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Recurrent Spontaneous Abortions – An Update on Diagnosis and Management

S. Pildner von Steinburg, K. T. M. Schneider

Recurrent spontaneous abortions (RSA), defined as three or more consecutive miscarriages, affect 1 % of couples trying to conceive. Risk of abortion is 15 % in every pregnancy, increasing with the number of previous miscarriages. While 50–70 % of sporadic abortions are attributed to chromosomal defects, mostly trisomies, in RSA there are different underlying disorders of uterine, genetic, infectious, endocrine, immune or thrombophilic etiology, but about 25–40 % are of still unknown etiology. While specific therapy for uterine, infectious, and endocrine disorders may be applied, treatment options for some immunologic and thrombophilic disturbances are still under examination. Careful counseling must be offered to patients with RSA of unknown etiology, as not all treatment options widely offered are based on sufficient evidence yet. **J Reproduktionsmed Endokrinol 2009; 6 (1): 11–6.**

Key words: recurrent spontaneous abortions, etiology, management, genetic counseling, thrombophilia

■ Introduction

Miscarriage is the spontaneous loss of pregnancy before the fetus has reached viability, i.e. before 24 weeks of pregnancy. It is the commonest complication of pregnancy, occurring in about 15 % of clinically recognized pregnancies, with an increasing risk [1] determined by the number of previous abortions (Tab. 1). However, pregnancy loss is assumed to affect nearly 50 % of all pregnancies [2]. 25–50 % of all women experience sporadic miscarriages. 50 % of these occur due to chromosomal abnormalities, mostly trisomies. Thus, the risk increases with maternal age [3]: women aged 20–24 years have a risk of 9 % for miscarriage, for women aged 45 years or older it is 75 %. As maternal age has been continuously rising in the last decades, it is presumed that the number of abortions is increasing as well, although there is no solid data on that topic [4].

In contrast, recurrent spontaneous abortions (RSA), defined as three or more

consecutive miscarriages, affect about 1 % of couples in childbearing age [5]. With rising maternal age, the decision to perform diagnostics and therapy is taken in some cases already after two consecutive abortions. Changing the definition to two or more pregnancy losses, the incidence would rise up to 5 % of all couples trying to conceive [6].

■ Causes of Recurrent Abortions

Underlying disorders leading to RSA can be divided into the following groups: uterine or anatomic, infectious, endocrine, genetic, immunologic, and thrombophilic. Environmental influences such as consumption of alcohol, caffeine or cocaine, as well as cigarette smoking have been reported to attribute to sporadic miscarriages, although accurate data on toxin doses or exposure are diffi-

cult to obtain [4]. However, 25–40 % of RSA are of a still unknown etiology [1, 4]. Taking a thorough history of previous abortions and gestational age (Tab. 2) and of other obstetrical complications can lead to first insights in the etiology [7]. According to the variety of possible causes for repeated miscarriage it is necessary to consider a set of diagnostic tests (Tab. 3).

■ Uterine Anomalies

The exact incidence of uterine congenital anomalies in the female population is unknown, but studies on the incidence in RSA patients report a wide range from 2–37 % depending on diagnostic procedure and definition [4]. Although in a collective of women with known uterine anomaly the rate of miscarriage and preterm delivery is increased [8], data on success of surgical procedures recom-

Table 1: Risk of abortion according to the number of previous miscarriages [1].

Each pregnancy	11–15 %
After 1 miscarriage	12–24 %
After 2 consecutive miscarriages	19–35 %
After 3 consecutive miscarriages	25–46 %

Table 2: Distribution of gestational ages of miscarriage associated with different underlying causes [7].

	< 6 weeks	6–10 weeks no heart activity	6–10 weeks heart activity was present	10–14 weeks	> 14 weeks
Uterine/anatomic			++	+	
Hormonal	+++	++	+		
Infectious			+	+	+++
Genetic	+++	+++	++	+	+
Immunologic	+	+	++	+++	++
Thrombophilic	+	+	+	++	++

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Table 3: Diagnostic test proposed for patients/couples presenting with RSA

- Pelvic ultrasound scan; where necessary hysteroscopy*
- Early follicular-phase FSH, luteal-phase LH and progesterone
- TSH, TPO antibodies, oral glucose tolerance test
- Cervical swabs for (atypical) bacteria*
- Peripheral blood karyotype for both partners
- Antiphospholipid antibodies and lupus anticoagulant
- Factor V Leiden and prothrombin mutation, protein C, protein S
- Factor VIII, factor XII, polymorphisms of MTHFR, PAI-1, ACE*
- Where applicable karyotyping of abortus specimen*

* optional

mended have not been the focus of a randomized study.

