Thieme

Recurrent Spontaneous Miscarriage: a Comparison of International Guidelines

Rezidivierende Spontanaborte: ein Vergleich internationaler Leitlinien

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ABSTRACT

While roughly 30% of all women experience a spontaneous miscarriage in their lifetime, the incidence of recurrent (habitual) spontaneous miscarriage is 1–3% depending on the employed definition. The established risk factors include endocrine, anatomical, infection-related, genetic, haemostasis-related and immunological factors. Diagnosis is made more difficult by the sometimes diverging recommendations of the respective international specialist societies. The present study is therefore intended to provide a comparison of existing international guidelines and recommendations. The guidelines of the ESHRE, ASRM, the DGGG/OEGGG/SGGG and the recommendations of the RCOG were analysed. It was shown that investigation is indicated after 2 clinical pregnancies and the diagnosis should be made using a standardised timetable that includes the most frequent causes of spontaneous miscarriage. The guidelines concur that anatomical malformations, antiphospholipid syndrome and thyroid dysfunction should be excluded. Moreover, the guidelines recommend carrying out pre-conception chromosomal analysis of both partners (or of the aborted material). Other risk factors have not been included in the recommendations by all specialist societies, on the one hand because of a lack of diagnostic criteria (luteal phase insufficiency) and on the other hand because of the different age of the guidelines (chronic endometritis). In addition, various economic and consensus aspects in producing the guidelines influence the individual recommendations. An understanding of the underlying decision-making process should lead in practice to the best individual diagnosis and resulting treatment being offered to each couple.

ZUSAMMENFASSUNG

Während etwa 30% aller Frauen in ihrem Leben einen Spontanabort erleben, beträgt die Inzidenz für rezidivierende (habituelle) Spontanaborte 1–3% abhängig von der angewandten Definition. Zu den etablierten Risikofaktoren zählen endo-

krine, anatomische, infektiologische, genetische, hämostaseologische und immunologische Faktoren. Die Diagnostik ist jedoch durch teilweise divergierende Empfehlungen der jeweiligen internationalen Fachgesellschaften erschwert. Der vorliegende Artikel soll daher einen Vergleich der bestehenden internationalen Leitlinienempfehlungen geben. Hierzu werden die Leitlinien der ESHRE, ASRM, der DGGG/OEGGG/SGGG sowie die Empfehlungen des RCOG analysiert. Es zeigt sich, dass eine Abklärung bereits nach 2 klinischen Schwangerschaften indiziert ist und die Diagnostik anhand eines standardisierten Fahrplans erfolgen sollte, der die häufigsten Ursachen für wiederholte Spontanaborte umfasst. Die Leitlinien sind sich einig, dass der Ausschluss anatomischer Malformationen, eines Antiphospholipidsyndroms sowie von Schilddrüsendysfunktionen erfolgen sollte. Darüber hinaus empfehlen die Leitlinien die Durchführung einer Chromosomenanalyse beider Partner präkonzeptionell (oder aus dem Abortmaterial). Andere Risikofaktoren sind zum einen aufgrund fehlender diagnostischer Kriterien (Lutealphaseninsuffizienz), zum anderen aufgrund des unterschiedlichen Alters der Leitlinien (chronische Endometritis) nicht von allen Fachgesellschaften in die Empfehlungen aufgenommen. Zusätzlich haben unterschiedliche gesundheitsökonomische und Konsensusaspekte im Rahmen der Leitlinienerstellung Einfluss auf die einzelnen Empfehlungen. Das Verständnis der zugrunde liegenden Entscheidungsprozesse sollte in der Praxis dazu führen, dass für das jeweilige Paar die individuell beste Diagnostik und die sich daraus ableitende Therapie angeboten wird.

Introduction

Pregnancy loss from conception up to the 24th week of pregnancy or up to a foetal weight of 500 g [1] is defined by the WHO as abortion or miscarriage. Recurrent spontaneous miscarriage (RM) is defined by the WHO as the occurrence of 3 or more consecutive miscarriages before the 20th week of pregnancy. The American Society for Reproductive Medicine (ASRM), by contrast, defines RM as occurring after just two miscarriages with clinical evidence of pregnancy (sonographic or histopathological) [2–4].

Roughly 1–3% of couples who want to have children are affected by RM, sometimes with major consequences for their relationship and quality of life [5]. The established risk factors include endocrine, anatomical, infection-related, genetic, haemostasis-related and immunological factors. A cause can be found in only about 50% of women following standardised diagnostics, while it remains unclear in the other 50%, so there is an urgent need to establish new approaches for diagnosis and treatment. In the last few years, guidelines and recommendations dealing with the diagnosis and treatment of RM have been produced by various specialist societies. However, there are sometimes substantial differences in the approaches to diagnosis and treatment, not least in the definition of RM (▶ **Table 1**). For this reason, the current international guidelines of the European Society of Reproduction and Embryology (ESHRE) [6], the American Society of Reproductive Medicine (ASRM) [2,3] and the German, Austrian and Swiss Societies for Gynaecology and Obstetrics (DGGG/OEGGG/SGGG) [7], and the recommendations of the Royal College of Obstetricians and Gynaecologists (RCOG) [8] are compared in this article. The aim is to give an overview of the current status of the diagnosis and treatment of RM and to provide treating physicians with recommendations on management that may go beyond the current recommendations in their respective countries.

