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Clinical Reviews in Allergy & Immunology

ISSN 1080-0549

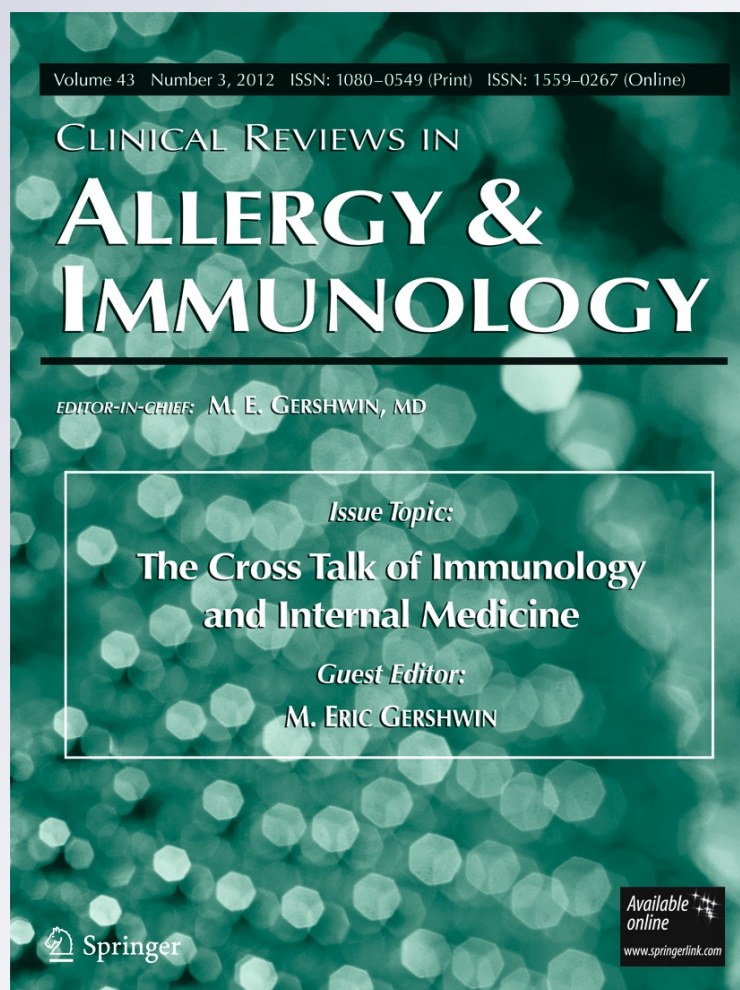
Volume 43

Number 3

Clinic Rev Allerg Immunol (2012)

43:265-274

DOI 10.1007/s12016-012-8316-0



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Recurrent Miscarriage, Antiphospholipid Antibodies and the Risk of Thromboembolic Disease

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Published online: 6 June 2012
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Abstract Miscarriage affects 15 % of women, and while most are sporadic, there is a subset comprising 2–5 % of couples that suffers recurrent miscarriage (RM). Much work has been carried out to try to identify the RM underlying mechanisms. A subgroup of women with RM has been demonstrated to be in a prothrombotic state before pregnancy. The long-term health implications of this hypercoagulability may imply an increased risk of thrombotic events, including ischemic heart disease. Moreover, the presence of antiphospholipid antibodies (aPL), rather than thrombophilic genetic defects (i.e., factor V Leiden or prothrombin G20210A mutation) in patients with RM, is a determinant of thrombotic events later in life, especially among those patients having also classic cardiovascular risk factors. These facts may have therapeutic implications. The efficacy of long-term thromboprophylaxis and its associated risk of bleeding is a complex problem in aPL-positive patients who have not developed previous thrombosis or in patients with antiphospholipid syndrome with isolated obstetric morbidity (i.e., RM). While most authors advocate the use of antithrombotic therapy only in patients with aPL and thromboembolic events, there is no consensus as to whether patients who have not experienced yet any thrombotic event might also be given prophylaxis. Low-dose aspirin may be effective in the prevention of

thrombosis for asymptomatic, persistently aPL-positive individuals who have additional thrombosis risk factors, i.e., hypertension and lupus anticoagulant have been found to be independent risk factors for thrombosis in aPL carriers, and therefore, the use of thromboprophylaxis in these high-risk subjects could be recommend.

Keywords Antiphospholipid antibodies · Antiphospholipid syndrome · Recurrent miscarriage

Introduction

Miscarriage affects 15 % of women [1], primarily in the first trimester, and while most are sporadic and nonrecurrent, there is a subset comprising 2–5 % of couples that suffers recurrent miscarriage (RM) [2]. These repetitive losses suggest the presence of a specific cause, and much work has been carried out to try to identify the underlying mechanisms. However, the current medical literature suggests that causes are identified in only ~50 % of patients [3, 4]. Thus, RM is a vexing problem facing many couples and doctors.