At least 30 % of women aged 35 years or older show uterine fibroids. Intramurally or submucosally located fibroids are often assumed responsible for IVF failure or early pregnancy loss and hysteroscopic resection of submucosal fibroids is recommended, although evidence for this recommendation is incomplete [9].

The Asherman syndrome, i.e. partial or complete obliteration of the uterine cavity due to traumatic lesion of the endometrium, occurs in two thirds of the reported cases after surgical evacuation of the uterus for miscarriage or termination of pregnancy [10]. The prevalence of the Asherman syndrome is unknown as a consequence of different awareness and diagnostic equipment of physicians. Hysteroscopic adhesiolysis is the treatment of choice, with better pregnancy rates than with expectant management, although high recurrence rates are described [10].

■ Infections

Uterine infections as a cause for recurrent spontaneous abortions in the first trimester are discussed controversially. As infections with chlamydia, ureaplasma, and mycoplasma are diagnosed more often in women with RSA, many experts screen for these infections although there is no data that treatment improves pregnancy outcomes [1]. Repeated second-trimester fetal losses fol-

lowing cervical dilatation or rupture of membranes can be attributed in many cases to bacterial infections, as well as early preterm delivery. These patients should be screened for bacterial vaginal infections and treated – if treatment is carried out before 20 weeks of gestation, it succeeds in preventing preterm delivery, as shown by a recent Cochrane meta-analysis [11]. In some German centers, a surgical procedure, a total cervix occlusion established by E. Saling (described in [12]), is applied successfully in these cases [13], although there are no randomized studies on this topic.

■ Endocrine Disorders

Many endocrine disturbances have been assumed to be responsible for RSA. Glucose metabolism, thyroid hormones, and sex hormones have been the target for many studies. If insulin-dependent diabetes is well-controlled, there is no risk for RSA or for congenital malformations [14]. But in diabetic women with high levels of blood glucose and glycosylated hemoglobin during the first trimester the risk for abortion is significantly increased [14]. Thyroid antibodies, especially thyroperoxidase (TPO) antibodies, have been associated with abortions but not with RSA, and therapeutic interventions besides corrections in hormone metabolism have to be further investigated [15].

The luteal phase defect has long been thought to be a cause of abortion, but the evidence linking the luteal phase defect to recurrent abortion is subject to criticism and their association remains speculative. Hyperprolactinemia is found to be associated with RSA and treatment with bromocriptine significantly improves live birth rates [16]. Despite many studies on the prevalence of PCOS in recurrent miscarriage, the extent to which PCOS contributes to recurrent miscarriage remains highly uncertain due to different definitions used. Some evidence suggests that weight loss, ovarian drilling and metformin could help to reduce the rate of miscarriage [17].

■ Genetic Disorders

As mentioned above, 50–70 % of sporadic abortions are due to genetic disorders. In women with RSA, the rate of karyotypic abnormalities is much lower.

The most common aberrant karyotypes are autosomal trisomies (up to 60 %), of which trisomy 16 is the most frequent, monosomy X (up to 20 %), polyploidy (up to 20 %) and structural anomalies (4 %). However, the earlier pregnancy loss occurs, the higher is the percentage of genetic anomalies: 90 % in anembryonic specimen, 50 % between 8 and 11 gestational weeks and approximately 30 % at 16–19 gestational weeks [7].

Detection of aneuploidy in abortus specimens increases the probability of aneuploidy in a following miscarriage: after abortion with detection of a trisomy in the specimen the risk for the same (homotrissomy) or a different trisomy (heterotrissomy) is increased. For individual risk assessment the knowledge of the type of trisomy and the maternal age are crucial, concerning all women with either spontaneous or recurrent abortions [18].

In 3–5 % of couples with RSA, one partner shows a balanced chromosome rearrangement, more likely the mother [7]. In these phenotypically normal parents, separation of chromosomes during meiosis may lead to an abnormal number of copies of chromosomal segments, causing partial trisomy or monosomy in the offspring. In couples with one or more early miscarriages plus one child stillborn or born with congenital malformation, the rate of chromosomal structural anomaly found in one partner rises up to 5.4 %. This probability is approximately 10 %, if a couple has had one or more early abortions and if there are relatives with further abortions or malformed children [18].

Also, microdeletions or single gene disorders may influence pregnancy outcome. Consanguinity increases the risk for these conditions. Alpha thalassemia major is an example of a single-gene disorder, leading to repeated pregnancy loss [7]. Inherited thrombophilic mutations are discussed in the respective chapter.

