Thieme

Recurrent Miscarriage: Diagnostic and Therapeutic Procedures. Guideline of the DGGG, OEGGG and SGGG (S2k-Level, AWMF Registry Number 015/050)

Diagnostik und Therapie von Frauen mit wiederholten Spontanaborten. Leitlinie der DGGG, OEGGG und SGGG (S2k-Niveau, AWMF-Registernummer 015/050)

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ABSTRACT

Purpose Official guideline of the German Society of Gynecology and Obstetrics (DGGG), the Austrian Society of Gynecology and Obstetrics (ÖGGG) and the Swiss Society of Gynecology and Obstetrics (SGGG). The aim of this guideline was to standardize the diagnosis and treatment of couples with recurrent miscarriage (RM). Recommendations were based on the current literature and the views of the involved committee members.

Methods Based on the current literature, the committee members developed the statements and recommendations of this guideline in a formalized process which included DELPHI rounds and a formal consensus meeting.

Recommendations Recommendations for the diagnosis and treatment of patients with RM were compiled based on the international literature. Specific established risk factors such as chromosomal, anatomical, endocrine, hemostatic, psychological, infectious and immunological disorders were taken into consideration.

ZUSAMMENFASSUNG

Ziel Offizielle Leitlinie der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (DGGG), der Österreichischen Gesellschaft für Gynäkologie und Geburtshilfe (ÖGGG) und der Schweizerischen Gesellschaft für Gynäkologie und Geburtshilfe (SGGG). Ziel der Leitlinie ist es, die Diagnostik und Therapie des wiederholten Spontanaborts (WSA) anhand der aktuellen Literatur sowie der Erfahrung der Mitglieder der Leitlinienkommission evidenzbasiert zu standardisieren.

Methoden Anhand der internationalen Literatur entwickelten die Mitglieder der beteiligten Fachgesellschaften in einem formellen Prozess einen Konsensus. Empfehlungen und Statements der Leitlinie wurden in einem formalen Prozess (DELPHI-Prozess, Konsenstreffen mit moderiertem Abstimmungsprozess) erarbeitet und konsentiert.

Empfehlungen Es wurden Empfehlungen zur Diagnostik und Therapie von Paaren mit WSA anhand der internationalen Literatur erarbeitet. Insbesondere wurde auf die bekannten Risikofaktoren wie chromosomale, anatomische, endokrinologische, gerinnungsphysiologische, psychologische, infektiologische und immunologische Störungen eingegangen.

I Guideline Information

Guidelines program of the DGGG, OEGGG and SGGG

Information on the guidelines program is available at the end of the guideline.

Citation format

Recurrent miscarriage: diagnostic and therapeutic procedures. Guideline of the DGGG, OEGGG and SGGG (S2k-Level, AWMF Registry Number 015/050). Geburtsh Frauenheilk 2018; 78: 364–381

Guideline documents

The complete long version, a short version, a PDF slideshow for PowerPoint presentations and a summary of the conflicts of interest of all the authors are available in German on the AWMF homepage under: http://www.awmf.org/leitlinien/detail/ll/015-050.html

Guideline authors

See ▶ **Table 1**.

▶ **Table 1** The following professional and scientific societies/working groups/organisations/associations have stated their interest in contributing to the compilation of the guideline text and participating in the consensus conference and nominated representatives to attend the consensus conference.

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Abbreviations

Ab	antibodies
ANA	antinuclear antibodies
aPL	antiphospholipid
APS	antiphospholipid syndrome
ASA	acetylsalicylic acid
ASRM	American Society for Reproductive Medicine
FVL	factor V Leiden
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GW	week of gestation
HLA	human leukocyte antigen
IVIG	intravenous immunoglobulin
LBR	live birth rate
LIT	lymphocyte immunization therapy
LMWH	low-molecular-weight heparin
NK	natural killer
PCO	polycystic ovaries
PGD	preimplantation genetic diagnosis
RCOG	Royal College of Obstetricians and Gynaecologists
RM	recurrent miscarriage
PT	prothrombin
SGA	small for gestational age
s/p	status post
TPO	thyroid peroxidase
TSH	thyroid-stimulating hormone
VTE	venous thromboembolism

II Guideline Application

Purpose and objectives

The aim of this guideline is to standardize the diagnosis and treatment of couples with recurrent miscarriage (RM) based on the most current national and international literature.

Targeted areas of patient care

Outpatient and/or inpatient care.

Target user groups/target audience

The recommendations of the guideline are addressed to gynecologists and their colleagues working in medical fields such as human genetics, psychotherapy, laboratory medicine, hemostasis, internal and general medicine and other professional staff involved in the care of patients with RM. Targeted patient group: couples with RM

Adoption of the guideline and period of validity

The validity of this guideline was confirmed by the respective boards/representatives of the participating professional medical societies, working groups, organizations and associations, by the board of the DGGG, SGGG and OEGGG and the DGGG/OEGGG/SGGG Guideline Commission in January 2018 and thereby approved in its entirety. This guideline is valid from February 1, 2018 through to January 31, 2021. The above-mentioned period of validity is only an estimate. The guideline can be updated earlier if urgently required. Should the guideline continue to reflect the current level of scientific knowledge, then the guideline's period of validity can be extended.

III Methodology

Basic principles

Because of the complex biological processes which occur in the context of RM and the heterogeneity of the studies published on this topic, there is widespread uncertainty about the optimal individual diagnosis and therapy of women with RM. An updated S2k-level guideline was therefore considered advisable to improve the quality of care. The guideline aims to provide information and advice for women with RM about appropriate diagnostic procedures and evidence-based treatment strategies. In addition, the recommendations of the guideline should serve as the basis for interdisciplinary decision-making.

This guideline is based on the S1 guideline "Recurrent Miscarriage: Diagnostic and Therapeutic Procedures" (AWMF 015/050), published in 2013, and the results of a recent literature search (as per September 2017). The relevant literature was assigned to the various chapters with the help of degree candidate Eva Preisl and Dr. Katharina Feil, both from the University Hospital for Gynecological Endocrinology and Reproductive Medicine, Innsbruck, Austria. A coherent draft version was compiled from the individual chapters, which was edited in a joint advance consensus. Statements and recommendations which took the form of unambiguous instructions were then extracted from the draft text. The revised text was subsequently circulated among all the member of the guideline commission. The members proposed changes to the text and voted on the final manuscript.

