusion.

Evaluation of mitochondrial DNA (mtDNA) content in the embryos is not recommended.

Artificial intelligence-powered tools for embryo/blastocyst quality assessment

Poor embryo/blastocyst quality and morphokinetic abnormalities are associated with reduced reproductive competence, also in the context of euploid ETs (Shear *et al.*, 2020; Zhan *et al.*, 2020; Bamford *et al.*, 2022). Nevertheless, embryo grading is highly subject to limited (especially inter-centre) reproducibility (Khosravi *et al.*, 2019; Cimadomo *et al.*, 2022; Fordham *et al.*, 2022). Artificial intelligence (AI)-powered tools are currently under investigation, which may standardize embryo evaluation and improve its reliability in the coming years (Kragh and Karstoft, 2021; Riegler *et al.*, 2021). In particular, AI may provide objective definitions of embryo quality and generalizable estimates of its impact on implantation failure/success, with evident implications also in the definition of RIF.

Similarly, omics analyses of IVF spent media are currently subject to intense academic, pre-clinical, and clinical investigations. Nevertheless, the data are still preliminary, and they have not been studied in the context of RIF, therefore they cannot be considered for the time being.

Investigating male factors

Investigating factors that can contribute to RIF in the male partner is widely applied and considered important by almost 80% of the participants of the survey on clinical practice in RIF. Such investigations include questioning about lifestyle (e.g. smoking, drugs), semen analysis, and sperm DNA fragmentation test (Cimadomo *et al.*, 2021).

Semen analysis, spermiogram, sperm fluorescent in situ hybridization, and sperm DNA-fragmentation

Semen analysis is part of the routine fertility workup before ART (Fig. 1) (ASRM, 2015; Vlaisavljevic *et al.*, 2021). Deviations in sperm concentration, motility, and morphology seem to be associated with lower conception rates (Jouannet *et al.*, 1988; WHO, 2021), but also low fertilization and poor embryo development. In a study comparing patients with RIF to controls, significantly better sperm motility and morphology were detected in the couples with RIF, indicating a lack of robustness of data to link sperm parameters with RIF (Ocal *et al.*, 2012).

Sperm fluorescent *in situ* hybridization (FISH) is a cytogenetic clinical diagnostic assay that assesses the frequencies of chromosomal abnormalities, considered useful in counselling RPL patients with previously failed ART (WHO, 2021). A retrospective case–control study showed no correlation of sperm aneuploidy FISH with RIF as an independent factor. However, around 24% of males with RIF having an abnormal FISH result were normozoospermic (Rodrigo *et al.*, 2019). Others reported aberrant FISH results in only 14.8% (4/27) of RIF patients without impact on implantation or pregnancy rates (Sarrate *et al.*, 2019).

There are several different sperm DNA-fragmentation (SDF) tests, and currently there is no standardization on the methodologies and threshold for normal values. In addition, there are conflicting data regarding SDF testing results and clinical pregnancy following ART (Evenson and Wixon, 2006; Cissen *et al.*, 2016; Simon *et al.*, 2017). A recent large retrospective cohort study including 1339 women undergoing 2759 IVF/ICSI cycles reported that there was no significant difference in LBR per first ET between ≤15% and >15% SDF groups: 38.2% (95% CI 34.5–41.9; $n = 665$) versus 41.9% (95% CI 34.2–49.7; $n = 155$; OR 1.2; 95% CI 0.8–1.7; $P = 0.4$). Similarly, cumulative LBR was not significantly different between groups with high or low SDF (Hervás *et al.*, 2022). While SDF is suggested to be a contributing factor to RPL and unexplained infertility, data specifically in patients with RIF are scarce. Furthermore, there is no consensus on the cost-effectiveness of the test in general or in couples with RIF (Minhas *et al.*, 2021; Hervás *et al.*, 2022).

Sperm FISH analysis and sperm DNA fragmentation (SDF) are not recommended.

Different treatments have been suggested as viable options for male partners of patients with RIF. These include improving semen quality, such as antioxidant use, and techniques to select functional sperm, such as magnetic-activated cell sorting (MACS), intracytoplasmic morphologically selected sperm injection and other sperm selection techniques, and surgical sperm retrieval (e.g. testicular sperm extraction (TESE)). However, so far, there are no studies that have evaluated these interventions in couples with RIF which were of sufficient quality to support any recommendations.

Lifestyle factors

Obesity, especially when accompanied by metabolic syndrome, correlates with poor semen quality (Ma *et al.*, 2019; McPherson and Tremellen, 2020; Tremellen and Pearce, 2020). Likewise, lifestyle habits in men, such as smoking, high caffeine intake or alcohol consumption and drug abuse, seem to not only negatively alter conventional semen parameters, but also other molecular aspects such as sperm DNA integrity or redox status (Rahban and Nef, 2020).

Lifestyle interventions in men can help to improve certain sperm parameters as well as embryo quality (Velotti *et al.*, 2021), but such interventions have not been evaluated with regard to their impact on RIF.

While lifestyle factors have been investigated during the fertility workup, it is recommended to review lifestyle factors and their optimization at the time of RIF, especially since lifestyle factors may have changed in the course of the ART treatment.