Historically, RM has been attributed to either genetic, structural, infective, endocrine, immune, or unexplained causes. Thrombophilic disorders are nowadays thought to play a part in the cause of RM, which widens the scope of investigations and management options for RM patients [5]. Several reports identify inherited predisposition to thrombophilia as one of the main causes of RM; in particular, if different factors potentially responsible for RM have been already excluded, such as endocrine diseases, uterine malformations, genetic alterations, and infectious diseases [6–10].

During pregnancy, in fact, many changes in the hemostatic balance may be observed, with a trend toward thrombophilia

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in order to be prompted for the hemostatic challenge of delivery [7, 11, 12]. For this reason, episodes of venous thromboembolism can be observed during pregnancy [7, 11, 12]. Moreover, women carrying further thrombotic risk factors, such as inherited or acquired thrombophilia, show an additionally increased risk of thrombotic events during pregnancy such as venous thromboembolism and/or abortion [13, 14].

Recent insight into the pathogenesis of RM has proposed a different view of thrombotic events in these patients. Occult cardiovascular, microvascular, or hemostatic dysfunction may result in pregnancy complications during reproductive years and in thrombotic disease later in life. We will analyze this challenging issue in the present review.

Definition of Recurrent Miscarriage

According to the Practice Committee of the American Society for Reproductive Medicine (ASRM) [15], recurrent pregnancy loss is a disease defined by two or more failed pregnancies. When the cause is unknown, each pregnancy loss merits careful review to determine whether specific evaluation may be appropriate. Early RM refers to pregnancies that end in demise before 10 weeks of gestation [16]. However, the interpretation of patients' clinical history is usually difficult. It is frequent that a patient reports a miscarriage towards 10–12 weeks (when the signs of imminent abortion appear), whereas actually the pregnancy has been demised for several weeks. Thus, probably many expulsions considered in the fetal period are in fact of embryonic nature.

Although some authors define RM as three or more consecutive spontaneous miscarriages [5, 17, 18], we and others [19–26], including the Practice Committee of the ASRM [15], agree that screening for causes of RM could be usefully extended to include women who have RM defined as two spontaneous abortions or three or more nonconsecutive miscarriages. From a practical point of view, this is a useful definition because it is clinically important to study and treat patients with a history of ≥ 2 miscarriages. This contention is supported by the following facts:

- 1) Many authors agree that two or more losses should be used as a criterion for proceeding with diagnostic studies and therapy because the anguish of couples with even two pregnancy losses demands search for causation [27–32].
- 2) Because miscarriage is a common phenomenon, diagnostic workup is not informative after a single event. However, some couples will have a persistent obstacle(s) to maintaining a pregnancy above and beyond the background risk of miscarriage, and the risk of subsequent

spontaneous abortion increases with the number of previous miscarriages. Data from various studies indicate that after one spontaneous abortion the couple has an imperceptible increase in the 15 % baseline risk for having another. But if two miscarriages occur, the subsequent risk increases to approximately 25–40 % risk for having a fourth miscarriage [29, 30, 33].

- 3) Carefully designed prospective studies of early pregnancy loss concluded that a woman's risk of miscarriage can be quantified by examining her past obstetric history, the single most important factor being the number of previous miscarriages [33–35].
- 4) Workup for couples with two spontaneous abortions will certainly include all who will go on to have three or more.
- 5) Support for evaluations after two miscarriages comes from the fact that a high proportion of couples with explainable causes, including thrombophilias such as the antiphospholipid syndrome (APS), are found even after two pregnancy losses [19, 20, 22, 24, 26].
- 6) There is little to suggest that requiring three losses, rather than two, increases the yield of detecting etiologic factors for recurrent spontaneous abortion [29].
- 7) Published data on the APS, which is a frequent cause of RM, showed no correlation between the severity of the disease (i.e., the number of previous miscarriages) and the prevalence of antiphospholipid antibodies [24].

The above notwithstanding, after three or more losses, a thorough evaluation is mandatory [15]. Moreover, it is remarkable that the revised classification criteria for the APS includes “three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded” [36]. Thus, a cutoff between abortion (embryonic loss) and fetal loss is established at 10 weeks pregnancy [16].

Pregnancy-Associated Changes in the Hemostatic System: Risk of Thromboembolism

Pregnancy has long been recognized as being a hypercoagulable state [11, 12, 37]. In normal pregnancy, there is a marked increase in the procoagulant activity in maternal blood characterized by elevation of factors VII, X, VIII, fibrinogen, and von Willebrand factor which is maximal around term. This is associated with an increase in prothrombin fragments (PF1+2) and thrombin–antithrombin complexes. There is a decrease in physiological anticoagulants manifested by a significant reduction in protein S activity and by acquired activated protein C resistance [11, 12, 37].