This guideline is classified as: S2k

Grading of recommendations

As no systematic search, selection, evaluation and synthesis of the evidence base was carried out, the guideline does not discuss levels of evidence. The recommendations are graded as follows (▶ **Table 2**):

▶ **Table 2** Grading of recommendations according to the respective syntax.

Description	Syntax
Strong recommendation, strongly binding	must
Recommendation, moderately binding	should
Open recommendation, not binding	may

Statements

Expert statements included in this guideline which are not recommendations for action but are simple statements of fact are referred to as "Statements". It is not possible to provide a level of evidence for these statements.

Achieving consensus and level of consensus

An interdisciplinary group voted on the statements and recommendations at three consensus conferences. The statements and recommendations of the guideline were discussed at consensus conferences held on 20th April 2017, 6th June 2017 and 19th September 2017 in Munich. Following a moderated formal consensus process, the participants of the conferences jointly consented to the statements and recommendations. The consent protocol is available on request.

During the compilation of this guideline, special consideration was given to existing recommendations (the guideline was first compiled in 2006 and revised in 2008 and 2013), the recommendations of the European Society of Human Reproduction and Embryology (ESHRE 2017), the Royal College of Obstetricians and Gynecologists [1], the American College of Obstetricians and Gynecologists (ACOG 2002) [2] and the American Society for Reproductive Medicine (ASRM 2012) [3].

During structured consensus-based decision-making (S2k/S3 level), authorized participants present at a session vote on draft Statements and Recommendations. Discussions during sessions may lead to significant changes in the wording of Statements and Recommendations, etc. The extent of agreement, which depends on the number of participants, is determined at the end of the session (▶ **Table 3**).

▶ **Table 3** Classification of extent of agreement in consensus decision-making.

Symbol	Level of consensus	Extent of agreement in percent
+++	Strong consensus	> 95 % of participants agree
++	Consensus	> 75–95 % of participants agree
+	Majority agreement	> 50–75 % of participants agree
–	No consensus	< 50 % of participants agree

Expert consensus

As the name implies, this refers to consensus decisions taken with regard to specific Recommendations/Statements without a previous systematic search of the literature (S2k) or when evidence is lacking (S2e/S3). The term “Expert Consensus” (EC) used here is synonymous with terms such as “Good Clinical Practice” (GCP) or “Clinical Consensus Point” (CPP) used in other guidelines. The level of recommendation is graded as previously described in the Chapter “Grading of recommendations” but only semantically (“must/must not” or “should/should not” or “may/may not”) and without using the symbols shown there.

IV Guideline

1 Introduction

Counselling and treating couples with RM is a diagnostic and therapeutic challenge as several possible causes for RM are known, but no risk factor for RM is identified in the majority of affected patients.

2 Incidence and Definition

Approximately 1–3 % of all couples of reproductive age experience recurrent miscarriage [4]. A miscarriage is defined as the loss of a fetus at any time between conception and the 24th week of gestation (GW) or the loss of a fetus weighing < 500 g [5]. The World Health Organization (WHO) definition of recurrent spontaneous miscarriage is: “three and more consecutive miscarriages before the 20th GW” [5]. The American Society for Reproductive Medicine (ASRM) already defines the occurrence of two consecutive miscarriages as RM [3, 6]. This definition increases the incidence of RM to 5 % of all couples of reproductive age [7]. This guideline takes the WHO definition (≥ 3 consecutive recurrent miscarriages) as the basis for its recommendations on diagnostic and therapeutic procedures.

If a woman has not previously given birth to a live infant, the loss of the fetus is referred to as primary RM; if the woman has had a previous live birth, the pregnancy loss is referred to as secondary RM [8]. Another classification, which refers to the course of the miscarriages, classifies miscarriages into repeated loss of embryonic pregnancy (sporadic loss) or loss of fetal pregnancy (detectable heart beat on sonography or histologically verifiable embryo) [3].

The risk of recurrent miscarriage varies significantly, depending on a number of different factors. In addition to maternal age, the number of previous miscarriages also affects the risk of recurrence. ▶ **Table 4** presents the data from a retrospective registry study [9].

▶ **Table 4** Probability of recurrent miscarriage depending on maternal age and the number of previous miscarriages, based on the study of Nybo-Andersen et al. [9].

Previous miscarriages	Risk of recurrence			
	25–29 years	30–34 years	35–39 years	40–44 years
1 miscarriage	~ 15 %	~ 16–18 %	~ 21–23 %	~ 40 %
2 miscarriages	~ 22–24 %	~ 23–26 %	~ 25–30 %	~ 40–44 %
≥ 3 miscarriages	~ 40–42 %	~ 38–40 %	~ 40–45 %	~ 60–65 %

3 Diagnosis and Treatment of Relevant Risk Factors

3.1 Lifestyle and behavior

3.1.1 Stress

Some studies have indicated that higher stress levels during pregnancy might be associated with an increased risk of pregnancy loss. A case-control study of 45 patients with RM concluded that stress levels were higher compared to 40 control patients [10]. A study of 301 patients with RM (defined as ≥ 3 miscarriages) compared to women wanting to children reported similar findings [11]. Because of the small number of cases, it is not possible, based on the currently available data, to conclude that stress increases the risk of miscarriage.

3.1.2 Coffee consumption

A few observational studies have reported a dose-dependent relationship between coffee intake and late loss of pregnancy [12]. A larger case-control study was also able to show that coffee consumption had an impact on early miscarriage [13]. Another retrospective case-control study demonstrated a significantly increased risk of RM following coffee consumption in the periconceptional period and in early pregnancy. It was not possible to show a linear association between the amount of coffee consumed and the risk of RM [14].

