

Recurrent Miscarriage: Diagnostic and Therapeutic Procedures. Guideline of the DGGG (S1-Level, AWMF Registry No. 015/050, December 2013)

Diagnostik und Therapie beim wiederholten Spontanabort.

Leitlinie der DGGG (S1-Level, AWMF-Registernummer 015/050, Dezember 2013)

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Key words

- recurrent miscarriage
- incidence
- diagnosis
- therapy
- recommendation

Schlüsselwörter

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- Inzidenz
- Diagnose
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- Empfehlung



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Bibliography

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Abstract

Purpose: Official guideline coordinated and published by the German Society of Gynecology and Obstetrics (DGGG). Aim of the guideline was to standardize the diagnosis and treatment of patients with recurrent miscarriage (RM). Recommendations were proposed, based on the current national and international literature and the experience of the involved physicians. Consistent definitions, objective assessments and standardized therapy were applied.

Methods: Members of the different involved societies developed a consensus in an informal process based on the current literature. The consensus was subsequently approved by the heads of the scientific societies.

Recommendations: Recommendations for the diagnosis and treatment of patients with RM were compiled which took the importance of established risk factors such as chromosomal, anatomical, endocrine, hemostatic, psychological, infectious and immunological disorders into consideration.

Zusammenfassung

Ziel: Offizielle Leitlinie, koordiniert und publiziert von der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (DGGG). Ziel der Leitlinie war es, die Diagnostik und Therapie des wiederholten Spontanaborts (WSA) anhand der aktuellen (inter-)nationalen Literatur sowie der Erfahrung der beteiligten Kolleginnen und Kollegen evidenzbasiert zu standardisieren. Dies erfolgte unter Verwendung einheitlicher Definitionen, objektiver Bewertungsmöglichkeiten und standardisierter Therapieprotokolle.

Methoden: Anhand der internationalen Literatur entwickelten die Mitglieder der beteiligten Fachgesellschaften in einem informellen Prozess einen Konsensus. Anschließend wurde dieser durch die Vorsitzenden der Fachgesellschaften bestätigt.

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

Information on the Guideline

Guidelines program

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

Citation format

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Guideline documents

The complete long version, a short version, and a PowerPoint slide version of this guideline as well as a summary of the conflicts of interest of all the authors is available in German on the homepage of AWMF:

<http://www.awmf.org/leitlinien/detail/ll/015-050.html>

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See ● **Table 1**.

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Abbreviations

Ab	antibodies
ACE	angiotensin-converting enzyme
ANA	antinuclear antibodies
APC	activated protein C
aPL	antiphospholipid
APS	antiphospholipid syndrome
ART	assisted reproductive technology
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
IUFD	intrauterine fetal death
IVIG	intravenous immunoglobulin
LBR	live birth rate
LMWH	low molecular weight heparin
MTHFR	methylenetetrahydrofolate reductase
PAI	plasminogen activator inhibitor
PCO	polycystic ovary
RCOG	Royal College of Obstetricians and Gynaecologists
PBB	polar body biopsy
PGD	preimplantation genetic diagnosis
PT	prothrombin
RM	recurrent miscarriage
SC	supportive care
TLC	tender loving care
VEGF	vascular endothelial growth factor
VTE	venous thromboembolism

II Application of the Guideline

Purpose and objectives

The guideline aims to standardize the diagnosis and treatment of recurrent miscarriage (RM) based on the most current national and international literature and the experiences of physicians.

Targeted patient care areas

Outpatient and inpatient care.

Target audience

In addition to gynecologists, this guideline is also aimed at professionals working in medical fields such as human genetics, psychotherapy, laboratory medicine, and internal as well as general medicine.

Targeted patient group: women wanting to have children as well as women with miscarriages

Period of validity

The validity of this guideline was confirmed by the boards/responsible persons of the participating professional medical associations/working groups/organizations/societies as well as by the board of the DGGG and the DGGG Guideline Commission in January 2014 and thereby approved in its entirety. This guideline is valid from December 31, 2013 to January 31, 2017. The period of validity has been estimated based on the guideline's contents. The guideline can be updated earlier if necessary; likewise, the guideline's period of validity can be extended if it continues to represent the current state of knowledge.

III Guideline

1 Methodology

During the compilation of this guideline, there was a special focus on previous recommendations (the guideline was first compiled in 09/2004, revised in 05/2008) and the ESHRE guideline of 2006 [1], as well as the guidelines of the Royal College of Obstetricians and Gynaecologists (RCOG 2011) [2], the American College of Obstetricians and Gynecologists (ACOG 2002) [3] and the American Society of Reproductive Medicine (2008) [4]. In addition, a search was done using PubMed and the Cochrane Library for current evidence-based studies. The guideline, which already existed in an earlier version from the year 2006, was adapted to take ac-

count of the recent literature and existing international guidelines. Drafts of the proposed guideline were circulated between authors, prompting some controversial discussions until an agreement was obtained. After several drafts had been circulated, all of the authors agreed to the version which was finally adopted. The Guideline Commission and the board of the DGGG approved the guideline in January 2014.