Methods

The guidelines of the ESHRE, ASRM, the DGGG/OEGGG/SGGG and the recommendations of the RCOG were compared with regard to current recommendations on diagnosis and treatment. The areas of genetics, anatomy, infectious disease, endocrinology, coagulation and immunology were analysed in particular (▶ **Tables 2** and **3**). The cited guidelines were published in the period 2011 to 2018. The 2011 recommendations of the RCOG were updated in 2014 and 2017, and the expert opinion of the ASRM was updated in 2012. The DGGG/OEGGG/SGGG guideline is updated every 3 years in a consensus process.

▶ **Table 1** Definition of RM in the guidelines.

ESHRE	DGGG/OEGGG/SGGG	ASRM	RCOG
≥ 2 miscarriages	≥ 3 consecutive miscarriages	≥ 2 miscarriages (after sonographic or histopathological confirmation of pregnancy)	≥ 3 consecutive miscarriages
Procedure recommended by the authors of this article			
In women < 35 years possibly after ≥ 2 miscarriages, adjusted to other factors, such as sonographic or histopathological confirmation of pregnancy, autoimmune diseases, anatomical anomalies or other existing risk factors. In women > 35 years after ≥ 3 consecutive miscarriages.			

ASRM = American Society for Reproductive Medicine; DGGG/OEGGG/SGGG = Deutsche, Österreichische und Schweizer Gesellschaft für Gynäkologie und Geburtshilfe [German, Austrian and Swiss Societies for Gynaecology and Obstetrics]; ESHRE = European Society of Human Reproduction and Embryology; RCOG = Royal College of Obstetricians and Gynaecologists; RM = recurrent (habitual) spontaneous miscarriage.

▶ **Table 2** Diagnosis of RM. Relevant differences between the guideline recommendations are shown in bold. The measures recommended by the authors' team are shown in italics.

	ESHRE	DGGG/OEGGG/SGGG	ASRM	RCOG
Genetics				
▪ Chromosome analysis of parents	Chromosome analysis **only with increased genetic risk**	*Microscopic chromosome analysis of both partners*	Microscopic chromosome analysis of both partners	Microscopic chromosome analysis of both partners **only with evidence of a structural chromosomal disorder in the aborted material**
▪ Chromosome analysis of embryo	Chromosome analysis of aborted material **not recommended**	*Chromosome analysis of aborted material* ***optional***	–	Chromosome analysis of aborted material **recommended from the 3rd miscarriage**
Coagulation	**No screening** for hereditary thrombophilia (**except with other risk factors** and for research purposes)	***Only women with risks for thromboembolic events:*** *Determination of factor V Leiden and prothrombin mutations and of antithrombin, protein C and protein S activity*	**Only in women with a positive personal or family history** of thromboembolic events	No explicit recommendation for women with RM
Immunology				
▪ APLS	ACA (IgM, IgG), β2-glycoprotein I antibodies; LAC	*ACA (IgM, IgG), β2-glycoprotein I antibodies; LAC* ***Non-criteria APLS with clinical manifestations***	ACA (IgM, IgG), β2-glycoprotein I antibodies; LAC	ACA (IgM, IgG) LAC
▪ ANA	*ANA for explanation of possible cause*	*If* ***elevated ANA titres*** *are diagnosed in RM patients, the antibodies should be further differentiated (SS-A/RO and SS-B/lupus anticoagulant [LAC] antibodies) to* ***exclude Sjogren syndrome or lupus erythematosus.***		
▪ other	HLA-DRB1*05:01/05:02 in Scandinavian women with secondary RM	*IgA antibodies against transglutaminase* *Other immunological tests only with pre-existing autoimmune disease*		
Anatomy	***3-D sonography*** *possibly SHG* *possibly HSG* *possibly* ***MRI***	Sonography HSC	SHG HSG possibly HSC **possibly MRI** **possibly 3-D sonography**	Sonography HSG *possibly HSC +* ***LSC*** **possibly 3-D sonography**
Endocrinology				
▪ Thyroid	Thyroid tests and monitoring of TSH	*Thyroid tests and monitoring of TSH*	Thyroid tests and monitoring of TSH	Thyroid tests and monitoring of TSH
▪ Prolactin	*Investigation if typical symptoms*	–	Investigation of hyperprolactinaemia	Data inconsistent
▪ Glucose	**No investigation** of glucose status	*Investigation of glucose status*	Investigation of glucose status	**No investigation** of glucose status
▪ PCOS	**No investigation of** PCOS or hyperandrogenaemia	*Investigation of PCOS and hyperandrogenaemia*	Investigation of PCOS and hyperandrogenaemia regarded as **controversial**	**No investigation** of PCOS and hyperandrogenaemia
▪ Luteal phase	Luteal phase tests not recommended	*Luteal phase tests* ***can be considered***	Luteal phase tests **can be considered**	Luteal phase tests **controversial**