3.1.3 Nicotine and alcohol consumption

There is a strong association between nicotine consumption and poor obstetric and neonatal outcomes such as ectopic pregnancy, stillbirth, placenta previa, premature birth, low birthweight and congenital malformation. Cessation of smoking should therefore be recommended to all pregnant women [15]. The impact of smoking and of cessation of smoking on the risk of RM is not clear. A retrospective study compared 326 patients with RM with 400 control patients who had had at least one live birth. The study showed that even passive smoking significantly increased the risk of RM [16]. Another study came to the conclusion that maternal nicotine, alcohol or coffee consumption was not associated with a higher probability of RM [17].

A prospective study, which evaluated the impact of paternal smoking on the risk of miscarriage, investigated 526 couples and was able to show that women who were heavy smokers (> 20 cigarettes per day) had a higher risk of early miscarriage. Heavy smoking (more than 20 cigarettes per day) had a significantly greater impact than moderate smoking (< 20 cigarettes per day) [18]. There are currently no studies on the impact of smoking cessation on the chances of giving birth to a live infant for couples with RM.

3.2 Genetic factors

3.2.1 Chromosomal anomalies

Embryonic/fetal chromosomal abnormalities are the most common cause of spontaneous miscarriage [19, 20]. The earlier the miscarriage occurs, the more likely that an embryonic/fetal chromosomal anomaly was present [21]. The risk of embryonic/fetal trisomy resulting from chromosomal aberrations increases with higher maternal age. The most common cause of miscarriage is trisomy 16, followed by trisomy 22. Triploidy was detected in approximately 15% of cytogenetically abnormal fetuses. Monosomy X is responsible for approximately 20% of miscarriages which occur in the first trimester of pregnancy. No association with maternal age has been found for monosomy X, polyploidy or structural chromosomal disorders [22]. A balanced chromosomal abnormality in one of the partners was confirmed in around 4–5% of couples who had 2 or more miscarriages [23]. In around 1% of pregnancies, an unbalanced set of chromosomes was detected during prenatal diagnostic procedures or after the birth [24, 25].

Consensus-based Recommendation 3-2.E1	
Expert consensus	**Level of consensus ++**
Cytogenetic analysis must be done if a woman experiences recurrent miscarriages. This can be done either by chromosome analysis of both partners prior to conception or using tissue samples from the miscarried fetus.	

It is not possible to carry out standard chromosomal analysis in around 18% of miscarried fetuses, and array analysis cannot be done in around 5% of miscarried fetuses [26]. Overall, molecular cytogenetic analysis only detected additional chromosomal disorders in around 5% of cases, and the routine use of array analysis to identify the cause of miscarriage is therefore not useful at present [26].

Consensus-based Recommendation 3-2.E2	
Expert consensus	**Level of consensus +++**
Both partners must undergo cytogenetic testing if a structural chromosomal disorder is detected in the tissue of the miscarried fetus. The couple must be informed of the findings during genetic counselling carried out by a specialist for human genetics or a physician with the relevant qualifications in accordance with national legal regulations.	

Consensus-based Statement 3-2.S1	
Expert consensus	**Level of consensus ++**
If a balanced chromosomal aberration is detected in one of the parents, the risk of miscarriage or of giving birth to an infant with a chromosomal disorder increases, depending on the chromosomes involved. This will affect antenatal diagnostic procedures in any further pregnancies.	

3.2.2 Monogenetic disease

X-linked dominant disorders that are lethal in males have an increased risk of miscarriage. But autosomal dominant and recessive disorders with severe malformations can also result in increased intrauterine mortality. In these cases, examination of the fetus should include genetic and pathological testing, particularly if the disorder was not identified prenatally.

Consensus-based Recommendation 3-2.E3	
Expert consensus	**Level of consensus ++**
If there are indications that monogenetic disease may be the cause of miscarriage, genetic counselling must include genetic testing.	

3.2.3 Results of association studies

Numerous studies suggest possible maternal, paternal or fetal genetic effects, but these appear to have very little impact on the risk of miscarriage [27].

Consensus-based Recommendation 3-2.E4	
Expert consensus	**Level of consensus +++**
Molecular genetic analysis for gene variants detected in association studies is not recommended for couples with RM.	

3.2.5 Therapeutic options

It is not possible to treat the causes of chromosomal disorders. Previous studies have not shown that PGD after IVF results in an increased rate of live births in women with RM compared to spontaneous pregnancies, not even for couples who are genetically at risk because one partner has a balanced chromosomal aberration. Neither the ESHRE and RCOG guidelines nor the ASRM Statement recommend preimplantation genetic diagnosis for couples with RM.

Consensus-based Recommendation 3-2.E5	
Expert consensus	**Level of consensus +++**
Preimplantation genetic diagnosis to prevent miscarriage is not recommended for couples with RM who have no familial chromosomal disorder and no monogenetic disease.	

3.3 Anatomical factors

3.3.1 Diagnosis of anatomical factors

3.3.1.1 Congenital malformations

Hysteroscopic examinations of patients who had 2, 3 and ≥ 4 consecutive miscarriages found no difference in the prevalence of congenital (uterine malformations) or acquired (adhesions, polyps, submucosal fibroids) intrauterine pathologies [28]. The increased probability of miscarriage in women with subseptate uterus is well known, but the cause of this association is unknown [29]. It is not clear whether there is an association between RM and other uterine malformations such as arcuate uterus or bicornuate uterus. Ludwin et al. [30] reported significantly better diagnostic results when using sonohysterography (SHG) to diagnose congenital uterine malformations compared with hysterosalpingography (HSG) or hysteroscopy. But it is difficult to evaluate statements comparing diagnostic methods, because even when hysteroscopy videos were presented to experienced international observers, interobserver agreement was found to be poor [31]. When diagnosing uterine malformations, the decision whether to use hysteroscopy – possibly in combination with laparoscopy or 3D sonography – must be made on an individual basis [32]. 3D sonography is recommended for the diagnostic workup of uterine malformations in high-risk populations and MRI and endoscopic examinations are recommended for diagnostic problems or suspected complex malformations [33].