2 Introduction

Caring for couples with RM is a challenge for clinicians as several possible causes of RM are known, but in the majority of patients no cause of RM is found. The psychological strain for couples is high, which can mean that extensive diagnostic investigations and a treatment strategy are requested after only a single miscarriage. Moreover, because of the lack of studies and the associated lack of evidence-based recommendations for therapy, a wide range of therapeutic approaches are currently used.

3 Incidence and Definition

Approximately 1–3% of all couples of reproductive age experience recurrent miscarriages. This can lead to serious problems for the couple's relationship and quality of life [5]. A miscarriage is defined as the loss of a fetus at any time between conception and the 24th week of gestation (GW) (WHO Guidelines) [2]. The WHO definition of recurrent miscarriage is: "3 or more consecutive miscarriages before the 20th GW" [2]. The American College of Obstetricians and Gynecologists defines just 2 consecutive miscarriages as RM [6], raising the incidence of recurrent pregnancy loss to 5% [7]. This guideline takes the WHO definition (≥ 3 consecutive miscarriages) as the basis for its diagnostic investigations and therapeutic procedures.

If a woman has not previously given birth, the loss of the fetus is referred to as primary RM; if a woman has had a previous live birth, the pregnancy loss is referred to as secondary RM [8].

The risk of recurrent miscarriage varies considerably, depending on a number of factors. In addition to maternal age, the number of previous miscarriages also affects the risk of recurrence. **Table 2** presents the data from a large retrospective register study carried out by Nybo-Andersen et al. [9].

4 Causes and Diagnostic Workup

4.1 Genetic factors

4.1.1 Chromosomal anomalies

The most common cause of recurrent miscarriage is embryonic/fetal chromosomal abnormality [10, 11]. However, the percentage of chromosomally abnormal fetuses decreases as the number of miscarriages increases. In a series of 1309 women who had 2–20 miscarriages in their first trimester of pregnancy, the percentage of embryonic/fetal karyotype anomalies in women with 2 miscarriages dropped continuously, from 63% to 11% in women who had 10 or more miscarriages [12].

Parental chromosomal anomalies are present in 3% of cases with more than 3 miscarriages [13]. The probability that one of the parents has a structural chromosomal abnormality increases to almost 5% if the couple has a previous history of stillbirth or already has a previous child with major congenital impairments.

Both Robertsonian translocations (which affects the acrocentric chromosomes 13, 14, 15, 21 and 22) and reciprocal translocations have been reported [13]. In two thirds of cases, the woman is the carrier of the translocation; the man is only the carrier in one third of cases. Structural aberrations such as paracentric or pericentric inversion are much rarer [10].

Table 2 Probability of recurrent miscarriage depending on maternal age and the number of previous miscarriages, following Nybo-Andersen et al. [9].

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

The risk of embryonic/fetal trisomy from incorrect distribution of chromosomes increases with higher maternal age. Trisomy 16 is the most common presentation (approx. 30%), followed by trisomy 22 (approx. 14%). Triploidy is present in around 15% of cytogenetically abnormal miscarriages. Turner syndrome is responsible for around 20% of miscarriages in the first trimester of pregnancy. No association with maternal age has been found for Turner syndrome, polyploidy or structural chromosomal disorders [14].

The earlier the miscarriage occurs, the greater the likelihood that an embryonic/fetal chromosome aberration was present. In the first trimester of pregnancy, a chromosome abnormality was found in around 50% of cases with RM, whereas the rate of chromosomal anomalies in RM cases in the second trimester was only around 20% [15, 16].

Chromosome analysis of both parents should be done if a patient has suffered 3 or more miscarriages; chromosome analysis should also be done if couples have had 1 or more miscarriages in combination with a prior stillbirth or a child with impaired intelligence or congenital malformations. Prior to every genetic diagnostic procedure the patient must be informed about the planned investigation by a qualified physician in accordance with the German Genetic Diagnosis Act. In addition, the patient must give her written consent to the procedure.

4.2 Anatomical factors

4.2.1 Uterine disorders

The incidence of uterine disorders in RM reported in the literature is 10–25% (compared to 5% in control groups) [17] or 3.2–6.9% [18]. Septate (and subseptate) uterus is known to be associated with an increased risk of miscarriage. Changes in the expression of VEGF receptors have been found in the endometrium covering the septal area. It is assumed that this affects vascularization during placentation, which would explain the increased risk of miscarriage if implantation occurs on the septum [19].

The differences between various studies may be due to poor interobserver agreement regarding the hysteroscopic diagnosis of septate uterus [20].

Hysteroscopy (alternatively, hysterosalpingography) is used to investigate potential uterine anomalies, potentially in combination with laparoscopy or 3D ultrasound; the choice of procedure depends on the individual case [17].

4.2.2 Fibroids

In an analysis of retrospective and prospective data obtained from patients with RM, the incidence of submucosal fibroids was found to be 2.6% (25/966) [21]. However, for methodological reasons the potential benefits of fibroid enucleation in patients with RM cannot be investigated in a blind randomized prospective study. An association with RM is unlikely for fibroids without a submucosal part which are located elsewhere in the uterus.

Hysteroscopy is the standard diagnostic procedure to assess whether submucosal fibroids are present.

4.2.3 Polyps

It is not clear whether – as with submucosal fibroids – intracavitary polyps increase the risk of miscarriage. Polyps – particularly diffuse micropolyps – are often associated with chronic endometritis [22]. Hysteroscopy is recommended for the diagnosis and localization of polyps.