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▶ **Table 2** Diagnosis of RM. Relevant differences between the guideline recommendations are shown in bold. The measures recommended by the authors' team are shown in italics. *(Continued)*

	ESHRE	DGGG/OEGGG/SGGG	ASRM	RCOG
Infectious disease				
Infection screening	–	*No screening by vaginal swabs in asymptomatic women*	Screening by vaginal swabs not recommended	–
Chronic endometritis	**Further studies** on the status of chronic endometritis in RM **necessary.**	*Endometrial biopsy **can** be performed to **exclude chronic endometritis** (CD138).*		

ACA = anticardiolipin antibody; ANA = antinuclear antibody; APLS = antiphospholipid syndrome; ASRM = American Society for Reproductive Medicine; CD138 = Cluster of Differentiation 138; DGGG/OEGGG/SGGG = German, Austrian and Swiss Societies for Gynaecology and Obstetrics; ESHRE = European Society of Human Reproduction and Embryology; HLA = human leucocyte antigen; HSG = hysterosalpingography; HSC = hysteroscopy; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; LAC = lupus anticoagulant; LSC = laparoscopy; MRI = magnetic resonance imaging; PCOS = polycystic ovarian syndrome; RCOG = Royal College of Obstetricians and Gynaecologists; RM = recurrent (habitual) spontaneous miscarriage; SHG = sono-hysterography; SS-A/RO = Sjogren syndrome antigen A antibody; SS-B = Sjogren syndrome antigen B antibody; TSH = thyroid stimulating hormone.

Genetics

Cytogenetic tests

A balanced chromosomal rearrangement in one of the partners is found in about 4–5% of RM couples [9]. The incidence of structural chromosomal disorder per couple increases from 0.7% in the ordinary population to 2.0% after 1 miscarriage, 4.4% after 2 miscarriages and 5.1% after 3 miscarriages. Moreover, a family history of miscarriages, stillbirths or malformation syndromes and intellectual disability can indicate familial chromosomal disorders, regardless of whether healthy children were born, including between the miscarriages.

The probability of a structural chromosomal disorder decreases with increasing maternal age at the second miscarriage and increases with a family history of miscarriage (2 or more miscarriages in first-degree relatives) [10]. According to the ESHRE guideline chromosomal analysis is not regarded as indicated with RM, though incorrectly calculated numbers are pointed out. An incidence of 1.9% was originally given for the confirmation of a balanced chromosomal aberration in couples with RM, but this was based on an insufficient consideration of the studies and also on an incorrect calculation in the only study referred to [11]. In this study, 406 balanced chromosomal aberrations were found in 20432 persons, which corresponds to a per-couple rate of about 4%; the error was corrected in the guideline provided online in 2019 (version 2, available at https://www.eshre.eu). It is argued in the ESHRE guideline that the risk of birth of a disabled child because of a parental balanced chromosomal rearrangement is negligible. This probability was originally given in the ESHRE guideline as 0.02% and corrected to 0.04% in 2019 but is actually 1/1.315 or approx. 0.08% [11, 12]. The authors of the German-language guideline were of the opinion that this is not negligible.

The international specialist societies do not agree on whether couples with RM should be offered chromosomal analysis and, if so, whether this should be done after two or after three miscarriages. It is recommended in the majority of the guidelines that microscopic chromosomal analysis (karyotyping) should be performed in both partners in the case of RM. A chromosomal disorder can be found in the aborted material by chromosomal analysis but the sensitivity for detection of the prognostically relevant small structural chromosomal rearrangements (especially balanced translocations) is often lower than with chromosomal analysis from whole blood. An alternative is to examine the aborted tissue by DNA array, which also detects smaller aberrations (deletions and duplications). This analysis is often more expensive than classic chromosomal analysis, however. The British ROCG guideline recommends primary (molecular) cytogenetic analysis of aborted material after the 3rd miscarriage.

Preimplantation tests

Aneuploidy screening (preimplantation genetic screening, PGS, or PGT-A, preimplantation genetic testing for aneuploidies) is often offered as a preimplantation test as part of assisted reproduction treatment; the aim is to achieve greater live birth rates (LBR) by transferring euploid embryos. However, women with a history of miscarriage have a high probability of becoming pregnant again spontaneously.