As a consequence, thorough genetic counseling with a family history of at least three generations and karyotyping of the partners should be part of the diagnostic procedures for RSA. Information available from cytogenetic testing of abortus specimens enables more detailed genetic counseling, independent from

the number of prior miscarriages. For example, a woman under 30 years of age with a history of one miscarriage due to trisomy bears an increased risk for trisomy in the next pregnancy and requires prenatal counseling or diagnostic procedures.

■ Immunologic Disorders

Pregnancy is an extraordinary challenge to the maternal immune system allowing the only partially identical fetus to grow. In recent publications, a cooperative interaction between the maternal immune system and fetal antigens to establish this allogenic unresponsiveness has been discussed [19]. Natural killer cells in the mucosal layer of the uterus have been implicated in this immune tolerance and it is widely hypothesized that disturbance of this immune tolerance may be involved in RSA, but mechanisms are not fully understood [20]. However, although many studies with different therapeutic concepts (e. g. paternal lymphocytes, intravenous immunoglobines) have addressed this topic, no consistent evidence has been established. A recent meta-analysis found intravenous immunoglobines not to significantly increase live birth rates when compared with placebo for treatment of recurrent miscarriage (OR 1.28; 95 %-CI: 0.78–2.10). Effects reported in secondary RSA base on a very small number of patients [21].

In general, maternal autoimmune disorders except for systemic lupus erythematosus improve during pregnancy. Apart from that, antiphospholipid syndrome (APS) often is only diagnosed on the basis of miscarriages. It is defined by detection of antiphospholipid antibodies (including lupus anticoagulant and anticardiolipin antibodies) and one of the following clinical symptoms: arterial or venous thrombosis, three or more unexplained miscarriages before 10 weeks, one or more unexplained fetal deaths after 10 weeks or one preterm delivery before 34 weeks associated with severe preeclampsia or growth retardation. It accounts for nearly 15–20 % of RSA. Although many different therapeutic regimens have been used, only a combination of heparin and aspirin was proven to be effective in a meta-analysis [22]. Low molecular heparin is widely used now, although not many data exist on its use. The biggest study using LMW

Table 4: Frequency of thrombophilic disorders [25–27] and association with RSA from meta-analyses of case-control studies [24, 28, 29]. Definition of first trimester RSA varies between studies.

Thrombophilia	Genetic mechanism	Frequency in healthy population/ frequency of genes	Association with RSA		
			OR	95 %-CI	Ref.
Antithrombin deficiency	Heterogeneous	0.02–0.04 %	0.9	0.2–4.5	[24]
Protein C deficiency	Heterogeneous	0.2–0.5 %	1.6	0.2–10.5	[24]
Protein S deficiency	Heterogeneous	0.1–1 %	14.7	1.0–218.0	[24]
Factor V Leiden mutation	A506G	3–7 %	2.0	1.1–3.6	[24]
Prothrombin mutation	G20210A	1–3 %	2.3	1.1–4.8	[24]
Factor XII deficiency			17.74	5.41–58.16	[29]
Mild hyperhomocysteinemia			4.2	1.3–13.9	[24]
MTHFR	C677T polymorphism	C/C: 47 % C/T: 43 % T/T: 10 %	0.95	0.33–2.69	[28]
PAI-1 polymorphism	675 - 4G/5G	4G/4G: 31 % 4G/5G: 47 % 5G/5G: 22 %	1.65	0.92–2.95	[29]
Lupus anticoagulant			7.8	2.3–26.5	[24]
Anticardiolipin antibodies			5.1	1.8–14.0	[24]

OR = odds ratio; 95 %-CI: 95 % confidence interval

heparin up to now showed a successful pregnancy outcome in 89 %, including 98 APS patients [23].

■ Thrombophilic Disorders

Pregnancy adaptations early lead to hypercoagulability, to prevent bleeding during establishment of the hemochorial placenta. Thrombosis of placental vasculature in cases of mothers with pre-existing thrombophilia was thought to be responsible for miscarriage. But in the last years, experiments with thrombomodulin-deficient mice reported tissue factor-dependent activation of blood coagulation directly causing cell death and inhibiting growth of trophoblast cells (summarised in [24]).

Known inherited risk factors of venous or arterial thromboembolism are deficiencies of antithrombin, protein C and protein S, factor V Leiden and prothrombin 20210A mutations, mild hyperhomocysteinemia, elevated levels of factor VIII, and factor XII deficiency.