3.3.1.2 Acquired malformations

Although the study populations consisted only of women undergoing IVF, a meta-analysis of 19 observational studies showed a higher but not statistically significant rate of miscarriages in women with intramural fibroids and no submucosal involvement (relative risk [RR] 1.24; 95% CI: 0.99–1.57) [34]. In an evaluation of retrospective and prospective data of patients with RM, the incidence of submucosal fibroids was 2.6% (25/966) [35]. These study data suggest an association between submucosal fibroids and the occurrence of miscarriage, but the quality of the data is poor. A Cochrane analysis which only included a few studies showed no significant reduction in the risk of miscarriage after uterine fibroids had been resected (intramural: OR 0.89, 95% CI: 0.14–5.48; submucosal: OR 0.63, 95% CI: 0.09–4.40) [36].

It is not clear whether – as with submucosal fibroids – intracavitary polyps also increase the risk of miscarriage.

Consensus-based Recommendation 3-3.E6	
Expert consensus	**Level of consensus +++**
Vaginal sonography and/or hysteroscopy is recommended in women with RM to rule out uterine malformations, submucosal uterine fibroids and polyps. Hysteroscopy is recommended to rule out intrauterine adhesions.	

3.3.2 Treatment for anatomical factors

Hysteroscopic septum dissection is recommended for women with RM and septate uterus [37]. A meta-analysis carried out in 2017 showed that no randomized studies on the therapeutic effect of septum dissection have been carried out to date [38]. But retrospective uncontrolled studies suggest that the surgical intervention is beneficial. Postoperative healing takes about 2 months [39], and there are no reasons to avoid pregnancy thereafter. Surgical intervention is not indicated for other uterine malformations such as bicornuate uterus, uterus didelphys and arcuate uterus [40–42].

Consensus-based Recommendation 3-3.E7	
Expert consensus	**Level of consensus +++**
Hysteroscopic septum resection is recommended to treat women with RM and septate uterus.	

Hysteroscopic adhesiolysis is the therapy of choice to treat intrauterine adhesions [43]. It is not clear whether or to what extent intrauterine adhesions affect the risk of miscarriage and whether adhesiolysis will reduce the risk of RM.

Consensus-based Recommendation 3-3.E8	
Expert consensus	**Level of consensus ++**
Hysteroscopic adhesiolysis is recommended to treat women with RM and intrauterine adhesions.	

There are no randomized studies on the therapeutic benefits of fibroid resection in women with RM.

Consensus-based Recommendation 3-3.E9	
Expert consensus	**Level of consensus ++**
Surgical resection should be performed in women with RM and submucosal fibroids.	

A meta-analysis showed that hysteroscopic resection of intrauterine polyps visible on ultrasound carried out before intrauterine insemination can increase clinical pregnancy rates [44]. The resection of persistent polyps can be considered if there is no other explanation for RM.

Consensus-based Recommendation 3-3.E10	
Expert consensus	**Level of consensus ++**
Hysteroscopic resection should be carried out to prevent miscarriage in women with RM and persistent polyps.	

3.4 Microbiological factors

3.4.1 Diagnostic workup of microbiological factors

Because the association between infections and RM is unclear, general screening for vaginal infections which goes beyond the routine screening carried out as part of prenatal care is not recommended. However, chronic endometritis, as evidenced by the finding of plasma cells in the endometrial biopsy, was detected in 7–67% of otherwise asymptomatic women with RM and in 30–66% of women with recurrent implantation failure [45–49]. Endometrial biopsy may be performed in women with RM to exclude chronic endometritis (supported by immunohistochemical staining for the plasma cell surface antigen CD138).

Consensus-based Recommendation 3-4.E11	
Expert consensus	**Level of consensus +++**
Infectious screening using vaginal swab specimens is not recommended in asymptomatic women with RM.	

Consensus-based Recommendation 3-4.E12	
Expert consensus	**Level of consensus ++**
An endometrial biopsy may be performed in women with RM to rule out chronic endometritis (supported by immunohistochemical staining for the plasma cell surface antigen CD138).	

3.4.2 Treatment for microbiological factors

Pregnant women suspected of having a vaginal infection should receive proper testing and treatment [50, 51]. Antibiotic therapy with doxycycline (e.g. 200 mg 1–0–0 for 14 days) is indicated for chronic endometritis; in the event of persistent endometritis as evidenced by the persistence of plasma cells, treatment can consist of ciprofloxacin with/without metronidazole [45].

Consensus-based Recommendation 3-4.E13	
Expert consensus	**Level of consensus ++**
Antibiotic therapy may be administered to women with RM and chronic endometritis to prevent miscarriage.	

3.5 Endocrine factors

3.5.1 Diagnostic workup of endocrine factors

According to a retrospective analysis, manifest hyperthyroidism is associated with increased miscarriage rates [52]. This also applies to manifest hypothyroidism. It is still unclear, however, whether latent hypothyroidism (i.e. increases in TSH concentrations despite thyroid hormone concentrations within normal ranges) also increases the risk of miscarriage. A meta-analysis of two studies reported that the LBR was not lower for women with RM and TSH concentrations of > 2.5 mU/L [53]. Increased levels of thyroid hormone autoantibodies appear to be associated with higher rates of spontaneous miscarriage [54]. PCOS, hyperandrogenemia (which is often PCOS-related [55]), insulin resistance [56, 57] and diabetes [58] are all associated with a higher tendency to miscarry. PCOS per se is not a predictive factor for miscarriage or RM [59], whereas obesity per se appears to increase the rate of miscarriages.

Consensus-based Recommendation 3-5.E14	
Expert consensus	**Level of consensus ++**
An endocrine workup determining TSH levels is recommended in women with RM. If TSH levels are found to be abnormal, fT3, fT4 and thyroid hormone autoantibody concentrations must also be determined.	

Consensus-based Recommendation 3-5.E15	
Expert consensus	**Level of consensus +++**
The BMI of women with RM should be determined. Women with a BMI ≥ 30 kg/m^2 may be investigated further to determine whether they have a metabolic syndrome.	