The LBR per cycle after artificial fertilisation is about 35% with PGT-A, whereas the probability of a live birth in the next cycle of a spontaneously occurring pregnancy after RM is about 60% [13].

According to the studies to date, there is no evidence that PGT-A leads to an increased LBR after RM compared with spontaneous pregnancies. This also applies for couples with a genetic predisposition due to a balanced chromosomal aberration in one partner. Couples with a structural chromosomal rearrangement who become pregnant naturally have a markedly higher rate of miscarriage, however, than couples who become pregnant after PGS, which can lead to considerable psychological stress. No specialist society currently recommends preimplantation screening for couples with RM (▶ **Table 3**).

▶ **Table 3** Treatment of RM. Relevant differences between the guideline recommendations are shown in bold. The measures recommended by the authors' team are shown in italics.

	ESHRE	DGGG/OEGGG/SGGG	ASRM	RCOG
Genetics	PID/PGT-A not recommended	*PID/PGT-A not recommended*	PID/PGT-A not recommended	PID/PGT-A not recommended
Coagulation	*Anticoagulation in hereditary thrombophilia only for thrombosis prophylaxis in the mother (and in studies)*	Anticoagulation in hereditary thrombophilia only for thrombosis prophylaxis in the mother	No explicit recommendation on treatment in women with RM	Inadequate data on anticoagulation with heparin for secondary prophylaxis in women with RM and thrombophilia (no recommendation)
Immunology				
▪ APLS	Low dose aspirin (75–100 mg daily) in combination with unfractionated/low molecular weight heparin **from positive pregnancy test.**	*Low dose aspirin (75–100 mg daily) in combination with unfractionated/low molecular weight heparin* ***from positive pregnancy test. Aspirin until 34 + 0 weeks of pregnancy, unfractionated/low molecular weight heparin until 6 weeks post partum***	Treatment of APLS with low dose aspirin in combination with unfractionated heparin	Treatment of APLS with low dose aspirin in combination with unfractionated/low molecular weight heparin
▪ other	–	*Immunoglobulins, allogeneic lymphocyte therapy, lipid infusions, TNF-α blockers and glucocorticoids only in clinical studies*	i. v. administration of immunoglobulins is not recommended	**Warning about the possibility of an increase in maternal and foetal morbidity** if immunomodulatory treatments are given
Anatomy	**Insufficient data for septum resection/myoma or polyp resection and adhesiolysis**	*Septum resection* *Intrauterine adhesiolysis* *Myoma resection (submucous)* *Resection of polyps*	Septum resection	**Insufficient data for septum resection**
Endocrinology				
▪ Thyroid	TSH < 2.5	*TSH < 2.5*	TSH < 2.5	TSH < 2.5
▪ Prolactin	*Bromocriptine*	–	Bromocriptine	Data inconsistent
▪ Glucose	Optimal control of diabetes mellitus No recommendation on metformin for impaired glucose tolerance	*Optimal control of diabetes mellitus* *No recommendation on metformin for impaired glucose tolerance*	Optimal control of diabetes mellitus No recommendation on metformin for impaired glucose tolerance	Optimal control of diabetes mellitus No recommendation on metformin for impaired glucose tolerance
▪ Luteal phase	**No luteal phase support**	*Luteal phase support* ***can be considered***	Luteal phase support **can be considered**	Luteal phase support **regarded as controversial**
Infectious disease				
▪ Chronic endometritis	**Further studies** on the status of chronic endometritis in RM **necessary.**	*If chronic endometritis is confirmed* ***antibiotic therapy can be given.***	–	–

APLS = Antiphospholipid syndrome; ASRM = American Society for Reproductive Medicine; DGGG/OEGGG/SGGG = German, Austrian and Swiss Societies for Gynaecology and Obstetrics; ESHRE = European Society of Human Reproduction and Embryology; i. v. = intravenous; PGT-A = preimplantation diagnostics for aneuploidies; PID = preimplantation diagnostics; RCOG = Royal College of Obstetricians and Gynaecologists; RM = recurrent (habitual) spontaneous miscarriage; TNF-α blocker = tumour necrosis factor alpha blocker; TSH = thyroid stimulating hormone.

Anatomy

Diagnosis

Women with RM appear to have a higher incidence of uterine anomalies, with a reported rate between 3 and 25 % [14, 15]. Whether the presence of uterine anomalies leads to RM is unknown [16]. The increased probability of miscarriage with subseptate uterus is recognised. How far RM is associated with other congenital or acquired uterine anomalies such as polyps, myomas or adhesions is unclear.