4.2.4 Cervical insufficiency

Miscarriages in the second and third trimester of pregnancy are often associated with cervical insufficiency. But the pathophysiology or potential diagnostic markers are still unknown.

4.3 Microbiological factors

The importance of microbiological factors in recurrent miscarriage is controversially discussed; general screening over and above standard prenatal screening is not currently recommended.

Bacterial vaginosis in the first trimester of pregnancy has been reported to be a risk factor for miscarriage in the second trimester and for preterm birth [23, 24]. However, there is currently no evidence for an association with miscarriages in the first trimester of pregnancy [25].

4.4 Endocrine factors

Possible endocrine causes of RM include luteal phase deficiency, thyroid dysfunction and a complex of metabolic disorders associated with obesity, PCO syndrome, hyperandrogenemia and insulin resistance.

Luteal phase deficiency is not a proven cause of RM, as there are no defined standard values for progesterone concentrations in the luteal phase. Luteal phase deficiency as a relevant factor for RM can only be considered in patients with considerably shortened luteal phases and premenstrual spotting lasting several days.

When assessing thyroid function it is important to differentiate between manifest and latent dysfunction and increased thyroid autoantibody concentrations. The data for manifest hypothyroidism and hyperthyroidism are limited because of the low prevalence of these conditions. An association is generally assumed but could not be confirmed with certainty [26].

Latent hypothyroidism is one of the most common thyroid dysfunctions occurring in cases with RM. The Endocrine Society considers a TSH value of 2.5 mU/l as the upper limit in infertile women, with a level of evidence of 1 [27]. Based on the assumption that latent hypothyroidism is present in women with TSH values of 2.5 mU/l and above, several studies have reported an increased risk of miscarriage even in cases with latent hypothyroidism [28, 29]. If increased thyroid autoantibodies are additionally present, the association with recurrent miscarriage is considered to be established [30].

Because of the overlap of pathophysiologies, it is difficult to differentiate between obesity, PCO syndrome, hyperandrogenemia and insulin resistance as the cause of RM.

However, several studies described an association between obesity and RM [31, 32].

4.5 Psychological factors

Evidence-based medicine has not found a direct link between RM or fertility disorders in general and purely psychological factors such as (daily) stress [33]. Postulating the existence of mono-causal reasons or linear cause-and-effect relationships does not

do justice to the complexity of the human reproductive system [34, 35]. Based on the current state of knowledge, it is only possible to presume that there may be an indirect impact due to changes in the behavior of the pregnant woman (for example, ingestion of stimulants or poor nutritional status) [36]. The explanatory models for spontaneous abortion or RM (e.g. in [37]) used in the (older) psychosomatic literature can either not be verified empirically because of their theoretical presuppositions or it has not yet been possible to replicate them.

4.6 Immunological factors

4.6.1 Alloimmune factors

According to current studies, activation of the immune system (Th1 response) creates less favorable conditions for implantation and is associated with an increased probability of RM [38–40]. It has not yet been clearly proven that an increase in the Th1/Th2 ratio or in the T4/T8 index leads to an increased risk of miscarriage, even though many authors assume that it does. The same applies to increased TNF- α secretion as demonstrated by lymphocyte stimulation test or increased serum TNF- α levels [41]. Determination of these ratios, indices or levels is not yet generally recommended for routine screening.

In patients with RM, analyses of natural killer cells (NK cells) in peripheral blood or of uterine NK cells or of paternal HLA-C allotypes and maternal KIR receptors (e.g., paternal HLA-G2 and the absence of the 3 activating KIR receptors in the mother), NK toxicity tests, or analysis of the HLA identity of both parents should only be done under study conditions [42, 43].

4.6.2 Autoimmune factors

Numerous studies have shown an association between the presence of thyroglobulin antibodies (TGAb), particularly thyroid peroxidase (TPO) antibodies, and the development of (early) RM, with the rate of miscarriage found to be 54% higher in women with detectable antibodies [44].

Even though only 0.01–0.02% of pregnant women had Graves' disease with TSH receptor activating antibodies (TRAb), rates of pregnancy complications were increased in mothers who did not receive treatment [45, 46].

The current data on the effect of antinuclear antibodies (ANA) on miscarriage rates is inconsistent, and determination of ANA is therefore not currently recommended as part of routine diagnostic procedures [47].

Celiac disease is characterized by gluten sensitivity; the association with RM is still controversially discussed. However, as part of diagnostic procedures for RM, testing for immunoglobulin A (IgA) antibodies against tissue transglutaminase can be done under study conditions, followed by a biopsy of the small intestine if findings are positive [48].

Non-specific antibodies against anionic phospholipids such as cardiolipins and β 2 glycoproteins, also known as antiphospholipid antibodies (aPLab), have been detected in women with RM. However, according to the definition in [Fig. 1](#), antiphospholipid (aPL) syndrome is only present if both clinical and laboratory criteria for aPL syndrome are fulfilled. Around 2–15% of women with RM suffer from aPL syndrome [15]. It is important to determine whether aPL antibody titer is still moderate to high at follow-up after 12 weeks during diagnostic workup.