3.5.2 Treatment for endocrine factors

It is important to diagnose and treat manifest hyperthyroidism or hypothyroidism. A meta-analysis of studies of IVF patients with increased levels of thyroid hormone autoantibodies (RM was no inclusion criterion) and pregnant women with higher levels of TPO antibodies showed that substitution of thyroid hormones decreased the rate of miscarriages [54]. No statement was made about the rate of live births. However, other studies such as the study by Negro et al. published in 2016 [60] were unable to demonstrate the effect. It is therefore possible that patients with RM and TPO autoantibodies benefit from the substitution of thyroid hormones in terms of a lower rate of miscarriages, but currently there is no data specifically on patients with RM.

Consensus-based Recommendation 3-5.E16	
Expert consensus	**Level of consensus +++**
Manifest hypothyroidism or hyperthyroidism must be treated before conception.	

Consensus-based Recommendation 3-5.E17	
Expert consensus	**Level of consensus ++**
Thyroid hormone substitution therapy can be administered to prevent miscarriage in women with RM and latent hypothyroidism, i.e. pathologically increased TSH concentrations despite fT3 and fT4 concentrations within normal ranges or the presence of TPO autoantibodies.	

A meta-analysis found that the administration of metformin had no effect on the risk of sporadic miscarriage [61], and the guideline can therefore not make any recommendation regarding the administration of metformin.

There are many medical reasons why women with a high BMI should lose weight (cf. the S3 guideline on "Gestational Diabetes", AWMF guideline 057/008). A Danish cohort study [62] showed that the risk of miscarriage increases for women with a BMI ≥ 30 kg/m^2 (OR 1.23; 95 % CI: 0.98–1.54).

Consensus-based Recommendation 3-5.E18	
Expert consensus	**Level of consensus +++**
Women with RM and a high body mass index should be encouraged to lose weight.	

3.6 Psychological factors

Evidence-based medicine has not been able to show that RM can be directly caused by psychological factors such as stress alone [10, 63, 64].

Consensus-based Recommendation 3-6.E19	
Expert consensus	**Level of consensus +++**
Women with a prior history of mental illness, women who are involuntarily childless, and women who lack or have only limited social resources or are struggling with feelings of guilt related to processing their experience of RM must be given information about psychosocial assistance and support (including self-help groups and internet forums).	

Consensus-based Recommendation 3-6.E20	
Expert consensus	**Level of consensus +++**
A psychotherapist must be called in if there is a suspicion that the patient is suffering from reactive depression following RM to determine whether the affected patient/couple require(s) further treatment.	

Consensus-based Statement 3-6.S2	
Expert consensus	**Level of consensus +++**
The efficacy of "tender loving care" as a therapeutic intervention to prevent miscarriage in women with RM is not proven. However, tender loving care can provide psychological support.	

3.7 Immunological factors

3.7.1 Diagnosis of immunological factors

3.7.1.1 Alloimmune factors

Activation of the immune system (particularly of the Th1 response) results in unfavorable conditions for implantation and is associated with an increased probability of RM [51, 65 – 69]. It has not yet been clearly proven that an increase in the Th1/Th2 ratio or T4/T8 index leads to an increased risk of miscarriage [51, 66, 70 – 73]. Several studies have pointed to an increase in natural killer cells in peripheral blood (pNK cells) in patients with RM compared to healthy controls [74 – 77]. Recent studies have also pointed to a significant increase in uterine natural killer cells (uNK cells) in patients with idiopathic RM [78, 79].

Consensus-based Recommendation 3-7.E21	
Expert consensus	**Level of consensus ++**
Alloimmune investigations such as determining the Th1/Th2 ratio or the T4/T8 index, analysis of pNK and/or uNK cells, NK toxicity tests, lymphocyte function tests, molecular genetic testing for non-classical HLA groups (Ib) or KIR receptor families and determination of HLA should not be done in women with RM outside clinical studies, unless there is evidence of a pre-existing autoimmune disorder.	

3.7.1.2 Autoimmune factors

Although the data are not consistent, the majority of studies report increased ANA titer levels in women with RM [80 – 86]. Celiac disease is characterized by gluten sensitivity; its association with RM is still controversially discussed. Testing for immunoglobulin

A (IgA) antibodies against tissue transglutaminase can be done in women with a history of food sensitivity (food intolerances, irregular bowel motions) and RM, followed by biopsy of the small intestine if the findings are positive [87].

Testing for antiphospholipid syndrome using clinical and laboratory parameters is recommended in women with RM (▶ **Fig. 1**). Non-specific antibodies against anionic phospholipids such as cardiolipins and β2 glycoproteins, also known as antiphospholipid antibodies (aPLAb) have been detected in some women with RM. However, according to the definition given in ▶ **Fig. 1**, antiphospholipid (aPL) syndrome is only present if both clinical and laboratory criteria are fulfilled. Between 2% and 15% of women with RM suffer from aPL syndrome [88]. During the diagnostic workup, it is important to determine whether aPL antibody titer is still moderate to high at the 12-week follow-up after first determining the titer, i.e., whether it is in the > 99th percentile compared to unremarkable controls [89].

A few studies have considered the possibility of so-called "non-criteria" aPL syndrome, particularly when manifestations (livedo reticularis, ulcerations, renal microangiopathies, neurological disorders and cardiac manifestations) are present and the diagnostic criteria for classic aPL syndrome are not fulfilled or only in part (e.g., low aPLAb titer or s/p 2 miscarriages) [89].

Clinical criteria

- ≥ 1 venous or arterial thrombosis
- 1 or 2 unexplained miscarriages of morphologically normal fetuses after the 10th GW, ≥ 3 miscarriages before the 10th GW
- ≥ 1 late miscarriage or preterm birth before the 34th GW because of placental insufficiency or preeclampsia

Laboratory criteria (detected on 2 separate occasions at an interval of 12 weeks)

- Anti-cardiolipin antibodies (IgM, IgG) – moderate to high titer
- Anti-β2 glycoprotein 1 antibodies (IgM, IgG) – high titer
- Lupus anticoagulant

▶ **Fig. 1** Diagnostic criteria for antiphospholipid syndrome [89]. Clinical and laboratory criteria can be present either in combination or singly. By definition, however, *at least one clinical and one laboratory criterion* must be present to make a diagnosis of antiphospholipid syndrome. [rerif]

Consensus-based Recommendation 3-7.E22	
Expert consensus	**Level of consensus +++**
Testing for antiphospholipid syndrome based on clinical and laboratory parameters (▶ **Fig. 1**) is recommended for women with RM.	