The guideline of the DGGG/OEGGG/SGGG recommends hysteroscopy (HSC) to diagnose a uterine anomaly, possibly in combination with laparoscopy (LSC), or 3-D sonography or MRI [7]. The ESHRE guideline likewise advises exclusion of uterine anomalies and recommends that this be done by 3-D sonography [6]. The

RCOG also supports sonographic investigation and recommends further diagnosis of anomalies by means of 3-D sonography or HSC in combination with LSC [8]. The ASRM also recommends exclusion of uterine anomalies and the diagnostic methods of choice are hysterosonography, hysterosalpingography, MRI, 3-D sonography or HSC.

Treatment

A meta-analysis from 2017 showed that no randomised studies on the therapeutic effect of septum dissection had been conducted to date [17]. Hysteroscopic septum dissection is generally recommended or can be recommended for women with RM and a uterine septum [18]. A recent retrospective multicentre study, however, did not show any benefit of septum dissection with regard to LBR or the rate of miscarriage [19]. Operative intervention is not indicated for other congenital uterine anomalies such as bicornuate uterus, uterus didelphys und arcuate uterus [20].

Other conditions such as removal of adhesions, myomas or polyps are listed mainly in the DGGG/OEGGG/SGGG guideline (exception: myomas are also mentioned in the ASRM). The treatment of choice of intrauterine adhesions is hysteroscopic adhesiolysis [21, 22]. Whether intrauterine adhesions influence the risk of miscarriage in general or only above a certain degree or whether adhesiolysis reduces this risk is unclear, however. Nevertheless, the German-language guideline recommends resection of uterine adhesions.

There is evidence, however, that myoma enucleation leads to an improved pregnancy rate, especially in the case of myomas impinging on the uterine cavity. Consideration of myoma resection depending on its position is therefore recommended in both the DGGG/OEGGG/SGGG and the ASRM guidelines [21].

A meta-analysis and a systematic review showed that hysteroscopic resection of intrauterine polyps visible on ultrasound prior to intrauterine insemination can increase the clinical pregnancy rate but a clear benefit with regard to the rate of miscarriage was not shown [23, 24]. If there is no other explanation for the cause, resection of persisting polyps can be considered for RM patients according to the DGGG/OEGGG/SGGG guideline.

Infectious Disease

Diagnosis

Bacterial vaginosis

The influence of bacterial, viral or parasitic vaginal infections on RM remains controversial so no guideline includes general screening in asymptomatic patients to prevent miscarriage. Because of the association between vaginal dysbiosis and pregnancy complications (cervical insufficiency, premature rupture of the membranes with amniotic infection syndrome), the German-language guideline recommends investigation in a suspected case and appropriate treatment as part of antenatal care [25, 26].

Chronic endometritis

Chronic endometritis (CE), which has a prevalence of 7–67% in women with RM, is presented as a risk factor in some studies [28, 74–76]. Endometrial biopsy with subsequent immunohistochemical examination is necessary for diagnosis of CE. This detects plasma cells with an antibody against syndecan-1 (CD138), which has largely replaced conventional haematoxylin-eosin staining [75]. The recommendation to exclude CE is currently found only in the German-language guideline, while the ESHRE interprets the studies as not yet sufficient. The guidelines of the ASRM and RCOG do not contain any reference to CE but these guidelines are older.

Treatment

Bacterial vaginosis

Only the German-language guideline mentions a study in which treatment of confirmed bacterial vaginosis between the 12th and 22nd week of pregnancy by giving clindamycin (300 mg orally twice daily for 5 days) significantly reduced the incidence of miscarriage in the 2nd trimester and the rate of premature birth [27]. However, this study does not result in an explicit recommendation.

Chronic endometritis

The DGGG/OEGGG/SGGG recommends antibiotic therapy, e.g., with doxycycline (200 mg daily for 14 days) if CE is confirmed. After the treatment, an increase of 19% in the LBR was described, and patients with repeated implantation failure also benefited from this in further IVF treatment [28, 29]. Nevertheless, the ESHRE guideline refrains from making a treatment recommendation.

Endocrinology

Diagnosis

Impaired glucose tolerance and PCOS

Endocrine factors can play an important part in RM. Disorders of glucose tolerance, especially poorly controlled diabetes mellitus, can be regarded as risk factors for RM [30, 31]. All the parameters of the metabolic syndrome including obesity and associated hyperandrogenaemia as well as polycystic ovarian syndrome (PCOS) [32, 33] are noted by the guidelines as positive risk factors. The ESHRE guideline does not recommend exclusion of PCOS or measurement of glucose status as the authors, while they see this as associated with RM, do not find clear evidence from current data that treatment leads to an improved LBR [34]. Investigation of hyperandrogenaemia is also not recommended by the ESHRE. The authors of the ARM guideline recommend investigation of diabetes mellitus or impaired glucose tolerance, whereas exclusion of PCOS and/or hyperandrogenaemia is not among the diagnostic recommendations.