Interventions for RIF

The pressure on clinicians to intervene in cases with RIF is considerable and comes, in part, from an expectation from their patients. Nearly 80% of clinicians offer treatments preconception and 75% offer additional treatments during the next ART cycle. Preconception treatments mainly focus on lifestyle advice (73–97%), vitamin supplementation (83%), antioxidant therapy (71%), and treatments for endometritis (90%) and endometriosis (80%), but endometrial injury (57%) and immune-modulation therapy (46%) are also offered. Widely practised interventions during ART include personalized luteal phase support (83%), cycle segmentation and freeze-all (70%), and p-ET (62%). Popular strategies employed in the ART lab include PGT-A (68%), assisted hatching (61%), the addition of growth factors to culture media (27%) and time-lapse microscopy (40%). TESE is offered by 57% of clinicians, with fewer clinicians offering physiological ICSI (41%) or MACS (20%). Most interventions are applied empirically and without diagnostic rationale. Sixty-nine per cent of the clinicians completing the survey consider oocyte or sperm donation a valuable option in RIF (Cimadomo *et al.*, 2021).

The offer of a considerable range of interventions is not guided by evidence of efficacy but by a perceived need to act. Given this challenging landscape, this good practice document aims to support clinical practice by providing the evidence in a summary of the most relevant studies. The results of these studies should be interpreted with caution for several reasons. First, the definition of RIF applied varies, and consequently, the study cohort of one study may differ significantly from that of another. Variations in what constituted the fertility workup before ART add to the heterogeneity, as do differences in ET strategy. Moreover, sample sizes tend to be small and, in most cases, interventions are evaluated without any attempt to diagnose the cause of RIF or irrespective of the results of the diagnostic investigations.

A summary of all interventions and whether they are recommended, to be considered or are not recommended is provided in Fig. 5. Details on the justification for the recommendations are included below and in Supplementary Data S2.

Intentional endometrial injury

Endometrial injury or endometrial scratch is performed to improve the receptivity of the endometrium towards the transferred embryo. The biological mechanism of action is not fully understood.

A meta-analysis by Busnelli *et al.* (2021) reported that, based on three RCTs, there was no significantly increased chance of pregnancy and LBR in women who underwent intentional endometrial injury (random effects model, RR 1.43; 95% CI 0.79–2.61; $P = 0.24$; $I^2 = 52\%$ and RR 1.55; 95% CI 0.81–2.94; $P = 0.18$; $I^2 = 46\%$, respectively). A consistent positive effect of endometrial injury on clinical PR (CPR) was reported in two observational studies (Raziel *et al.*, 2007; Matsumoto *et al.*, 2017). A more recent RCT including 211 women also reported no significant difference in clinical pregnancy (foetal heartbeat), pregnancy loss, or multiple pregnancies between patients with RIF who underwent hysteroscopy and intentional endometrial injury versus hysteroscopy only (Zahiri *et al.*, 2021). A Cochrane review on endometrial injury in women undergoing IVF reported similar data from a subanalysis on RIF (Lensen *et al.*, 2021). To date, studies of the efficacy of endometrial scratching have been empirical, as tests that would define a cause of RIF for which endometrial injury could represent a relevant therapy are not yet established.

Intentional endometrial injury is not recommended.

Granulocyte colony-stimulating factor administration

G-CSF plays a role in embryo implantation and the continuation of pregnancy by temporarily suppressing immune response through its effects on lymphocytes, macrophages, and T helper-2 cells (Moldenhauer *et al.*, 2010). Its use may be associated with recruiting dendritic cells, promoting Th-2 cytokine secretion, activating Tregs, favouring the local immune responses, vascular remodelling of the endometrium, and cellular adhesion pathways (Rahmati *et al.*, 2014). When administered systemically, G-CSF has been reported to play a role in embryonic development, implantation, and trophoblastic growth (Würfel, 2015), while local intrauterine administration could improve endometrial receptivity (Rahmati *et al.*, 2014).

Few studies, summarized in two meta-analyses including some of the same RCTs, evaluated the effect of subcutaneous or intrauterine G-CSF administration in patients with RIF (Busnelli *et al.*, 2021; Hou *et al.*, 2021). Subcutaneous G-CSF administration was associated with an increased chance of clinical pregnancy compared with no treatment in both meta-analyses (RR 2.29; 95% CI 1.58–3.31; 4 RCTs; $n = 333$) (Busnelli *et al.*, 2021) (RR 1.73; 95% CI 1.33–2.23; 6 RCTs; $n = 497$) (Hou *et al.*, 2021). Intrauterine administration had no impact on CPR in the review by Busnelli *et al.* (2021) (RR 1.53; 95% CI 1.00–2.33; 2 RCTs; $n = 257$), while the other review reported an increased chance of clinical pregnancy with intrauterine G-CSF (RR 1.39; 95% CI 1.09–1.78; 4 RCTs; $n = 479$) (Hou *et al.*, 2021). The analysis for LBR failed to show a benefit (RR 1.43; 95% CI 0.86–2.36; 3 RCTs; $n = 372$) (Hou *et al.*, 2021). Two more recent RCTs on intrauterine G-CSF administration in patients with RIF confirmed conflicting results (Karimi *et al.*, 2020; Torky *et al.*, 2021).

Side-effects or adverse events for G-CSF administration include mucositis, splenic enlargement, hepatomegaly, transient hypotension, epistaxis, urinary abnormalities, osteoporosis, exacerbation of rheumatoid arthritis, anaemia, and pseudogout (Moffett and Shreeve, 2015).

Overall, there is conflicting evidence on whether intrauterine G-CSF administration improves LBR in patients with RIF. For subcutaneous G-CSF administration, it was considered that prior to a possible recommendation for clinical practice, the suggested positive impact on pregnancy rates in RIF patients needs further corroboration, both in terms of follow-up to live birth and safety aspects.

G-CSF administration (either intrauterine or subcutaneous) is not recommended.