Association of the above mentioned thrombophilic disorders with adverse

pregnancy outcome have been subject to studies since the 1990ies. Table 4 summarizes the frequencies of genetic disorders in a healthy population [25–27] and results of recent meta-analyses concerning association with RSA [24, 28, 29].

As mentioned above, hyperhomocysteinemia is a predisposition to thrombophilia. Hyperhomocysteinemia may be induced by malnutrition with folic acid deficiency, potentially caused by a fast food diet. Another quite common cofactor is a variant in the MTHFR gene (Tab. 4), a C-to-T substitution at cDNA position 677, which may lead to an increased level of plasma homocysteine. Although initial studies suggested an association between homozygosity for MTHFR C677T itself and RSA, a meta-analysis could not confirm such an association [28]. But 23 % of the white population show a combined heterozygosity for C677T and another known polymorphism of the MTHFR gene, A1298C [30]. It has been shown that this compound heterozygosity for C677T and A1298C, but not homozygosity for A1298C alone, is associated with increased fasting and post-methionine

load homocysteine plasma levels [30] and with recurrent pregnancy loss [31, 32]. In all these variants, homocysteine levels usually stay within normal range if sufficient folic acid substitution is applied. Thus, such a predisposition could be missed when no genetic testing has been performed. Therefore, the regular folic acid intake is essential especially for carriers of a predisposing MTHFR genotype.

Buchholz et al report that homozygosity for the D allele of the angiotensin-converting enzyme (ACE) gene, which results in elevated plasminogen activator inhibitor- (PAI-) 1 concentrations and hypofibrinolysis, is associated with an elevated risk of RSA; and the combination of the D/D ACE genotype with two 4G alleles of the PAI-1 promoter, which further increases PAI-1 plasma levels, is significantly more frequent in RSA patients compared with controls [33].

There is also an association of some of the thrombophilic disorders mentioned above (factor V and prothrombin mutation, protein C, protein S and antithrombin deficiency, PAI-1 and MTHFR polymorphism) with obstetric complications later in pregnancy, as late fetal loss, pre-eclampsia and fetal growth retardation [24]. This implicates that careful counseling of patients concerned and management of high-risk pregnancies in cooperation with specialized centers is necessary.

■ Management

A proposed set of diagnostic tests for RSA patients is summarized in Table 3. If diagnostic testing suggests infectious or endocrine causes for RSA, specific treatment should be applied. The expected success rates of surgical procedures because of uterine anomalies have to be discussed with the couple, and if applicable pre-implantation testing may be offered.

It is important to understand that – independent of the therapeutic management offered – the overall miscarriage rate cannot decrease below about 15 %, comprising genetic or nidation failures. Furthermore, about one third of couples with a history of three consecutive miscarriages have lost pregnancies purely by chance alone, due to sporadic fetal

aneuploidy. Such couples have a 75-% chance of a successful pregnancy next time with no therapeutic intervention [4].

■ Progesterone

In a recent Cochrane meta-analysis [34], a subgroup analysis of three trials involving women who had recurrent miscarriages (three or more consecutive miscarriages), progesterone treatment showed a statistically significant decrease in miscarriage rates compared to placebo or no treatment (OR 0.38; 95 %-CI: 0.20–0.70). But no evidence was established to support the routine use of progesterone to prevent sporadic miscarriage in early to mid-pregnancy.

■ Aspirin

In APS, a combination of heparin and aspirin was proven to be effective in a meta-analysis [22]. In patients with known thrombophilic predisposition of various etiologies (Factor V or prothrombin mutation, protein S deficiency), Gris et al reported significantly higher live birth rates in the group of women treated with heparin alone compared those treated with aspirin alone – which showed a live birth rate of 29 % comparable to untreated women [35]. Concerning this result, other authors raised methodological concerns because of inclusion in the trial not before the 8th week of pregnancy and the randomization procedure [24]. However, a later trial with a similar study design confirmed the results [36].

On the contrary, the only intervention study concerning factor XII deficiency and RSA was performed with aspirin, showing reduced miscarriage rates, but included only a small number of patients [37].