Thyroid dysfunction

Thyroid dysfunction, predominantly hypothyroidism, should be investigated, according to all guidelines. Measurement of both thyroid-stimulating hormone (TSH) and thyroid antibodies (TPOAb in hypothyroidism and TRAb in hyperthyroidism) and the concentration of free T3/T4 is recommended.

Hyperprolactinaemia

Hyperprolactinaemia as a risk factor is mentioned in the ESHRE guideline and the guideline of the ARM. Both refer to two studies, though these showed inconsistent results [35, 36]. Investigation is therefore recommended only if typical symptoms are present.

Luteal phase insufficiency

With regard to luteal phase insufficiency, different recommendations are found in the international guidelines. This is due not least to the lack of an international definition. The authors of the German-language guideline cite a luteal phase length of less than 12 days and low luteal progesterone levels (without stating a threshold) as diagnostic parameters but at the same time they state that these parameters were never clearly associated with RM. In the expert opinion of the ASRM, likewise, a shortened luteal phase is mentioned as a possible cause of RM but more specific recommendations regarding the diagnosis of this and regarding the minimal duration of the luteal phase are not made. Like the authors of the German-language guideline, they assess the diagnosis and interpretation of the findings as problematic due to the small amount of data. The green-top guideline of the RCOG does not give details of the diagnosis of luteal phase insufficiency. The authors of the ESHRE guideline cite a progesterone level of < 10 ng/ml or the sum of three serum progesterone levels below 30 ng/ml as threshold. On the other hand, the temperature curve, length of the luteal phase (< 11 days) and diameter of the preovulatory follicle show low sensitivity and specificity [37].

Treatment

Impaired glucose tolerance and PCOS

A potential positive effect of taking metformin to reduce the rate of miscarriage has not been shown to date from the current data [38]. Therefore, none of the guidelines recommends use of metformin for RM. However, weight reduction in obese patients has a positive effect in connection with RM: a cohort study from Denmark showed that the rate of miscarriage increases above a BMI ≥ 30 kg/m^2 [39]. From this is derived the recommendation of the authors of the S2K guideline of the DGGG/OEGGG/SGGG regarding weight reduction in women with RM and increased BMI. The ESHRE also recommends lifestyle advice, which should include the effects of diet, smoking and alcohol consumption.

Thyroid dysfunction

In the case of hypothyroidism, achieving a TSH level below 2.5 mU/ml is recommended uniformly [40]. The TSH levels should also be monitored. The authors of the German-language guideline recommend adjusting the thyroxine dosage in pregnancy by 50 % of the preconception dosage, especially if thyroid autoantibodies are elevated.

The ESHRE mentions thyroid dysfunction and the presence of thyroid autoantibodies as a cause of disorders of folliculogenesis, spermatogenesis, fertilisation and embryogenesis and thus as a cause of subfertility and RM [41]. The authors likewise specify a target TSH of ≤ 2.5 mU/ml and recommend thyroid hormone replacement [42, 43].

Hyperprolactinaemia

Treatment of hyperprolactinaemia with bromocriptine is recommended by the ESHRE and by the ASRM.

Luteal phase insufficiency

The currently inconsistent data regarding the definition of luteal phase insufficiency do not permit any conclusion regarding treatment recommendations [37, 44, 45]. In the German-language guideline, however, consideration of luteal phase insufficiency in the treatment of RM is recommended [46]. The authors of the ASRM recommendations come to a similar conclusion since progesterone replacement in the luteal phase can achieve a benefit in selected cases. The authors of the guidelines of the RCOG and ESHRE recommend neither investigation nor treatment of luteal phase insufficiency.

Coagulation

Diagnosis

Congenital thrombophilic coagulation disorders are established predisposing factors for thromboembolic events and have also been suggested as risk factors for RM. Up to 15 % of the Caucasian population has a corresponding coagulation disorder [47]. In fact, patients with a history of habitual miscarriage and confirmed factor V Leiden (FVL) or prothrombin mutation have an increased risk of miscarriage in a subsequent pregnancy compared with non-thrombophilic RM patients [48]. A deficiency of the antithrombogenic proteins S and C and of antithrombin is regarded as a miscarriage risk. While there is a physiological decrease in the concentrations of protein C and S in pregnancy so that evaluation is limited during pregnancy and for at least 6 weeks afterwards, genetic tests for factor V Leiden or prothrombin mutation are independent of this. No indication is seen for measurement of D-dimers [7]. In review articles, “thrombophilia screening” is not regarded as indicated when there is a history of pregnancy complications [49]. The question of the therapeutic consequence of an abnormal finding is more complex, however.