Intravenous intralipid infusion

Intravenous intralipid infusion has been proposed to have a role in immune modulation through the reduction of platelet aggregation, a decrease of IL-2, tumour necrosis factor-α, and IL-1β production as well as suppression of NK cell levels and activity.

Few RCTs have evaluated the effectiveness of intravenous intralipid during ART in patients with RIF. A systematic review and meta-analysis reported a higher CPR (172/417 versus 119/

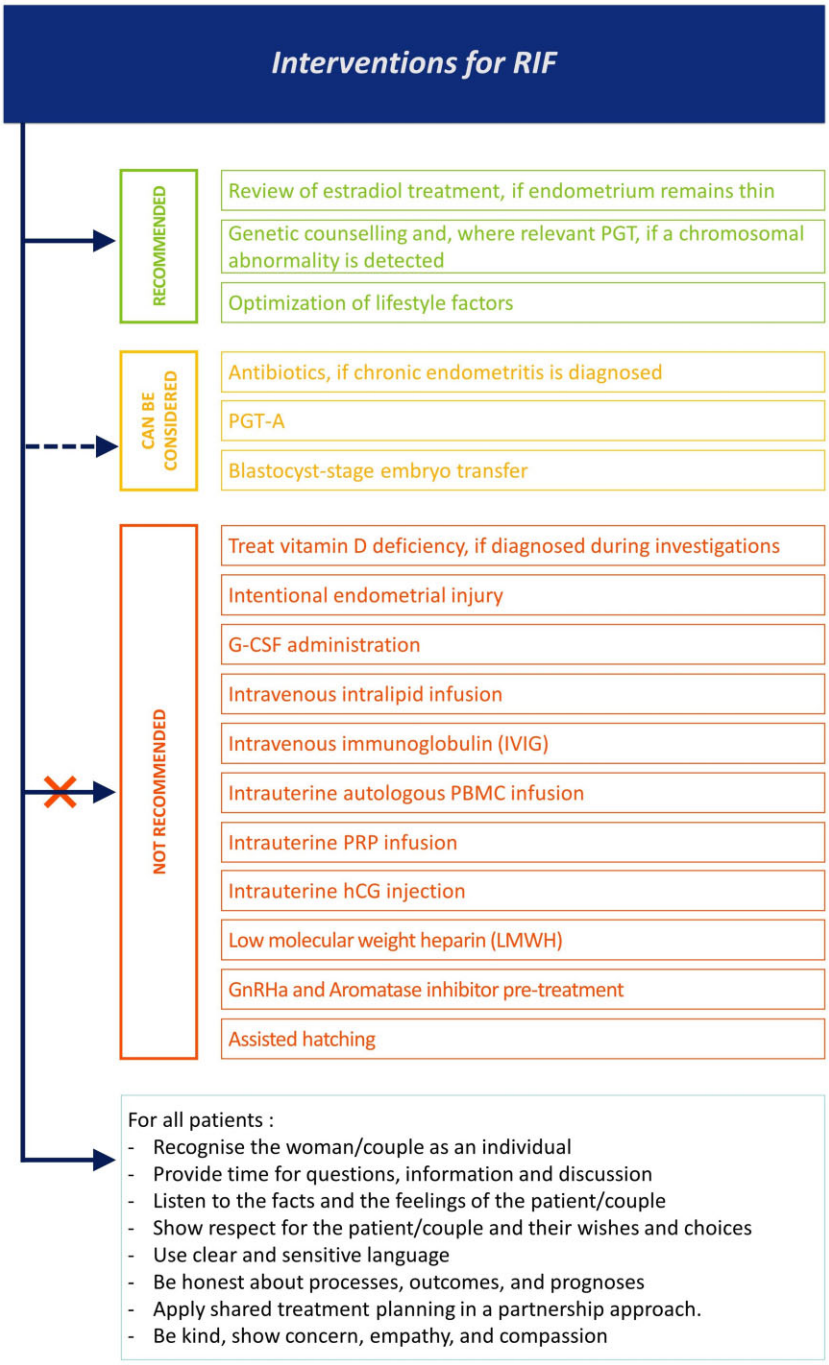

Figure 5. Summary of interventions for patients with RIF. The details on the evidence in support of the recommendations and other factors considered are provided in the body of this paper as well as the Supplementary Data. AI, aromatase inhibitor; GnRHa, GnRH agonist; G-CSF, granulocyte colony-stimulating factor; mtDNA, mitochondrial DNA; PBMC, peripheral blood mononuclear cells; PGT-A, preimplantation genetic testing for aneuploidies; PRP, platelet-rich plasma; RIF, recurrent implantation failure.

426; RR 1.55; 95% CI 1.16–2.07; 5 RCTs; $I^2 = 44.2\%$) and LBR (132/417 versus 73/426; RR 1.83; 95% CI 1.42–2.35; 5 RCTs; $I^2 = 0\%$) with the intervention but concluded there is limited evidence to support the use of intravenous intralipid at the time of ET in women with a history of RIF (Rimmer *et al.*, 2021).

In a multicentre study evaluating intravenous intralipid and prednisone in 64 patients with RIF, higher CPRs were found in treated patients (44% versus 9%; $P < 0.001$) with OR at 8.13 (95% CI 4.49–14.72; $P < 0.0001$) (Kolanska *et al.*, 2021). Most studies to date have evaluated intravenous intralipid as an empirical intervention without targeting any diagnosed underlying pathology. In a cohort study that evaluated lipid infusions in 94 patients with RIF with an immune profile of endometrial over-immune activation, a LBR of 54% following the next ET was observed (Lédée *et al.*, 2018). However, larger controlled studies are required to confirm this.