The overall fibrinolytic activity is impaired during pregnancy, but returns rapidly to normal following delivery [38]. This is largely due to placental derived plasminogen activator inhibitor type 2, which is present in substantial quantities during pregnancy, and partially due to thrombin activatable fibrinolysis inhibitor [38]. D-dimer, a specific marker of fibrinolysis resulting from breakdown of cross-linked fibrin polymer by plasmin, increases as pregnancy progresses [11, 12, 37].

Local hemostasis at the placental trophoblast level is characterized by increased tissue factor expression and low expression of its inhibitor. Microparticles that are membrane vesicles that are shed from various cellular surfaces, derived from maternal endothelial cells and platelets, and from placental trophoblasts may contribute to the procoagulant effect [12, 39]. Local anticoagulant mechanisms on placental trophoblasts are important for counterbalance of the procoagulant milieu [11, 12, 37].

The evolutionary advantage of this hypercoagulability may be to counteract the inherent instability associated with hemochorial placentation, which is unique to human beings. However, overall, there is a 4- to 10-fold increased thrombotic risk throughout gestation and the postpartum period [12, 40]. It is well known that many cases of pregnancy loss, both early and late, are caused by an exaggerated hemostatic response during pregnancy, leading to thrombosis of the placental vasculature and subsequent pregnancy loss [12, 37].

Several investigations have focused on certain inherited or acquired thrombophilic factors that may predispose to arterial and/or venous thrombosis and their possible association with pregnancy complications, including RM [14, 16, 40–43]. The pathogenic theory of placental thrombosis affecting the fetal–maternal circulation and leading to RM or fetal death has been put forward since the early 1980s, when the antiphospholipid syndrome was recognized as an etiological cause for recurrent fetal loss. In the last years, the discovery of the frequent mutations in the factor V Leiden and prothrombin genes generated an increased interest in the relationship between thrombophilia and venous thromboembolism, but also with various obstetrical complications, such as RM, fetal loss, preeclampsia, intrauterine fetal growth restriction, etc. that may have an impaired placental circulation as the common determinant [14, 40, 43, 44].

Recurrent Miscarriage, Congenital Thrombophilia, and Vascular Thrombosis

As previously stressed, several studies have analyzed inherited thrombophilic factors that may predispose to arterial and/or venous thrombosis and their possible association

with RM [14, 16, 40–43]. A meta-analysis of 31 studies [41] revealed an association between recurrent (two or more) fetal loss of <13 weeks and factor V Leiden, activated protein C resistance, prothrombin gene mutation, and protein S deficiency. Conversely, it was demonstrated that methylenetetrahydrofolate reductase, protein C, and anti-thrombin deficiencies were not associated with RM. A second meta-analysis of 16 studies [42] reported an association between RM, defined as two or more losses in the first two trimesters, and maternal carriers of factor V Leiden or prothrombin gene, compared with those without these inherited thrombophilic mutations. Other studies have shown that the total number of mutations is a significant risk of RM, suggesting that there may be an additive effect of a number of thrombophilic mutations superimposed on the hypercoagulable state of pregnancy, and that would increase the risk of clotting [45].

Therefore, the majority of studies report an increased prevalence of genetic thrombophilic mutations among women with RM. Moreover, few studies provide evidence of other abnormalities in the hemostatic pathways preceding RM [47]. It has been reported that women with a history of RM at 4–7 of weeks' gestation have an excess of thromboxane production, and between weeks 8 and 11, they are relatively prostacyclin deficient, compared with women with no previous history of pregnancy loss [46]. These changes were greatest among those whose pregnancy ended in abortion. The shift in the thromboxane to prostacyclin ratio in favor of the prothrombotic agent thromboxane may lead to vasospasm and platelet aggregation in the trophoblast, causing the development of microthrombi and placental necrosis [46, 47].

Another study [48] reported the cases of two women in whom a significant decrease in the level of protein C and shortening in the rate of fibrinopeptide A generation (indicating activation of coagulation) could be detected several weeks in advance of pregnancy loss. In the second pregnancy of one of these two women, similar hematological changes were documented, but these were reversed by the administration of heparin, and the patient went on to deliver at term. Moreover, in a longitudinal study of pregnant women with antiphospholipid syndrome, patients with significantly higher levels of thrombin–antithrombin complexes (a global marker of thrombotic potential) ended more frequently in pregnancy loss [49].