The current ESHRE guideline does not recommend any screening for hereditary thrombophilia in a woman with RM who is seeking advice, except in the context of scientific studies and if there are further risk factors for thromboembolism. The ASRM recommendations support nuanced investigation of thrombophilia with RM when there is a positive personal or family history of thromboembolic events, while the RCOG guideline does not express an opinion explicitly. The German-language recommendation is most specific; it supports further investigation only for women with risks for thromboembolic events, advising investigation for factor V Leiden or prothrombin mutations and measurement of the activity of antithrombin and proteins C and S. The DGGG/OEGGG/SGGG guideline does not consider thrombophilia investigation as indicated for miscarriage prophylaxis and hence as an embryo-related indication.

Treatment

Despite the varied effects of heparins at the molecular level [50] there are currently no high-level prospective randomised studies that show a clear benefit of anticoagulation with a low-molecular-weight heparin to prevent miscarriage in women with RM with or without confirmed hereditary thrombophilia [51 – 56].

An individualised approach appears necessary from the maternal indication when there is a markedly increased risk of venous thromboembolism (VTE) in thrombophilic pregnant women due to coagulation disorders.

Both the ESHRE and the DGGG/OEGGG/SGGG guidelines advise anticoagulation in pregnancy only in the case of a maternal indication: in the case of hereditary thrombophilia, the mother should be treated only for thrombosis prophylaxis (and in studies). The ASRM and RCOG guidelines make no explicit recommendations, though the British guidelines makes a cross-reference to the recommendations on thrombosis prophylaxis.

Immunology

Diagnosis

Various mechanisms are necessary to prevent rejection of the foetus by the mother's immune system. Studies to date of immunological aspects of RM concentrate on antiphospholipid syndrome (APLS), autoantibodies, cytokines, HLA polymorphisms and HLA expression on trophoblasts as well as natural killer cells in peripheral blood and in the endometrium.

Antiphospholipid syndrome

APLS is regarded as an established risk factor for RM; it occurs in 5–20 % of RM patients and already includes the definition of recurrent spontaneous miscarriage in its diagnostic criteria (▶ **Table 4**) [57]. The diagnostic criteria include clinical criteria, on the one hand, such as arterial or venous thrombosis and pregnancy complications (≥ 1 miscarriage after the 10th week of pregnancy or ≥ 3 miscarriages after the 10th week of pregnancy), and, on the other hand, serological criteria such as demonstration at least twice of antiphospholipid antibodies (ACA: anti-cardiolipin Ab, anti-β2-glycoproteins, LAC: lupus anticoagulant) [58]. The antiphospholipid antibody titre should be checked again 12 weeks after the first measurement and should then be again in the middle to high range (> 99th percentile measured in normal subjects) [59]. It is suggested that the pathophysiology involves an increased tendency to thrombosis as well as a direct influence on the trophoblast [60]. Secretion of pro-inflammatory cytokines such as TNF, IL-1 and IL-6 is also increased in APLS, leading to increased activation of the immune system [61]. All guidelines recommend testing for IgG/IgM ACA, LAC and β2-glycoprotein I antibodies, though the RCOG guideline does not specifically mention the β2-glycoprotein I antibodies. If clinical manifestations are present (livedo reticularis, ulcerations, renal microangiopathy, neurological and cardiac disorders), "non-criteria APLS" should be investigated according to the DGGG/OEGGG/SGGG.

▶ **Table 4** APLS diagnostic criteria (modified from [59]). APLS can be diagnosed when at least one clinical and one laboratory criterion is met.

Clinical criteria	Laboratory criteria (found twice at an interval of 12 weeks)
▪ ≥ 1 venous or arterial thrombosis ▪ ≥ 1 unexplained miscarriage with morphologically normal foetuses > 10 weeks of pregnancy ▪ ≥ 3 unexplained miscarriages < 10 weeks of pregnancy ▪ ≥ 1 premature birth < 34 weeks of pregnancy because of placental insufficiency or pre-/eclampsia	▪ Anti-cardiolipin Ab (IgM, IgG): medium to high titre ▪ Anti-β2-glycoprotein-1 Ab (IgM, IgG): high titre ▪ Lupus anticoagulant

APLS = antiphospholipid syndrome, Ab = antibody

Other immunomodulatory abnormalities

If there are food sensitivities, measurement of IgA transglutaminase antibodies to exclude coeliac disease can be considered, according to the German-language guideline. It has been shown that approximately 6 % of women with coeliac disease suffer from RM and RM patients with coeliac disease can benefit from a gluten-free diet [62 – 64]. Other specialist societies do not recommend testing for coeliac disease.

Antinuclear antibodies (ANA) are an indication of autologous activation of the immune system. A review article from the year 1996 showed an increased prevalence of ANA in 10 of 12 case control studies in patients with RM compared with healthy controls [65]. However, these changes were not significant in all studies. Nevertheless, only the ESHRE guideline currently contains a recommendation to test for ANA in the case of RM, even if only to explain the possible cause. Since higher ANA titres can be linked with autoimmune diseases such as lupus erythematosus and Sjogren syndrome [66, 67], the DGGG/SGGG/OEGGG recommends intensified diagnostic tests to exclude these diseases if elevated ANA are found. The antibodies should be further differentiated (SS-A/RO and SS-B/LAC antibodies) so as to diagnose neonatal lupus syndrome or foetal AV block promptly.