4.7 Congenital thrombophilic factors

Numerous studies in recent decades have discussed a possible association between RM and maternal (but also paternal) thrombophilia. Many procoagulation factors have been investigated, in-

cluding factor V Leiden (FVL) mutation; prothrombin (PT) G20210A mutation; antithrombin, protein C, protein S, protein Z and factor XII deficiency; increased factor VIII or lipoprotein A levels [50]. The pathomechanism may be thrombophilia-related uteroplacental thrombosis affecting placental and embryonic/fetal growth [51]. However, up to 15% of the Caucasian population have at least one of the above-listed thrombophilia parameters [52]. Other factors include polymorphisms in the genes of methylenetetrahydrofolate reductase (MTHFR C677T), angiotensin-converting enzyme (ACE) or plasminogen activator inhibitor (PAI); the reported prevalence of these factors is > 10% [52]. The prevalence of these variations in the general population mediates against the idea of hereditary thrombophilia as a monocausal factor in RM.

Given the differences in ethnicity and the associated differences in the prevalence of thrombophilia in investigated populations, the international data on hereditary thrombophilia in women with RM needs to be critically reviewed, as a study which looked exclusively at Caucasian women found no correlation between hereditary thrombophilia and RM [53].

Prospective cohort studies also found no correlation between miscarriage and maternal thrombophilia [54,55]. This means that not every pregnant woman with hereditary thrombophilia must automatically be considered at risk for (recurrent) miscarriage. But it is important to differentiate this combination from women with prior recurrent miscarriage and verified specific thrombophilia, as carriers of FVL appear to have significantly lower rates of live births compared to women with the corresponding wild type of the clotting factor in subsequent untreated pregnancies [56,57].

Because of the inconsistent data in international guidelines (ASRM, Bates, RCOG), general testing for hereditary thrombophilia is no longer recommended in women with RM [1,4,58]. The British guideline considers that investigations into maternal thrombophilia (FVL and PT mutation, protein S deficiency) are only indicated in the case of idiopathic miscarriage in the second trimester of pregnancy [1]. The ASRM recommendations propose testing for thrombophilia in women with RM only if these women have a medical or familial history of thromboembolic events [4].

As a step-by-step diagnostic approach, we recommend investigating the following factors in women with RM: antithrombin activity, APC resistance, molecular genetic testing for prothrombin mutation. If results appear to indicate APC resistance, testing for FVL mutation should be done in a second step.

Protein S and protein C activity should additionally be determined in women with a medical or familial history of thromboembolic events; investigations should be performed at least 8 weeks from the last pregnancy or intake of sexual steroids. According to the currently available data, testing for MTHFR polymorphism is not necessary.

4.8 Idiopathic RM

Idiopathic RM is present if the criteria for a diagnosis of RM are met, and genetic, anatomical, endocrine, established immunological or hemostatic factors have been ruled out.

The percentage of idiopathic RM in the total population of women with RM is 50–75% [3].

Clinical criteria

- ▶ ≥ 1 venous or arterial thrombosis
- ▶ 1 or 2 unexplained miscarriages of morphologically normal fetuses > 10th GW
- ▶ ≥ 3 miscarriages < 10th GW
- ▶ ≥ 1 late miscarriage or preterm birth < 34th GW because of placental insufficiency or preeclampsia

Criteria for laboratory findings

(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 [49]. Clinical and laboratory criteria can be present either singly or in combination. By definition, at least one clinical and one laboratory criterion must fulfilled for a diagnosis of antiphospholipid syndrome.

5 Treatment

5.1 Genetic factors

It is not possible to treat chromosome disorders. Preventing miscarriages in cases with proven maternal or paternal chromosome disorders can only be done by selecting cytogenetically unremarkable gametes or embryos. However, a combination of assisted reproductive technology (ART) treatment and preimplantation genetic diagnosis (PGD) is required for this. In cases of maternal chromosome disorders it may be possible to carry out a polar body biopsy (PBB) in specialized centers. But this procedure only tests for incorrect distributions of chromosomes in the oocyte; the male set of chromosomes is not investigated. PIGD will also show incorrect paternal chromosome distribution. Since February 1, 2014, PIGD is permissible in Germany after individual approval by an ethics commission. The use of donated sperm is permitted whereas egg donation is not legal in Germany.

5.2 Anatomical factors

5.2.1 Uterine disorders

A Cochrane meta-analysis [59] showed that there are no prospective randomized studies on the impact of septal dissection, and posited benefits are only based on retrospective uncontrolled studies. Based on the currently available data we nevertheless consider septal dissection useful in selected women with RM. Postoperative healing appears to take around 2 months [60], and pregnancy is tenable at the end of this period.

5.2.2 Fibroids

There are currently no prospective randomized and controlled studies on the benefits of fibroid resection. The indications for fibroid enucleation in patients with RM must depend on the patient's general status and history (hypermenorrhea, size and location of the fibroids, etc.).

5.2.3 Polyps

It is currently not clear whether the presence of polyps increases the risk of miscarriage and whether their resection decreases the risk.

5.2.4 Cervical insufficiency

A recent multicenter randomized study found no benefit for cerclage compared to conservative treatment for the prevention of preterm birth [61]. Similarly, there are no clear data on the benefits of pessary placement or early total cervical occlusion.

5.3 Microbiological factors

Because data are still controversial, generalized screening for microbiological factors is currently not recommended. In the event of a repeat pregnancy, testing and treatment should be provided if there is a suspicion of vaginal infection [40,62].