Balanced against the possible benefits of intra-lipid infusions are side effects or adverse events, and these have been reported to include hepatomegaly, jaundice, cholestasis, splenomegaly, thrombocytopenia, leukopenia, and fat overload syndrome

(Moffett and Shreeve, 2015). Taken together, intravenous lipid infusions are, therefore, not recommended.

Intravenous intralipid infusion is not recommended.

Intravenous immunoglobulin

The intravenous injection of IgG (IVIG) is suggested to have immunomodulatory actions by neutralizing autoantibodies, down-regulation of B-cell and T-cell function, and blockage of Fc receptors.

The review of Abdolmohammadi-Vahid *et al.* (2019) included two cohort studies and two cross-sectional studies focussing on IVIG in RIF and showed a significant difference in the IVIG group compared to controls in LBR (cohort studies: OR 2.17; 95% CI 1.30–3.61; $P = 0.003$ and cross-sectional studies: OR 7.57; 95% CI 4.53–12.64; $P < 0.00001$) and PR (cohort studies: OR 1.82; 95% CI 1.14–2.89; $P = 0.01$ and cross-sectional studies: OR 11.12; 95% CI 6.43–19.23; $P < 0.00001$). One more recent observational study reported significantly increased LBR and CPR in treated women (OR 1.76; 95% CI 1.08–2.89; $P = 0.02$ and OR 2.08; 95% CI 1.28–3.36; $P = 0.003$, respectively) (Ho *et al.*, 2019; Busnelli *et al.*, 2021). While the studies report a benefit for IVIG, study populations are small and RCTs are lacking.

Side effects or adverse events of IVIG include aseptic meningitis, renal failure, thromboembolism, haemolytic reactions, anaphylactic reactions, lung disease, enteritis, dermatologic disorders, and infectious diseases. An additional ethical concern that has been raised is the diversion of IVIG from patients with serious conditions, necessitating strict allocation of the limited supplies available (Moffett and Shreeve, 2015).

Intravenous immunoglobulin (IVIG) is not recommended.

Intrauterine autologous peripheral blood mononuclear cells infusion

The rationale supporting this treatment is the local production of cytokines by such stimulated peripheral blood mononuclear cells (PBMCs), which could improve blastocyst invasion into the endometrium (Yu *et al.*, 2014; Fan *et al.*, 2021).

A meta-analysis of studies with RIF patients experiencing ≥3 failed ETs showed a beneficial effect of intrauterine PBMCs infusion with regard to LBR and PR (RR 1.93; 95% CI 1.35–2.76; $P < 0.001$; 1 RCT + 3 studies and RR 1.92; 95% CI 1.48–2.49; $P < 0.001$; 2 RCTs and 6 quasi-experimental studies) (Maleki-Hajiagha *et al.*, 2019). Two more recent RCTs and one study confirmed these findings (Chakrabarti *et al.*, 2019; Nobijari *et al.*, 2019; Pourmoghadam *et al.*, 2020). Other meta-analyses including the same dataset have been published, but in all studies and RCTs, the study populations are small and the definitions for RIF are inconsistent. Furthermore, techniques to prepare PBMCs differed substantially between studies (co-cultured in the presence of hCG, corticotrophin-releasing hormone, HMG, a mixture of fresh and co-cultured PBMCs).

Comprehensive data regarding side effects, complications, and adverse pregnancy outcomes are not available (Maleki-Hajiagha *et al.*, 2019). Taken together, while a role for PBMCs in specific patients with RIF might be identified, at present their empirical use is not recommended.

Intrauterine autologous peripheral blood mononuclear cells (PBMCs) infusion is not recommended.

Intrauterine platelet-rich plasma infusion

Platelet-rich plasma is an autologous concentrate of platelets in plasma. Cytokines and growth factors present in PRP are considered to exert a regenerative effect on tissues and cells, including the endometrial lining (Mouanness *et al.*, 2021).

Busnelli *et al.* reported a significantly increased chance of clinical pregnancy after intrauterine PRP administration (fixed effects model: RR 2.45; 95% CI 1.55–3.86; $P = 0.0001$; $I^2 = 0\%$; 2 RCTs; $n = 195$) (Nazari *et al.*, 2019; Zamaniyan *et al.*, 2020; Busnelli *et al.*, 2021). A more recent RCT from the same group confirmed these findings (Nazari *et al.*, 2022). Women included in the trials were not selected for thin endometrium.

A previous meta-analysis, which did not include the most recent RCT and employed less stringent inclusion criteria, included three RCTs and four cohort studies and reported a significantly higher probability of clinical pregnancy in the PRP group (RR 1.79; 95% CI 1.37–2.32; $P < 0.001$; $I^2 = 16\%$; $n = 625$) (Maleki-Hajiagha *et al.*, 2020). From a network meta-analysis of 16 studies, it was concluded that among different immunomodulatory therapies evaluated in RIF, PRP was the most effective treatment towards improving LBR (Liu *et al.*, 2022a). The authors did add a caveat that additional high-quality studies are necessary to verify the conclusions from their analysis owing to the restricted number of included studies.

Aghajanzadeh *et al.* (2020) reported from a study of 30 patients with RIF that there is no significant improvement in the implantation or OPR of frozen-thawed embryo recipients treated with PRP as compared to previous cycles without PRP (implantation rate 6.7% versus 0.0%, with or without PRP). In another small retrospective cohort study, PRP in 15 patients with RIF and 39 with thin endometrium (<8 mm) resulted in significantly improved CPR (27.2% versus 9.6%, respectively), but no increase in EMT in the PRP cycle compared to the previous ET cycle (Enatsu *et al.*, 2022). Comprehensive data regarding side effects, complications, and adverse pregnancy outcomes were not available. Furthermore, PRP is characterized by its absolute platelet concentration, which is any concentration above that of whole blood, causing wide variance between studies. Information regarding PRP preparation in individual studies is insufficiently reported (Maleki-Hajiagha *et al.*, 2020). Consensus on the method of platelet isolation and platelet concentration is imperative for clinical implementation.