The DGGG/OEGGG/SGGG guideline recommends preconception interdisciplinary care in the case of pre-existing autoimmune disorder but without specifying this more precisely.

Furthermore, according to the ESHRE, possible testing for HLA-DRB1 can be performed in Scandinavian women with secondary spontaneous miscarriage. A distinction between primary and secondary RM with regard to immunological risk factors with reference to possible testing for HLA-DRB1 is discussed only in the guideline of the ESHRE but appears reasonable in light of recent studies [68, 69].

Treatment

Antiphospholipid syndrome

All guidelines advise treating APLS by giving low-dose aspirin (75–100 mg daily) in combination with unfractionated/low-molecular-weight heparin, which is also supported by a recent Cochrane

analysis [70]. Only the DGGG/OEGGG/SGGG and the ESHRE specify the regimen: the treatment should be started at the same time as the positive pregnancy test. The DGGG/OEGGG/SGGG in addition specifies that aspirin is stopped at 34 + 0 weeks of pregnancy and heparin is stopped six weeks post partum. This also applies for "non-criteria" APLS.

Other immunomodulatory treatments

The German-language guideline recommends giving immunoglobulins, allogeneic lymphocyte transfusion, lipid infusions, TNF-α blockers and glucocorticoids only in the context of clinical studies. By contrast, the RCOG points to the possibility of increasing maternal and foetal morbidity if immunomodulatory treatments are given. The cause of the different recommendations may be the different publication times of the guidelines (between 2011 and 2018).

Conclusion

Diagnosis in couples with RM presents a particular challenge to treating physicians. In addition to the gynaecological aspects, noting the different course of the miscarriages, a detailed history should also include an in-depth family history. A clearly structured and standardised diagnostic approach is advisable so as to explain the scope of further diagnostic tests to the couples and also to initiate targeted treatment subsequently. However, the existence of different guideline recommendations makes decisions regarding the necessary diagnosis and treatment more difficult. This starts at the time a diagnosis is made as the guidelines use different definitions for RM. When considered more closely, however, diagnostic investigation of the most common causes after just two clinical pregnancies appears justified, as recommended by the ASRM. This was also supported by a recent meta-analysis [71]. In this meta-analysis no difference was found in the prevalence of uterine anomalies (such as subseptate uterus, bicornuate or unicornuate uterus, polyps or adhesions) and APLS in women with two or three miscarriages. Whether the prevalence of chromosomal anomalies, thrombophilia and thyroid disease differs after two or three miscarriages could not be finally clarified from this meta-analysis [71]. A recent Danish registry study showed clearly that both the woman's age and the pregnancy history should be considered in deciding when investigation is recommended. A prediction model for the probability of live birth based solely on these two parameters was insufficient [72]. Therefore, the decision on how many miscarriages should occur before starting to investigate should depend both on the woman's age and number of miscarriages and also on the mother's other diseases [71 – 73].

Moreover, it is apparent that the guidelines essentially concur regarding evidence-based diagnosis and treatment at the time the guidelines were produced (differences of up to 8 years between the individual guidelines) (▶ **Tables 2** and **3**, differences marked in bold). These include exclusion of anatomical malformations, APLS and thyroid dysfunction. The guidelines also recommend preconception chromosomal analysis of both partners, though the RCOG recommends this only when a structural chromosomal disorder is found in the aborted material.

Risk factors such as luteal phase insufficiency cannot be included in evidence-based guideline recommendations due to the current lack of a definition and the resulting controversial study situation. More recent risk factors such as CE are mentioned only in the German-language and ESHRE guidelines as the RCOG and ASRM recommendations are simply too old to contain more recent developments. Finally, the differences in the recommendations can be attributed to the complex consensus process involved in preparation of the guidelines, which often leads to newer methods of diagnosis and treatment not being included in the recommendations, and this can also have financial causes. Since individual situations require an adapted procedure, it may be necessary to deviate from current guidelines. The approaches to diagnosis and treatment recommended by the authors' team in a normal case are marked in italics in ▶ **Tables 2** and **3** and largely correspond to the recommendations of the DGGG/OEGGG/SGGG. The diagnostic spectrum should naturally be extended only with consideration of the respective clinical situation.

Conflict of Interest

Bettina Toth: shareholder of Reprognostics GbR, research funding: Teva, Bayer, Ferring. Fees/reimbursement of costs: Deutsche Gesellschaft für Gynäkologie und Geburtshilfe [German Society of Obstetrics and Gynecology]. Ferring, MSD, Exeltis, Merck Serono, Teva, Bayer. The remaining authors state that they have no conflicts of interest.

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