Consensus-based Recommendation 3-7.E23	
Expert consensus	**Level of consensus +++**
Interdisciplinary care must be offered to women with RM and an autoimmune disease already present prior to conception.	

Consensus-based Recommendation 3-7.E24	
Expert consensus	**Level of consensus ++**
Testing for non-criteria antiphospholipid syndrome based on clinical and laboratory parameters should be done in women with RM, particularly if clinical manifestations are present (livedo reticularis, ulcerations, renal microangiopathies, neurological disorders and cardiac manifestations).	

3.7.2 Treatment for immunological factors

3.7.2.1 Glucocorticoids

The results of existing clinical studies which administered glucocorticoids to women with RM are inconsistent [90–93]. Treatment with glucocorticoids – particularly at higher doses – can induce side effects such as gestational diabetes, arterial hypertension, preterm birth, low birthweight (SGA) and disorders of neurological development in the infant [94–96]. This type of treatment should therefore be reserved for patients with pre-existing autoimmune diseases which require therapy with glucocorticoids even during pregnancy.

Consensus-based Recommendation 3-7.E25	
Expert consensus	**Level of consensus ++**
Glucocorticoids must not be administered outside clinical studies as prophylaxis to prevent miscarriage in women with RM but without pre-existing autoimmune disease.	

3.7.2.2 Intravenous immunoglobulins

A few studies have pointed out that intravenous administration of immunoglobulins (IVIG) reduces the concentrations and activities of natural killer cells in peripheral blood and affects Th1-mediated immune response [97]. The studies were very heterogeneous and the majority were done in patients with idiopathic RM but without a specific immunological diagnostic workup prior to starting therapy. The data is inconsistent [97–100].

A recent meta-analysis which included 11 randomized studies of the type described above found no significantly higher LBR for the group of patients who received IVIG (RR 0.92; 95% CI: 0.75–1.12) compared to placebo or standard care [101]. A subgroup analysis showed a trend towards a benefit from IVIG in the cohort of patients with secondary RM compared to placebo (RR for no live births 0.77; 95% CI: 0.58–1.02; p = 0.06). There are currently no clearly defined indications for the administration of immunoglobulins, and they should therefore not be administered outside

clinical studies. Side effects which can even include anaphylactic shock and the transmission of infectious pathogens are rare, but the incidence of occurrence is significantly higher in the verum group compared to controls.

Consensus-based Recommendation 3-7.E26	
Expert consensus	**Level of consensus ++**
Therapy with intravenous immunoglobulins to prevent miscarriage should not be given to women with RM outside clinical studies.	

3.7.2.3 Lipid infusion

Current studies showed that soybean-oil-based lipid infusions reduced both NK cell activity and the formation of pro-inflammatory cytokines [102 – 106]. Small observational studies have shown that lipid infusions administered to women with RM or implantation failure and increased NK cell activity achieved the same live birth rates as treatment with IVIG [107 – 109]. A randomized placebo-controlled double-blind study carried out in Egypt investigated the impact of a single lipid infusion in a cohort von 296 women (with no tubal pathology and aged less than 40 years) undergoing IVF. The investigated women all had ≥ 3 idiopathic RM (consecutive clinical miscarriages after spontaneous conception or IVF/ICSI) and had elevated levels of peripheral blood NK cells (pNK cells > 12 %) [110]. No significant difference in the rate of biochemical pregnancies was found between groups, but the rate of intact pregnancies > 12th GW and the rate of live births (37.5 vs. 22.4 %, respectively; p = 0.005) was significantly higher in the group which had received a lipid infusion.

Consensus-based Recommendation 3-7.E27	
Expert consensus	**Level of consensus +++**
Lipid infusion to prevent miscarriage should not be administered to women with RM outside clinical studies.	

3.7.2.4 Allogeneic lymphocyte transfer (LIT)

The transfer of allogeneic lymphocytes (usually paternal lymphocytes, rarely donor lymphocytes, also known as lymphocyte immunization therapy) is a means of readying the maternal immune system to cope with the embryo's foreign antigens (HLA). The data on the uses of this therapy in women with RM is inconsistent. Two recent meta-analyses pointed to higher LBR in patients with idiopathic RM who received LIT. However, these meta-analyses were strongly influenced by the weighting of an Asian study, published in 2013, which showed a positive effect [111 – 113]. Older studies found no benefit [114 – 116], meaning that, here too, further studies will be necessary. It should be noted that the transfusion of blood products can lead to complications (e.g., transmission of infections, formation of irregular autoantibodies, induction of autoimmune disorders).

Consensus-based Recommendation 3-7.E28	
Expert consensus	**Level of consensus +**
Allogeneic lymphocyte transfer to prevent miscarriage should not be carried out in women with RM outside clinical studies.	

3.7.2.5 TNF-α receptor blockers

Subgroups of patients with RM have been reported to have increased TNF-α concentrations, abnormal TNF-α/IL-10 ratios or numbers of TNF-α-producing CD3+CD4+ lymphocytes, and these subgroups could benefit from the administration of TNF-α receptor blockers (e.g., adalimumab or infliximab) [100, 117]. However, only one retrospective study has looked at this issue to date. In addition to TNF-α receptor blockers, the study also used low-dose acetylsalicylic acid (ASA), low-molecular-weight heparin (LMWH) and immunoglobulins [100]. Well-known side effects ranged from skin reactions to infections and even rare adverse events such as drug-induced lupus [118]. There are also concerns regarding the possible induction of malignant disease by TNF-α blockers [119]. At present, the administration of TNF-α receptor blockers should be reserved for controlled clinical studies and for specific conditions (e.g., autoimmune diseases such as Crohn's disease or chronic polyarthritis).

Consensus-based Recommendation 3-7.E29	
Expert consensus	**Level of consensus ++**
Therapy with TNF-α receptor blockers should not be given to women with RM outside clinical studies.	