Overall, the evidence available is not considered sufficient to support the use of PRP infusions.

Intrauterine platelet-rich plasma (PRP) infusion is not recommended.

Intrauterine hCG injection

The infusion of hCG may help to initiate and control blastocyst invasion and improve immune tolerance from the mother (Zenclussen *et al.*, 2006).

Based on two observational studies, the effect of intrauterine hCG injection in women with RIF (≥3 failed ET) and normal EMT (8–16 mm) was reported to significantly increase LBR (OR 1.78; 95% CI 1.02–3.09; $n = 303$; $P = 0.04$) and CPR (fixed effects model: OR 1.81; 95% CI 1.23–2.65; $n = 482$; $P = 0.002$; $I^2 = 0\%$)

(Huang *et al.*, 2018; Liu *et al.*, 2019; Busnelli *et al.*, 2021). Liu *et al.* (2019) showed a beneficial effect of intrauterine hCG injection on implantation rate (OR 1.71; 95% CI 1.08–2.71; $P = 0.02$).

A less stringent systematic review on intrauterine hCG administration in patients with RIF (≥2 failed ET) also showed increased LBR and CPR in the treatment group versus controls (27.8 versus 18.0%; RR 1.52; 95% CI 1.18–1.96; 3 studies; $n = 870$ and 41.8 versus 31.2%; RR 1.30; 95% CI 1.14–1.50; 6 studies; $n = 1432$, respectively) (Xie *et al.*, 2019). A recent RCT including 98 women compared intrauterine hCG injection with placebo and reported significantly higher CPR (23/49 (46.9%) versus 11/48 (22.9%)) and implantation rates (28/120 (23.3%) versus 16/118 (13.6%)) with hCG treatment (Torky *et al.*, 2021). The review of Conforti *et al.* (2022), while not focussed on women with RIF, concluded that the possible benefit of intrauterine hCG injection may be limited to cleavage-stage ET.

While the evidence is suggestive of a benefit, the data are mainly derived from (small, uncontrolled) studies rather than RCTs. Furthermore, there is significant heterogeneity between the studies concerning hCG dosage and timing of administration, the volume of perfusion fluid, and the type of transfer cycle (fresh or frozen). From this, it is concluded that there is insufficient evidence to support a recommendation for applying intrauterine hCG injection in clinical practice.

Intrauterine hCG injection is not recommended.

Low molecular weight heparin

Low molecular weight heparin (LMWH) was found to have a significant impact on LBR in women with acquired thrombophilia. It has been postulated that the anticoagulation effect of heparin prevents placental thrombosis and infarction, and promotes the establishment and continuation of pregnancy (Nelson and Greer, 2008). Considering a possible association of thrombophilia with RPL and RIF, the use of LMWH has been expanded to these patients undergoing ART, even in the absence of acquired or inherited thrombophilia.

A meta-analysis investigated the use of LMWH in patients with RIF (≥3 failed ET) but failed to show an effect of LMWH on LBR (RR 1.38; 95% CI 0.64–2.96; 2 RCTs; $n = 71$) and CPR (RR1.39; 95% CI 0.87–2.23; 2 RCTs; $n = 218$) (Busnelli *et al.*, 2021). The observational study by Berker *et al.* (2011) also failed to show a difference in LBR or PR.

The included studies had small study populations including a mix of patients with RIF, some with thrombophilia and some who were not tested or negative for thrombophilia (Potdar *et al.*, 2013; Siristatidis *et al.*, 2018; Busnelli *et al.*, 2021). LMWH has a good safety profile in pregnancy, even if it may cause bruising and bleeding.

Low molecular weight heparin (LMWH) is not recommended to increase the chance of pregnancy or live birth in women with RIF.

GnRH agonist and aromatase inhibitor pre-treatment

Considering endometriosis may be an underlying and undiagnosed cause of RIF, it was hypothesized that empirical GnRH agonist and aromatase inhibitor treatment before ET may improve pregnancy outcomes (Steiner *et al.*, 2019).

In an RCT, 67 women with at least two implantation failures were randomized to receive GnRH agonist (0.1 mg/day) from Day 21 of the cycle preceding frozen-thawed ET. The dose was reduced to 0.05 mg/day from Cycle Day 2. The control group received no GnRH agonist. No significant differences were found in CPR (25.8% versus 19.4%) or implantation rate (13.55% versus 10.52%) in the study versus the control group (Davar *et al.*, 2020). In a retrospective cohort study, infertile patients aged 36–43 years undergoing their third or more ET after autologous IVF or ICSI were included. The study group ($n = 290$) received a single injection of 3.75 mg long-acting triptorelin acetate on Day 2 of the preceding cycle, followed by hormone replacement therapy (HRT). The control group ($n = 194$) received HRT only. Clinical pregnancy rate (49.0% versus 35.1%), OPR (37.6% versus 22.7%), and LBR (36.6% versus 22.1%) were significantly higher in the study group compared to controls, respectively. Miscarriage rates did not differ between groups (Pan *et al.*, 2022).