5.4 Endocrine factors

The data on the effect of luteal phase supplementation in patients with RM have still not been sufficiently validated. Because of the unclear data, luteal phase supplementation, e.g. using micronized progesterone applied vaginally, should only be considered in cases where luteal phase insufficiency is clinically very probable, i.e. in patients with significantly shorter luteal phases and RM. Manifest hypothyroidism or hyperthyroidism must always be investigated and treated, particularly in women with child-wish. Patients with latent hypothyroidism – particularly patients with increased levels of thyroid autoantibodies or Hashimoto thyroiditis – should receive thyroid hormone substitution with the goal of reducing TSH levels until they are within lower ranges [30]. The Endocrine Society recommends reducing the levels to under 2.5 mU/l in infertile patients [27]. During pregnancy thyroxin doses should be increased by around 50% of the initial dose. Thyroid hormone substitution can be discontinued again postpartum in patients with latent hypothyroidism.

A general recommendation to prescribe metformin cannot be given. Decisions on treatment based on the off-label use of metformin must be made individually on a case-by-case basis and after definitive proof of insulin resistance in the patient. Metformin has not been approved for use during pregnancy, although no increased malformation rates have been reported after metformin administration during pregnancy. The current S3-guideline dealing with type II diabetes in pregnancy recommends switching from metformin to insulin.

5.5 Psychological factors

The concept of “tender loving care (TLC)”, which is often used in the context of RM, goes back to 2 publications by Stray-Pedersen [63,64]. However, the ASRM Practice Committee has pointed out that there was no real control group, as division into the TLC group or the control group was done based on the patients' place of residence, and differences between the two groups with regard to lifestyle factors, social support and other psychological variables were unknown [65]. According to the tenets of evidence-based medicine, the TLC concept therefore still lacks scientific validation in the form of randomized controlled studies. Two other studies which looked at the benefits of supportive care (SC) have also not yet been replicated under controlled study conditions.

5.6 Treatments for immunological factors

5.6.1 Alloimmune factors

Glucocorticoids

There are currently no studies which have been able to demonstrate an improvement in LBR for patients with RM and abnormal B-cell and T-cell concentrations or NK toxicity after glucocorticoid administration [66,67]. Therefore this type of treatment

should be reserved for (pre-existing) autoimmune disorders which require glucocorticoid treatment even during pregnancy.

Intravenous immunoglobulins and lipid infusion

There is some evidence that intravenous immunoglobulins (IVIG) can reduce the concentrations of natural killer cells in peripheral blood [68] and that lipid infusion reduces NK cell activity and pro-inflammatory cytokine formation [69,70]. Nevertheless, the data for women with RM is inconsistent [68,71–73]. No clear indications for the administration of immunoglobulins or for lipid infusion have been defined yet, which is why any administration should only be done under study conditions. Side effects of IVIG, which can include anaphylactic shock or the transmission of infectious pathogens are rare, but the patient must be informed about such side effects prior to administration.

Allogeneic lymphocyte infusion

(“lymphocyte immunization”)

To date, meta-analyses have not been able to show a benefit for patients with RM [74]. 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 diseases).

G-CSF/GM-CSF

Two studies to date have shown that patients with RM can benefit from G-CSF administration in the first trimester of pregnancy [75,76]. There are currently no findings of fetal impairment after administration. It is not yet clear which subgroup of patients with RM will benefit from G-CSF administration, and further (randomized) studies will be necessary before a general recommendation.

TNF- α receptor blockers

Currently there is only one randomized study in which TNF- α receptor blockers were used in addition to low molecular weight heparins (LMWH) and immunoglobulins in patients with RM [73]. Side effects are well known and range from skin reactions to infections and even rare adverse events such as drug-induced lupus [77]. There are also concerns with regard to the potential induction of malignant disease after the administration of TNF- α blockers [78].

At present, TNF- α receptor blockers should only be administered in the context of controlled clinical studies or for specific conditions (e.g., for autoimmune diseases such as Crohn's disease or chronic polyarthritis).

5.6.2 Autoimmune factors

Although women with autoimmune thyroiditis and hypothyroidism benefit from medication which adjusts their TSH levels to <2.5 mU/ml, there are currently no findings showing that this is also the case for women who have only hypothyroidism [28,79]. There are currently no valid data for patients with Hashimoto thyroiditis which show that the additional administration of selenium (200 μ g) or aspirin (100 mg) increases the rate of live births. Antibodies should be monitored prior to the 22nd GW in pregnant women known to have Graves' disease, with pharmacological treatment potentially indicated in these patients. Pharmacological treatment can consist of propylthiouracil (100–150 mg/8 h) in the first trimester of pregnancy and methimazole in the second and third trimester [45,46].

Because of the inconsistent data on the prevalence of ANA in women with RM, current treatment strategies (aspirin, glucocorticoids, low molecular weight heparin) are inconsistent, and this guideline cannot offer any recommendations.

In women with verified ANA, further testing must be done to differentiate between antibodies and exclude the presence of SS-A/

Ro and SS-B/La antibodies, which occur with Sjögren's syndrome or systemic lupus erythematosus. In addition to neonatal lupus syndrome, antibodies can lead to the occurrence of AV (atrioventricular) block already in the fetal period.