3.7.2.6 Treatment for autoimmune factors

Because of the inconsistent data on the prevalence of antinuclear antibodies in women with RM, the current therapy strategies (ASA, glucocorticoids, low-molecular-weight heparin) are inconsistent and the guideline cannot offer any recommendations. There is currently only one retrospective study on the therapy of women with celiac disease and RM (n = 13) [120]. The women in the study benefitted from a gluten-free diet.

Therapy with low-dose acetylsalicylic acid and low-molecular-weight heparin is recommended for women with RM and antiphospholipid syndrome. Treatment with acetylsalicylic acid and heparin must be initiated as soon as the pregnancy test is positive. Aspirin administration must continue until GW 34 + 0, with heparin administration continuing for at least 6 weeks post partum. Numerous studies have shown that patients with RM and APS benefited from the administration of aspirin (50–100 mg/d) and low-molecular-weight heparin in prophylactic doses [121 – 125]. In contrast to the administration of LMWH and aspirin, other therapeutic approaches such as the administration of corticoids, immunoglobulins or aspirin alone did not result in any significant improvement in the LBR of patients with RM and APS [121].

Based on current studies, non-criteria aPL syndrome should be treated in exactly the same way, as a few studies have indicated a

potential benefit from the administration of LMWH in combination with ASA [126 – 130].

Consensus-based Recommendation 3-7.E30	
Expert consensus	**Level of consensus +++**
Therapy with low-dose acetylsalicylic acid and low-molecular-weight heparin is recommended for women with RM and antiphospholipid syndrome. Treatment with acetylsalicylic acid and heparin must be initiated as soon as the pregnancy test is positive. Aspirin administration must continue until GW 34 + 0, with heparin administration continuing for at least 6 weeks post partum.	

Consensus-based Recommendation 3-7.E31	
Expert consensus	**Level of consensus +++**
Therapy with low-dose acetylsalicylic acid and low-molecular-weight heparin is recommended for women with RM and non-criteria antiphospholipid syndrome. Treatment with acetylsalicylic acid and heparin must be initiated as soon as the pregnancy test is positive. Aspirin administration must continue until GW 34 + 0, with heparin administration continuing for at least 6 weeks post partum.	

3.8 Coagulation

3.8.1 Diagnosis of congenital thrombophilic factors

Hereditary thrombophilic parameters are present in up to 15 % of the Caucasian population [131]. In recent years, the assessment of maternal thrombophilia as an important risk factor for RM has significantly changed. Thrombophilia testing done only to prevent miscarriage is not recommended. International guidelines (ASRM, ACCP, RCOG) do not recommend routine testing for hereditary thrombophilia in women with RM [1, 3, 132 – 134]. The RCOG guideline considers testing for maternal hereditary thrombophilia to be only indicated in the context of scientific studies [133]. The ASRM recommendations propose thrombophilia testing for women with RM only if they have a medical or familial history of thromboembolic events [1, 3, 132 – 134].

Abnormalities in thrombophilic parameters may be an indication to treat pregnant women for medical reasons (prevention of thrombembolic events). Anticoagulation therapy to prevent maternal thromboembolism may be justified in pregnant women who have an increased risk of thromboembolic events (VTE) due to specific conditions (e.g., antithrombin deficiency, homozygous FVL mutation, combined heterozygous FVL and PT mutation, etc.) and in women with additional risk factors for VTE in pregnancy (immobilization, surgery, excessive weight gain, etc.) (ACOG 2013, AWMF 2015).

Consensus-based Recommendation 3-8.E32	
Expert consensus	**Level of consensus ++**
Testing for thrombophilia to prevent miscarriage is not recommended.	

Consensus-based Recommendation 3-8.E33	
Expert consensus	**Level of consensus +++**
Women with RM who are at risk of thromboembolic events must be tested for thrombophilia. This includes determination of antithrombin activity and plasma protein C and protein S levels and molecular genetic analysis for factor V Leiden mutation and prothrombin G20210A mutation.	

3.8.2 Treatment for women at risk of thrombophilic events

3.8.2.1 Heparin

Unfractionated and low-molecular-weight heparins differ with regard to their molecular weight, plasma protein binding, biological half-life and rate of side effects. In addition to their anticoagulation effect, they also have numerous effects at the molecular level of the embryo-maternal interface which are still not completely understood [135]. No heparins cross the placenta. The administration of low-molecular-weight heparin(s) during pregnancy is considered comparatively safe [136]. The administration of heparins in pregnancy represents an off-label use. If the administration of heparin in pregnancy is indicated, low-molecular-weight heparins should be used because of their superior side-effects profile and ease of administration [132]. The enthusiasm at the turn of the century about the impact of prophylactic heparin administration in women with RM (in whom APS had been excluded) on the prevention of miscarriage could not be confirmed in either large prospective randomized studies [137 – 139] or in more recent meta-analyses [140].

The general maternal administration of heparin in subsequent pregnancies to women with RM without confirmed thrombophilia is not indicated because of the lack of proof of efficacy [141 – 143]. There is also no evidence for a beneficial effect of administering heparin prior to or during the conception period on the prevention of further miscarriages.

To what extent subgroups of patients (e.g., patients with confirmed hereditary thrombophilia) actually benefit from the administration of heparin in subsequent pregnancies requires further studies, such as the currently recruiting, multinational ALIFE2 trial [144]. At present, the general administration of heparin outside clinical studies for the indication “prevention of miscarriage” alone is not indicated, even in thrombophilic women with RM (in whom APS has not been confirmed) [132, 145].

Consensus-based Recommendation 3-8.E34	
Expert consensus	**Level of consensus ++**
Treatment with heparin with the sole purpose of preventing miscarriage is not recommended for women with RM. This also applies to women with hereditary thrombophilia.	

Consensus-based Recommendation 3-8.E35	
Expert consensus	**Level of consensus ++**
Thromboprophylaxis for maternal indication should be given during pregnancy to women with RM and an increased risk of thromboembolic events.	