In another retrospective cohort study, infertile women who failed two blastocyst transfers underwent a third frozen blastocyst transfer (Steiner *et al.*, 2019). Prior to the third ET, 143 women received 2 months of GnRH agonist (3.75 mg intramuscular leuprolide acetate monthly) only, 176 received GnRH agonist and aromatase inhibitor (5 mg oral letrozole daily for 60 days), and 204 received no pre-treatment. CPR and LBR were higher among women who received GnRH agonist plus letrozole compared with women who received GnRH agonist-only or women without pre-treatment (CPR: 63%, 42%, and 40%, respectively; $P < 0.0001$; LBR: 56%, 36%, and 34%, respectively; $P < 0.0001$). However, there was no difference between no pre-treatment and GnRH agonist-only pre-treatment.

Taken together, while a role for GnRH agonist and aromatase inhibitor pre-treatment in specific patients with RIF might be identified, at present, their empirical use is not recommended.

GnRH agonist and aromatase inhibitor pre-treatment is not recommended.

Preimplantation genetic testing for aneuploidies

While the rationale for offering preimplantation genetic testing (PGT) for structural rearrangements (PGT-SR) for RIF couples with a diagnosed chromosomal disorder seems clear, PGT for aneuploidies (PGT-A) is also offered to RIF couples in general. Treatment benefit is suggested from the deselection of embryos diagnosed with uniform whole-chromosome aneuploidies, namely the main embryonic cause of pregnancy loss and implantation failure in humans. Specifically, aneuploid blastocysts transferred in the context of blinded non-selection or unblinded cohort studies resulted in a high lethality rate per transfer and miscarriage rate per clinical pregnancy (respectively, 98% and >86% in the study by Capalbo *et al.* (2022)) (Tiegs *et al.*, 2021; Capalbo *et al.*, 2022), thus supporting the use of PGT-A in populations of patients subject to higher embryo aneuploidy rates, such as advanced maternal age women.

Busnelli *et al.* included two RCTs (Blockeel *et al.*, 2008; Rubio *et al.*, 2013) and three observational studies (Yakin *et al.*, 2008; Greco *et al.*, 2014; Sato *et al.*, 2020) investigating the potential role of PGT-A in improving IVF outcomes in women with RIF. The meta-analysis of RCTs failed to show an improvement in both clinical pregnancy and LBR (random effects model: RR 1.07; 95% CI 0.36–3.15; $P = 0.90$; $I^2 = 89\%$ and RR 0.98; 95% CI 0.32–2.94; $P = 0.97$; $I^2 = 87\%$) in women who underwent PGT-A.

Comparable results were obtained by Yakin *et al.* (2008); however, they used the old-fashioned FISH approach analyzing a limited number of chromosomes in conjunction with the Day 3-biopsy.

In contrast, the retrospective studies where embryo testing was conducted by either array comparative genomic hybridization or NGS approaches on blastocyst biopsies, concluded that PGT-A could be considered a good strategy for women with RIF as a reduced number of ETs were required to achieve pregnancy and live birth (Cozzolino *et al.*, 2020; Ni *et al.*, 2020; Tong *et al.*, 2021).

Non-invasive means of assessing embryo euploidy are the focus of much current research, but this approach is at too early a stage to yet be considered as an option in clinical practice.

Preimplantation genetic testing for aneuploidies (PGT-A) can be considered.

Blastocyst-stage ET

Blastocyst-stage embryos may have a better chance of implantation owing to a lower risk of embryo aneuploidy, better synchronization with the endometrium, and fewer uterine contractions at the time of transfer. A systematic review of 27 studies in ART patients showed, with a low quality of evidence, that LBR after a fresh transfer was higher in the blastocyst transfer group compared to the cleavage-stage ET group (OR 1.27; 95% CI 1.06–1.51; $I^2 = 53\%$; 15 studies; $n = 2219$ women) (Glujovsky *et al.*, 2022).

A prospective cohort study with 575 patients with RIF compared single frozen/thawed blastocyst-stage transfer with frozen/thawed double-cleavage-stage ET and reported higher CPR (OR 1.27; 95% CI 1.11–1.47); implantation rate (OR 1.51; 95% CI 1.21–1.89); and OPR (OR 1.43; 95% CI 1.19–1.73) in the patients undergoing single blastocyst ET (Zhang *et al.*, 2019).

Blastocyst-stage embryo transfer can be considered.

Assisted hatching

The inability of the blastocyst to escape from its zona pellucida is considered one of the pathways leading to unsuccessful ART, including implantation failure. Assisted blastocyst hatching could, in that respect, be an option to facilitate implantation.

A systematic review, including one RCT and one observational study, evaluated assisted hatching on ART outcomes in patients with RIF after at least three failed ETs and exclusion of probable causes of RIF (Busnelli *et al.*, 2021). Assisted hatching did not increase CPR (RCT data: RR 0.78; 95% CI 0.48–1.27; $P = 0.31$; observational data: OR 1.42; 95% CI 0.45–4.48; $P = 0.55$) or LBR (observational data: OR 1.92; 95% CI 0.48–7.67; $P = 0.36$) (Primi *et al.*, 2004; Rufas-Sapir *et al.*, 2004; Busnelli *et al.*, 2021).

Other studies, excluded in the review based on their definition of RIF, reported similar outcomes for CPR. Two studies additionally reported that the contribution of assisted hatching by partial zona dissection to successful implantation was related to the patient's age: patients older than 38 years showed a markedly higher PR after assisted hatching (Stein *et al.*, 1995; Kanyo *et al.*, 2016). Valojerdi *et al.* (2008) commented that a benefit of assisted hatching was found in the patients with frozen-thawed embryos, as the rates were statistically significantly higher in the test group as compared with those of the control group (31.2% and 12.8%, respectively). Yet another study compared the benefit of assisted hatching in patients with optimal versus suboptimal embryo quality and reported better results in patients with optimal embryo quality (Grace *et al.*, 2007).