Ultrasound monitoring of the fetus is recommended in such cases to exclude fetal bradycardia, and corticosteroid administration may be initiated. Prenatal care of pregnant women should be done in cooperation with experienced rheumatologists.

At present there is only one retrospective study on the treatment of women with celiac disease and RM ($n = 13$) [80]. The women in the study benefited from a gluten-free diet. However, further (randomized) studies which would permit a general recommendation to be made, e.g. for women positive for tissue transglutaminase antibodies without clinical symptoms, are still lacking. Possible treatment recommendations should be discussed with gastroenterologists.

Numerous studies have shown that patients with RM and APS benefit from the administration of aspirin (100 mg/d) combined with low molecular weight heparin (LMWH) [81]. Treatment should be initiated as soon as the pregnancy test is positive; aspirin administration should be continued till GW 32+0 and LMWH should continue to be administered for at least 6 week postpartum. In contrast to the combination of LMWH and aspirin, other therapeutic approaches such as the administration of corticoids, immunoglobulins or aspirin alone did not lead to any significant improvement in the LBR of patients with recurrent miscarriage and APS [81].

5.7 Treatment of thrombophilia

5.7.1 Heparin

If administration of heparin in pregnancy is therapeutically indicated, low molecular weight heparins should be administered because of their superior side-effects profile and ease of administration [58].

At the turn of the century it was hoped that the prophylactic administration of heparin could prevent miscarriages in women with RM in whom APS was excluded, but this hope has not been confirmed in more recent studies [82] (• Table 3).

While older cohort studies reported a positive effect of heparin administration on the rates of live births in subsequent pregnancies, these effects could not be confirmed in prospective randomized studies (• Table 2). Because of the current lack of studies confirming the positive effect of heparin administration on subsequent pregnancies, the administration of heparin is not generally indicated for women with idiopathic RM [95–97]. There is also no evidence for the benefit of heparin administration prior to or during conception to prevent further miscarriages.

At present, the administration of heparin outside clinical studies is not recommended for the indication “prevention of miscarriage” alone, even in thrombophilic women with RM (in whom APS has not been confirmed) [58,82].

Irrespective of the above, anticoagulation therapy may be justified to prevent maternal thromboembolism (VTE) in thrombophilic pregnant women with specific conditions (antithrombin deficiency; homozygote FVL mutation, compound heterozygote FVL and PT mutation, etc.) which put them at increased risk of VTE and in women presenting with additional risk factors for VTE in pregnancy (e.g., immobilization, surgery, excessive weight gain, etc.), and appropriate anticoagulation therapy must be considered for this group of patients.

Heparin should be administered during pregnancy and postpartum in cases with a positive history of thromboembolic events.

The general maternal administration of heparin is not indicated in women with a familial history of thromboembolism who do not have a history of thromboembolic events themselves and who are not thrombophilic.

With the exception of scientific studies, there is currently no data which supports routine testing for individual polymorphisms (e.g., ACE, PAI) followed by therapeutic treatment.

5.7.2 Acetylsalicylic acid (ASA)

A non-randomized study found that ASA monotherapy (40 mg/d) in women with recurrent early miscarriage and hereditary factor XII deficiency could prevent a further miscarriage in subsequent pregnancies [98]. However, the use of ASA in pregnancy to prevent miscarriage represents an off-label use.

5.8 Treatment of idiopathic RM

The rate of live births for women with idiopathic RM who did not receive treatment is 35–85% [94,99]. A meta-analysis of randomized therapeutic studies reported that the LBR of women in the control groups was between 60 and 70% [100]. Empirical therapies are routinely used, particularly to treat women with idiopathic RM.

This is quite understandable in view of the frustration felt by affected couples after tests have been inconclusive as well as the strong desire for some form of treatment. However, especially in these cases, couples should receive evidence-based counselling and treatment.

6 Summary

The following diagnostic procedures are useful for patients with RM:

- Genetic factors:** Chromosome analysis of both parents, genetic counselling in the event that one of the parents has an abnormal karyotype; chromosome analysis of the aborted fetus or embryo can help affected parents come to terms with the miscarriage.
- Anatomical factors:** Diagnostic hysteroscopy to exclude subseptate or septate uterus, intracavitary polyps and fibroids.
- Microbiological factors:** Microbiological screening is not generally recommended at present because of the contradictory data. If a woman with a history of RM becomes pregnant again, testing and treatment should be initiated at the slightest suspicion of vaginal infection.
- Endocrine factors:** Detailed history of menstrual cycles to exclude significantly shortened luteal phases; testing is required to exclude hyperthyroidism or hypothyroidism and autoimmune thyroiditis.
- Psychological factors:** Detailed exploration of the emotional impact of RM on the patient (particularly to determine whether the patient is experiencing feelings of guilt) should be done routinely together with an investigation into the patient's social resources (partnership, friends and family). The patient may be given information on psychosocial counselling, self-help groups and internet forums [101].
- Immunological factors:** Antiphospholipid syndrome (based on the definition given in • Fig. 1) should be excluded.
- Thrombophilic factors:** If the patient with RM has a familial or medical history of thromboembolic events: full screening for thrombophilia (FVL or PT mutation; protein C, protein S or AT deficiency, homocysteine levels, factor VIII); if the patient does not present with thrombophilic risk factors: determination of antithrombin, APC resistance and prothrombin (G20210A) mutation.