■ Heparin

It seems obvious that heparin is the therapy of choice for prevention of recurrent miscarriage in patients with thrombophilia. However, no placebo-controlled, randomized studies confirm this hypothesis. In the study by Gris et al, the live birth rate was 23 out of 80 women (29 %) in the aspirin group versus 69 out of 80 (86 %) in the enoxaparin group in patients with known thrombo-

philic predisposition [35]. In another cohort study with patients with hereditary thrombophilia and RSA, 26 of the 37 pregnancies (70 %) in heparin-treated patients resulted in live births, compared with 21 of 48 (44 %) in untreated patients (OR 3.03; 95 %-CI: 1.12–8.36). The beneficial effect was seen mainly in women with no previous live births (OR 9.75; 95 %-CI: 1.59–52.48) [38]. A German observational study, the ETHiG trial, designed for assessment of low molecular weight heparin efficacy for prophylaxis of thromboembolism, included 810 pregnant women with prior thrombosis or hereditary thrombophilia. Of the 272 pregnant women starting dalteparin before 12 weeks of gestation, 270 (99 %) had a history of prior miscarriage, but showed under therapy with dalteparin only 31 (11 %) pregnancy losses [39]. The LIVE-ENOX trial randomized for two different doses of enoxaparin (40 and 80 mg) for treatment of women with inherited thrombophilia and showed no difference in live birth rates (84 % and 78 %, respectively) [40]. Critics argue that in many reports the prognosis of women with RSA is good and do not support general recommendations for the use of heparin for RSA in women with thrombophilia, without well-designed randomized trials available [24]. Thus, it is necessary to understand that heparin for RSA in women with thrombophilia is widely used but evidence is not sufficient yet. However, German guidelines for RSA recommend treatment of women with thrombophilia with heparin [41].

First evidence for the use of heparin for RSA of unknown etiology came from a trial by Tzafettas et al who compared pregnancy outcome of two groups of women with a history of two or more miscarriages, 24 with known and 27 with excluded thrombophilia. Both groups were treated with heparin and aspirin, and similar live birth rates of 83.3 % and 85.1 % were reported [42]. However, a recently published study investigated pregnancy outcome of 340 women with unexplained recurrent pregnancy loss randomized either to treatment with enoxaparin and folic acid or folic acid alone [43]. The rates of early miscarriage of 4.1 % vs. 8.8 %, respectively, were regarded as a significant effect of low molecular weight heparin, but are very low in comparison to other studies. An-

other recently published, prospective, randomized trial compared treatment of 160 women with RSA of unknown etiology with enoxaparin alone or prednisone, aspirin and progesterone or placebo [44]. They reported live birth rates of 81 %, 85 % and 42 %, respectively, showing efficacy of treatment. A German study, the ETHiG II trial, is still recruiting [45]. It was designed to include a sufficient number of patients for a randomized placebo-controlled treatment, to strengthen evidence and answer some of the still open questions.

■ Psychological Support

Since the 1980ies it is known that dedicated care may beneficially influence pregnancy outcome in patients with unexplained recurrent miscarriage. Regular specific antenatal counseling and psychological support during the first trimester in women with three or more consecutive abortions led to a live birth rate of 86 % as compared to a success rate of 33 % observed in women who were given no specific antenatal care [46]. Thus, success of the above-men-

tioned interventions has to be tested against tender loving care before evidence-based decisions can be taken.

■ Summary

Recurrent spontaneous abortions have to be considered as a multi-causal condition, with genetic fetal or parental chromosomal abnormalities, anatomic, infectious, endocrine, immunologic, and thrombophilic factors playing a role in their etiology, which are not mutually exclusive. A set of diagnostic tests for RSA patients is proposed. If diagnostic testing suggests infectious or endocrine causes for RSA, specific treatment should be applied. Surgical procedures may be offered for uterine anomalies. There is evidence for the use of progesterone in RSA. Patients with antiphospholipid syndrome should receive a combination of heparin and aspirin, patients with inherited thrombophilia in the majority of cases heparin, although evidence is incomplete. For RSA of unknown etiology, heparin is suggested to be effective, randomized studies are still in progress.

■ Practical Aspects

- Recurrent spontaneous abortions have to be considered as a multi-causal condition, with genetic fetal or parental chromosomal abnormalities, anatomic, infectious, endocrine, immunologic, and thrombophilic factors playing a role in its etiology.
- If diagnostic testing suggests infectious or endocrine etiology, specific treatment should be applied; surgical procedures may be offered for uterine anomalies.
- Patients with antiphospholipid syndrome should receive a combination of heparin and aspirin, patients with inherited thrombophilia in the majority of cases heparin, although evidence is incomplete.
- For RSA of unknown etiology, heparin is suggested to be effective, randomized studies are still in progress; dedicated care may beneficially influence pregnancy outcomes as well.
- However, independent of the therapeutic management offered, the overall miscarriage rate cannot decrease.

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