3.8.2.2 Acetylsalicylic acid (ASA)

The use of ASA in pregnancy to prevent miscarriage represents an off-label use. The administration of ASA in low doses starting in the 1st trimester of pregnancy reduces the risk of placenta-associated complications in late pregnancy [146], although it has not been possible to confirm any protective effect on the rate of miscarriages. The prospective randomized ALIFE trial in women with idiopathic RM reported that administration of aspirin prior to conception (80 mg/day) did not reduce the rate of miscarriages compared to placebo [138]. A systematic Cochrane meta-analysis found no benefit from the prophylactic administration of ASA in women with idiopathic RM (RR 0.94; 95% CI: 0.80–1.11) [147]. This also applies to the administration of aspirin prior to conception [148].

Consensus-based Recommendation 3-8.E36	
Expert consensus	**Level of consensus +++**
Acetylsalicylic acid therapy to prevent miscarriage is not recommended for women with RM.	

3.8.3 Monitoring during pregnancy – D dimers

Consensus-based Recommendation 3-8.E37	
Expert consensus	**Level of consensus +++**
Monitoring of plasma coagulation markers (D dimers, prothrombin fragments, etc.) during pregnancy is not recommended in women with RM. Determination of these markers must not be used as an indication to initiate therapy to prevent miscarriage.	

3.9 Idiopathic RM

3.9.1 Diagnosis of idiopathic RM

Idiopathic RM is present if the criteria for a diagnosis of RM are met, and genetic, anatomical, endocrine, established immunological and hemostatic factors have been ruled out. The percentage of idiopathic RM in the total population of women with RM is high and amounts to 50–75% [2]. The percentage of live births for women with idiopathic RM who did not receive treatment is 35–85% [138, 149].

Consensus-based Recommendation 3-9.E38	
Expert consensus	**Level of consensus +++**
The term “idiopathic RM” is only used if the diagnostic workup described in this guideline is carried out and no cause of RM has been found.	

3.9.2 Therapy for idiopathic RM

A Cochrane meta-analysis of nine randomized studies which included 1228 women with idiopathic RM who had had at least two spontaneous miscarriages found no statistically significant effect of ASA with/without heparin on the LBR compared to placebo [147]. A randomized study of 364 women with idiopathic RM found that ASA administration had no impact on LBR compared to ASA and nadroparin or placebo [138]. Another meta-analysis of six randomized studies of 907 women with idiopathic RM also found no improvement in live birth rates following the administration of ASA and heparin [147].

Consensus-based Recommendation 3-9.E39	
Expert consensus	**Level of consensus ++**
Treatment with acetylsalicylic acid with or without additional heparin to prevent miscarriage is not recommended in women with idiopathic RM.	

A meta-analysis, published in 2017, of 10 randomized studies of 1586 women with idiopathic RM reported a positive effect following therapy with progestogens in the first trimester of pregnancy, both in terms of the rate of miscarriages (RR 0.72; 95% CI: 0.53–0.97) and the rate of live births (RR 1.07; 95% CI: 1.02–1.15). Synthetic progestogens, but not natural progesterone, were associated with a lower risk of recurrent miscarriage [150]. Synthetic progestogens can therefore be administered to women with idiopathic RM in the first trimester of pregnancy to prevent miscarriage. However, the optimal time for administration and the optimal dosage of the progestin are not yet clear.

In the PROMISE trial, a total of 836 women with idiopathic RM were randomized to receive either placebo or 400 mg micronized progesterone applied by vaginal suppository [151]. Treatment was initiated soon after positive urinary pregnancy test and continued up to and including the 12th week of gestation. The LBR was the same in both study arms (63 and 66%, respectively). However, a randomized study of 700 women with RM carried out in Egypt reported significantly higher live birth rates compared to placebo (91 vs. 77%) for 2 × 400 mg progesterone administered intravaginally, starting in the luteal phase [152].

Consensus-based Recommendation 3-9.E40	
Expert consensus	**Level of consensus ++**
Treatment with natural micronized progesterone in the first trimester of pregnancy to prevent miscarriage is not recommended for women with idiopathic RM.	

Consensus-based Recommendation 3-9.E40	
Expert consensus	**Level of consensus ++**
Synthetic progestogens can be administered to women with idiopathic RM in the first trimester of pregnancy to prevent miscarriage.	

The effect of human chorionic gonadotropin (hCG) in doses of 5000–10 000 IE in the first and second trimester of pregnancy was evaluated in five randomized studies of 596 women with RM, including women with idiopathic RM. A Cochrane meta-analysis of these five studies found that the administration of hCG led to a significant reduction in the frequency of miscarriage. However, this positive effect was no longer statistically significant when the analysis was done without the two methodologically weaker studies (OR 0.74; 95% CI: 0.44–1.23) [153]. The studies did not include data on LBR. There was no separate subgroup analysis for women with idiopathic RM. It is therefore currently not possible to recommend the administration of hCG to treat women with RM.

Scarpellini et al. carried out a randomized study in 68 women with RM who had previously had at least 4 consecutive spontaneous miscarriages. The women were randomized to receive either placebo or rh-G-CSF (1 µg/kg/day) starting on the 6th day after ovulation [154]. LBR for the active study arm was 83% (29/35) compared to 48% in the control group (16/33). In a retrospective cohort study Santjohanser et al. reported on 127 women with RM (for the purposes of that study, RM was defined as at least 2 spontaneous early miscarriages) who had IVF/ICSI [155]. Forty-nine of the women received either rh-G-CSF at a dose of 34 million units/week or 2 × 13 million units/week until the 12th week of gestation. The LBR was 32% higher following G-CSF administration compared to 13–14% for other patient groups. As a number of issues (e.g., the optimal dose) relating to G-CSF therapy are still unresolved, G-CSF should only be administered in the context of a clinical study.

Consensus-based Recommendation 3-9.E41	
Expert consensus	**Level of consensus ++**
With the exception of clinical trials, administration of G-CSF to prevent miscarriage is not recommended for women with idiopathic RM.	

Consensus-based Recommendation 3-9.E42	
Expert consensus	**Level of consensus +++**
Treatment with acetylsalicylic acid with or without additional heparin to prevent miscarriage is not recommended in women with idiopathic RM.	

Conflict of Interest

Conflicts of interest are given in long version of the guideline.

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