Table 3 Intervention studies with heparin(s) administered to women with recurrent miscarriage with and without evidence of hereditary thrombophilia.

Study	Number of patients	Inclusion criteria	Intervention	Outcomes	Comments
Brenner et al., 2000 [83]	50 (61 pregnancies)	≥ 3 early miscarriages or ≥ 2 late miscarriages or 1 IUFD and maternal thrombophilia	Enoxaparin (40 mg) in women with only thrombophilia vs. enoxaparin (80 mg) for combined thrombophilia; additional ASA (75 mg) for APS; comparison with historical control group	Rate of live births: 75.4% (46/61) after intervention vs. 19.7% (38/193) in historical control group (p < 0.0001)	<ul style="list-style-type: none"> ▶ Not a purely prospective study (comparison with historical control group) ▶ No placebo group
Carp et al., 2003 [84]	85	≥ 3 miscarriages and maternal thrombophilia	No treatment vs. enoxaparin (40 mg)	Rate of live births: 43.8% (21/48) vs. 70.2% (27/37) (p < 0.02)	<ul style="list-style-type: none"> ▶ Randomization criteria unclear ▶ No placebo group
Gris et al., 2004 [85]	160	1 unexplained miscarriage after ≥ 10th GW and maternal thrombophilia (factor V Leiden, protein S deficiency, prothrombin mutation)	ASA (100 mg) vs. enoxaparin (40 mg)	Rate of live births: 33.8% (27/80) vs. 86.3% (69/80) (p < 0.001)	<ul style="list-style-type: none"> ▶ No untreated control group ▶ No placebo group ▶ No recurrent miscarriages
Brenner et al., 2005 (LIVE-ENOX study) [86]	180	≥ 3 early miscarriages or > 2 late miscarriages or 1 IUFD and maternal thrombophilia Start of study: 5th–10th GW	Enoxaparin (40 mg) vs. enoxaparin (80 mg)	Rate of live births: 84.3% (70/83) vs. 78.3% (65/83) (n. s.)	<ul style="list-style-type: none"> ▶ Study only done to determine dosages ▶ No untreated control group ▶ No placebo group ▶ Included aPL (~ 20% in each study arm) & MTHFR polymorphisms
Dolitzky et al., 2006 [87]	104	≥ 3 early miscarriages or ≥ 2 late miscarriages with positive heartbeat	ASA vs. enoxaparin (40 mg)	Rate of live births: 84% (42/50) vs. 81.5% (44/54) (n. s.)	<ul style="list-style-type: none"> ▶ No untreated control group ▶ No placebo group
Badawy et al., 2008 [88]	340	≥ 3 idiopathic miscarriages with positive heartbeat; excluded from the study if maternal thrombophilia present	Folic acid (up to 13rd GW) vs. folic acid & enoxaparin (20 mg)	Rate of live births: 88.8% (151/170) vs. 94.7% (161/170) (p = 0.07)	<ul style="list-style-type: none"> ▶ No untreated control group ▶ No placebo group ▶ Methodological limitations ▶ Very low rates of miscarriage (5.3 vs. 11.2%)
Fawzy et al., 2008 [89]	160	≥ 3 idiopathic miscarriages with embryonic pole present on imaging, excluded if maternal thrombophilia present	Enoxaparin (20 mg) vs. prednisone & progesterone (12th GW) & ASA (75 mg; up to 32nd GW) vs. placebo	Rate of live births: 80.7% (46/57) vs. 84.9% (45/53) (n. s.) vs. 48% (24/50) (p < 0.05)	<ul style="list-style-type: none"> ▶ Methodological limitations ▶ Unclear blinding (“single blinded”)
Laskin et al., 2009 (HepASA study) [90]	88	≥ 2 idiopathic miscarriages and antiphospholipid antibodies or/and hereditary thrombophilia or/and anti-nuclear antibodies and positive heartbeat or serially increased hCG levels	ASA monotherapy vs. dalteparin (5000 U) & ASA (81 mg)	Rate of live births: 79.1% (34/43) vs. 77.8% (35/45) (n. s.)	<ul style="list-style-type: none"> ▶ Underpowered ▶ Study discontinued after interim analysis ▶ No placebo group ▶ Included aPL (47.7% in each study arm) & ANA
Visser et al., 2011 (HABENOX study) [91]	207	≥ 3 early miscarriages (< 13th GW) or > 2 late miscarriages (< 24th GW) or > 1 IUFD & 1 early miscarriage Start of study: < 7th GW	Enoxaparin (40 mg) & placebo vs. enoxaparin & ASA (100 mg) vs. ASA monotherapy (100 mg); double-blinded for ASA	Rate of live births: 71% vs. 65% vs. 61% (n. s.)	<ul style="list-style-type: none"> ▶ Underpowered ▶ Study discontinued after interim analysis ▶ No placebo group for LMWH
Monien et al., 2009 [92]	82	“Unexplained early or late miscarriages” 27.8% of patients have “positive thrombophilia markers”	LMWH (n = 28) vs. LMWH & ASA (100 mg) (n = 54)	84% “total rate of live births”	<ul style="list-style-type: none"> ▶ Unselective administration of ASA (no randomization) ▶ No placebo group ▶ Unclear start of therapy ▶ Unclear exclusion criteria
Clark et al., 2010 (Spin study) [93]	294	≥ 2 idiopathic miscarriages < 24th GW Start of study: < 7th GW	Enoxaparin (40 mg) & ASA (75 mg) & close monitoring vs. close monitoring alone	Rate of live births: 78.2% (115/147) vs. 80.2% (118/147) (n. s.)	<ul style="list-style-type: none"> ▶ No placebo group ▶ Unclear thrombophilia status