Assisted hatching is not recommended.

Other treatments

Other treatments have been suggested for RIF, including additional interventions in the laboratory (e.g. time-lapse imaging), medical treatments (sildenafil), adaptations in the ET procedure (e.g. ultrasound-guided ET, performing a trial ET, ensuring the catheter tip is >15 mm from the fundus, recommending a full bladder at ET, cervical dilatation, cervical mucus removal, use of fibrin sealant, use of antibiotics, bed rest following the procedure), and adaptations in the ET strategy (e.g. frozen ET). To our knowledge, there are no studies evaluating the effect of these interventions on the chances of LBR in patients with RIF.

With regards to hyaluronic acid (HA)-supplemented ET medium, meta-analyses support an improvement in the LBR in the general ART population (OR 1.33; 95% CI 1.11–1.60) (Heymann *et al.*, 2020; Holt-Kentwell *et al.*, 2022). However, to our knowledge, the evidence specifically for women with RIF is limited to a single RCT showing a benefit of HA-enriched ET medium compared to routine ET medium in terms of clinical PR (Friedler *et al.*, 2007).

It should be added that couples diagnosed with RIF may benefit from moving to third-party donation for further ART cycles. While third-party donation brings a new set of challenges and requires support and stringent provision of information, it could bypass an underlying (unidentified) issue with the sperm, oocyte, or embryo. Studies are needed to confirm that resorting to ART with donated sperm or oocytes indeed improves the chances of pregnancy and live birth after RIF.

Treatment based on diagnostic findings

Few studies have evaluated interventions for RIF with an established underlying factor.

Some of these combinations of detected underlying factors and respective treatments have been covered in the previous section on investigations. The treatments covered include optimization of lifestyle factors following their re-assessment, review of estradiol treatment if the endometrium remains thin, hysteroscopy to rule out Asherman's syndrome, genetic counselling and where relevant PGT when a chromosomal abnormality is detected, and antibiotic treatment in case CE is detected. Any other abnormalities or dysfunctions identified (thyroid dysfunction, diagnosis of APS, uterine malformations, endometriosis, adenomyosis) should be followed-up in line with the respective applicable clinical guidelines.

Within the OPTIMUM trial, patients with RIF ($n = 116$) were treated according to an identified possible risk factor (e.g. CE with antibiotics, aberrant high Th1/Th2 cell ratios with vitamin D and/or tacrolimus, overt/subclinical hypothyroidism with levothyroxine, and thrombophilia with low-dose aspirin) (Kuroda *et al.*, 2021). In the patients aged <40 years and ≥40 years, the OPR in the OPTIMUM group was significantly higher than that in the control group (57.4% and 30.3% versus 21.4% and 0% per ET, respectively; $P < 0.01$). These data suggest that using diagnostics to assess the cause of RIF is likely to improve the efficacy of interventions, which would then be applied with more rationale than

at present. At present few validated tests of value in the context of RIF are available, but this is likely to change in the future.

Patient care and counselling

The fertility treatment journey, from the fertility workup to the actual treatments and pregnancy, affects the mental health of patients, and the effect is significantly higher in patients with unsuccessful treatments (Boivin *et al.*, 2022). Women with RIF have been reported to have significantly higher levels of stress as compared to fertile healthy controls and admitted to feelings of social isolation, sensitivity to comments, a need for parenthood, diminished sexual enjoyment, and rejection of a childfree lifestyle (Coughlan *et al.*, 2014b). 'Low levels of hope' is another factor closely related to mental health and emotional state. The study by Ni *et al.* (2021) showed that the levels of hope were significantly lower in patients after repeated IVF cycles as compared to those undergoing a first cycle. No information was available for the male partners in RIF couples.

It has been suggested that the stress level experienced by women with RIF may fluctuate in response to the amount of supportive care that they receive from the clinical staff, the results of investigative procedures (which influence the prognosis), and the experience and outcome of any subsequent treatment, but this has not been studied (Coughlan *et al.*, 2014b). Still, as psychosocial care is considered an essential part of fertility treatment and should be provided before, during, and after ART treatments (Gameiro *et al.*, 2015), efforts should be made to provide supportive care to couples with RIF.

There is no 'one-size-fits-all' model for supportive care for couples with RIF, but based on guidance on RPL (ESHRE Guideline Group on RPL *et al.*, 2023), the following approach can be applied:

- Recognize the woman/couple as an individual.
- Provide time for questions, information, repetition, and discussion, especially when the patient/couple is distressed or anxious.
- Listen to the facts and the feelings of the patient/couple.
- Show respect for the patient/couple and their wishes and choices.
- Use clear and sensitive language: explain terminology, avoid insensitive terms, and mirror the patient's preferred terms.
- Be honest about processes, likely outcomes, and prognoses, and avoid false reassurance. This includes being honest about the evidence and benefit (or lack of benefit) for the investigations and treatments that have been proposed for RIF and are being applied in clinical practice without solid ground. Patients/couples can further be reassured based on their individual estimation of the likelihood of implantation in the next cycle that simply continuing with ART treatment is a good option for them. Further support for this can be derived from a study showing that half of the patients with RIF achieve a live birth with ART within 5 years (Koot *et al.*, 2019).
- Apply shared treatment planning in a partnership approach. It was recently suggested that a multi-cycle approach could be beneficial in this respect, as it would consider cycle failure and how to cope with it from the start of the treatment process (Harrison *et al.*, 2022).
- Be kind, show concern, empathy, and compassion.

Discussion

In these recommendations for good clinical practice, the ESHRE WG encourages the reconsideration of RIF from being a medical condition with fixed diagnostic criteria to a clinical secondary phenomenon of ART that can arise at different moments in different patients, and which requires a degree of empathy and pragmatism to manage well. The recommendations provided are based on this approach, with a clear acknowledgement of the lack of a robust evidence base to support them. However, it is the nature and requirement of clinical medicine to advise what is best for a patient given their individual clinical context, even when hard data are scarce. It is to be hoped that, in the coming years, studies will be published that can provide a firmer basis for clinical recommendations and allow a clear consensus for the optimal management of RIF to emerge. Ideally, all investigations used in patients with RIF will have proven clinical utility and relevance. Tests will be performed to detect an underlying problem or assess a contributing factor to the implantation failures and linked to a specific intervention that has been shown to improve the chances of live birth in the next cycle. Additional tests that do not have a linked intervention can be considered for patient counselling and to estimate the relevance of continuing ART treatment or resorting to other reproductive options.

The need for further research in RIF

The need for research into the causes of implantation failure has been identified as one of the top 10 research priorities in medically assisted reproduction (Duffy *et al.*, 2021). This is indeed key to making progress in the clinical management of RIF. Further studies of empirical interventions in patients with RIF of unknown cause are unlikely to be helpful and may be considered a waste of research resources. Ideally, interventions should be tested in those with a clear cause of RIF and based on a biological rationale. To date, such studies have been few in number. Also, future clinical guidance in RIF would allow a set of relevant investigations, each with a specific linked treatment option shown to be effective for resolving the specific and detected indication.

In this respect, the herein proposed definition of RIF should be applied in future research studies as it will increase homogeneity both in the study population as well as across studies, which should be helpful towards meaningful study outcomes and feasible meta-analysis.

With regard to specific investigations and treatments, the following topics should be priorities for researchers:

- The role of vitamin D determination and supplementation (in case of low levels) in patients with RIF.
- The role of immunological factors as an underlying factor in RIF, methods to investigate these, and efficacy of targeted treatments.
- The role of decidualization as a potential therapeutic target to overcome inappropriate rejection of the implanting embryo.
- The relevance of endometrial receptivity tests, CE evaluation, and microbiome profiling in patients with RIF should be further evaluated.
- The role of thin endometrium, as well as the relevance of specific treatments to increase the chance of pregnancy in patients with RIF and detected thin endometrium.
- The clinical value of SDF tests
- Possible genetic predispositions to extreme IVF outcomes (Capalbo *et al.*, 2021), such as RIF.
- The value of treatments, such as intrauterine autologous PBMC infusion, intrauterine PRP infusion, and intrauterine hCG injection, to prevent implantation failure in a next cycle should be further evaluated.

- The value of antioxidant treatments should be further evaluated.

Apart from the clinical aspect of RIF, more insight and data are needed on the impact of RIF on the stress, mental health, and well-being of patients, and on supportive treatment options that could minimize such impact and lead to better care.

While awaiting the results of further studies and trials, the ESHRE WG recommends the approach summarized in Figs 3, 4, and 5, which is to individualize the diagnosis of RIF based on the chance of successful implantation for the individual patient or couple, and to restrict investigations and treatments to those supported by a clear rationale and data on their benefit. The current recommendations will be updated 4 years after publication.

Supplementary data

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

Data availability

The data underlying this article are available in the article and in its online supplementary material.

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Authors' roles

N.M. chaired the ESHRE Working Group on Recurrent Implantation Failure. N.V. and N.L.C. provided methodological support. All other authors contributed equally in writing the article, and all approved the final version for publication.

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Conflict of interest

N.M. declared consulting fees from ArtPRED (The Netherlands) and Freya Biosciences (Denmark); honoraria for lectures from Gedeon Richter, Merck, Abbott, and IBSA; being co-founder of Verso Biosense. He is Co-Chief Editor of *Reproductive Biomedicine Online* (RBMO). D.C. declared being an Associate Editor of *Human Reproduction Update*, and declared honoraria for lectures from Merck, Organon, IBSA, and Fairtility; support for attending meetings from Cooper Surgical, Fujifilm Irvine Scientific. G.G. declared that he or his institution received financial or non-financial support for research, lectures, workshops, advisory roles or travelling from Ferring, Merck, Gedeon-Richter, PregLem, Abbott, Vifor, Organon, MSD, Coopersurgical, ObsEVA, and ReprodWissen. He is an Editor of the journals *Archives of Obstetrics and Gynecology and Reproductive Biomedicine Online*, and Editor in Chief of *Journal Gynäkologische Endokrinologie*. He is involved in guideline developments and quality control on national and international level. G.L. declared he or his institution received honoraria for lectures from Merck, Ferring, Vianex/Organon, and MSD. He is an Associate Editor of *Human Reproduction Update*, immediate past Co-ordinator of Special Interest Group for Reproductive Endocrinology of ESHRE and has been involved in Guideline Development Groups of ESHRE and national fertility authorities. D.J.M. declared being an Associate Editor for *Human Reproduction Open* and statistical Advisor for *Reproductive Biomedicine Online*. B.T. declared being shareholder of Reprognostics and she or her institution received financial or non-financial support for research, clinical trials, lectures, workshops, advisory roles or travelling from support for attending meetings from Ferring, MSD, Exeltis, Merck Serono, Bayer, Teva, Theramex and Novartis, Astropharm, Ferring. The other authors had nothing to disclose.

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