Continued next page

Table 3 Intervention studies with heparin(s) administered to women with recurrent miscarriage with and without evidence of hereditary thrombophilia. (Continued)

Study	Number of patients	Inclusion criteria	Intervention	Outcomes	Comments
Kaandorp et al., 2010 (ALIFE study) [94]	364	> 2 idiopathic miscarriages < 20th GW (excluding biochemical pregnancy) Start of study: ASA & placebo prior to conception; LMWH administered after evidence of positive heartbeat	ASA (80 mg) vs. ASA & nadroparin (2 650 U) vs. placebo	Rate of live births: intention-to-treat group: 50.8% vs. 54.5% vs. 57.0% (n. s.) Group of women who were really pregnant: 61.6% vs. 69.1% vs. 67.0% (n. s.)	<ul style="list-style-type: none"> ▶ Underpowered ▶ Study discontinued after interim analysis ▶ Limited exclusion criteria ▶ ASA start prior to conception ▶ No placebo group for LMWH
Schenk et al., 2013 (ETHIG2 study)	434	> 2 early miscarriages or ≥ 1 late miscarriage Start of study: < 8th GW and positive heartbeat	Multivitamin preparation vs. multivitamin preparation & dalteparin (5 000 U) until at least 24th GW	Rate of live births (up to 24 + 0 GW): 86.6% (191/220) vs. 87.9% (188/214) (n. s.)	<ul style="list-style-type: none"> ▶ No placebo group ▶ To date, data have only been published in an abstract

ANA: antinuclear antibodies; APS: antiphospholipid syndrome; aPL: antiphospholipid antibodies; ASA: acetylsalicylic acid; GW: week of gestation; IUFD: intrauterine fetal death; LMWH: low molecular weight heparin; n. s.: not significant

The following therapeutic treatments can be effective:

1. **Genetic factors:** Polar body biopsy or preimplantation genetic diagnosis should be done if the affected couple has known genetic abnormalities. In contrast to egg donations, heterologous sperm donations are permitted in Germany.
2. **Anatomical factors:** Resection of uterine septum, removal of polyps.
3. **Microbiological factors:** None
4. **Endocrine factors:** Because of the currently limited data, luteal phase supplementation with progesterone to treat women with RM cannot be generally recommended and should only be prescribed in certain conditions. This may change, depending on the results of the PROMISE study. In cases with hypothyroidism – particularly patients with increased levels of antithyroid autoantibodies and Hashimoto thyroiditis – TSH values should be adjusted till they are within low normal ranges (≤ 2.5 mU/l). Hyperthyroidism must be treated. The administration of metformin cannot be recommended.
5. **Psychological factors:** Empathetic support counselling should be offered to the patient (and her partner) as part of “patient-centered care” (i.e., individually tailored information and the provision of emotional support) both within the patient-physician relationship and by additional medical staff. While the pregnancy is still ongoing, a patient with a prior history of RM should be able to have frequent contact with medical staff. From a psychological point of view, the prophylactic admission of patients to hospital is neither necessary nor desired by the patients themselves [102]. If required, referral to professional psychosocial grief counselling services can be considered to support the patient (the couple) with mourning rituals (“Moses basket”, “letter for the child”). If there is a suspicion that patient is developing signs of depression, a (medical or psychological) psychotherapist should be consulted to determine whether the patient requires additional treatment.
6. **Immunological factors:** Low molecular weight heparin and aspirin should be administered to treat antiphospholipid syndrome.

7. **Thrombophilic factors:** Administration of low molecular weight heparin should be considered for maternal indications of protein C or protein S deficiency, FVL mutation, PT mutation; monitoring of hemostatic status should be done in patients with qualitative or quantitative antithrombin deficiency.

The following diagnostic procedures and therapeutic treatments should currently only be carried out as part of a clinical study:

1. **Anatomical factors:** Antibiotic treatment for chronic endometritis.
2. **Immunological factors:** Determination of tissue transglutaminase antibodies to exclude celiac disease, gluten-free diet for women with celiac disease, determination of Th1/Th2 ratio (cytokine profiling), regulatory B-cells and T-cells, TNF- α , peripheral blood and uterine NK cells, NK toxicity test, KIR receptor profiling, KIR expression analysis, PIBF or HLA determination, particularly HLA-C; administration of TNF- α blockers, G-CSF, immunoglobulins, glucocorticoids, lipid infusion, allogeneic lymphocyte infusion, administration of aspirin if antinuclear antibodies are detected.
3. **Thrombophilic factors:** Low molecular heparin for embryonic or fetal indications, ASA 100 for factor XII deficiency.
4. **Microbiological factors:** Extensive antibiotic treatment for verified bacterial vaginosis in the 12th– 22nd week of gestation.

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