Furthermore, a study performed by us [50] reported that, outside of pregnancy, women with first trimester RM are in a prothrombotic state, manifested by an impaired fibrinolytic response. Other studies have also found impairment of fibrinolysis in RM patients [51–53]. It has also been described, using global markers of the hemostatic process, that women with RM have increased thrombin generation and increased maximum clot strength before pregnancy [54, 55].

Furthermore, the authors stressed that women, in such a state, are at significantly increased risk of miscarriage in future untreated pregnancies [55]. Other studies have also suggested that women with unexplained RM have a hypercoagulable state at baseline consisting in a relative trombomodulin resistance [56]. There is also evidence that circulating placental microparticles are increased in a subgroup of RM patients, indicating an acquired procoagulant state even outside pregnancy [17].

The long-term health consequences of the hypercoagulable state of RM patients are being increasingly recognized, but few studies have evaluated this issue; thus, several studies have found an increased risk of ischemic heart disease in the subgroup of women with a history of pregnancy loss [57–59]. A retrospective study of 130,000 women showed that a history of first trimester spontaneous pregnancy loss was associated with a significant increased risk of maternal ischemic heart disease [58]. This risk increased with the number of pregnancy losses. Moreover, among those with three or more pregnancy losses the risk of death or hospital admission for ischemic heart disease was 2.3 times greater than that among those with no previous history of miscarriage. In contrast, there was no association between therapeutic abortion and the subsequent risk of ischemic heart disease. The authors hypothesized that this may reflect common determinants, such as thrombophilic genetic defects or the presence of antiphospholipid antibodies (aPL). Moreover, the same authors have recently found [60] that there was an increased incidence of ischemic heart disease in the parents of women who experienced multiple miscarriages before their first birth, suggesting that RM and ischemic heart disease may have common pathophysiological pathways and genetic predispositions.

The long-term risk of thrombotic events after pregnancy among patients with RM associated with inherited thrombophilic factors different than APS and idiopathic RM has only been evaluated in a case–control study. This study, performed by us [61], evaluated the long-term risk for thromboembolic events after RM in APS patients compared with RM patients with thrombophilias different from APS and idiopathic RM patients. It showed a higher risk, although not statistically significant, of thromboembolic events among patients with RM, who tested positive only for genetic thrombophilias compared with patients with idiopathic RM. The former control group of patients in this study presented with thrombophilic genetic defects as the only etiologic factor for their pregnancy losses. It consisted of 42 patients with three or more consecutive spontaneous abortions before 10 weeks gestation. Thrombophilia, in this group, was defined as factor V Leiden mutation (17 patients), prothrombin G20210A gene mutation (12 patients), protein C deficiency (9 patients), or protein S deficiency (4 patients). No woman in this group had combined thrombophilia (two or

more findings), and all tested negative for aPL. The idiopathic RM control group was composed of 86 patients with three or more consecutive spontaneous RM, who tested negative for fertility studies including routine screening for systemic diseases, diabetes mellitus, thyroid dysfunction, polycystic ovary disease, a chromosome assessment of the woman and her partner, uterine abnormalities, endometrial and hormonal luteal phase defects, endometrial and cervical infection, and thrombophilia (plasma levels of protein S and C, antithrombin, factor V Leiden, prothrombin G20210A mutation, acquired protein C resistance, and aPL). No patient in the idiopathic RM group (0 %) and two patients in the thrombophilic genetic defects group (4.8 %) presented with thrombotic events in the 12-year follow-up. The thrombophilic genetic defects group had 7.1 thrombotic events per 1,000 patient-years, which is within the range of estimated risk reported in the literature for patients with inherited thrombophilia [62].

Genetic thrombophilias, such as factor V Leiden and prothrombin mutations, are widely accepted in daily clinical practice as a cause of RM, and thus, thromboprophylaxis is recommended in the next pregnancy in these patients [63]. However, some authors question this approach [8]. The use of long-term thromboprophylaxis in patients with RM having genetic thrombophilias and no previous thrombosis is, generally, not recommended. However, patients with RM having genetic thrombophilias may benefit from counseling about avoiding cardiovascular risk factors [58].

Recurrent Miscarriage, Acquired Thrombophilia, and Risk of Thrombotic Events: The Role of Antiphospholipid Antibodies

Antiphospholipid antibodies are detected in more than 10 % of patients with RM [20], and they have emerged as one of the most common causes of this reproductive complication [24]. Therefore, the most frequent acquired thrombophilia in RM patients is APS.

Thrombosis Risk in APS Patients

The APS is an autoimmune, multisystemic disorder associated with vascular thrombosis and/or pregnancy morbidity in the presence of circulating aPL [36]. However, in contrast with venous thromboses associated with congenital thrombophilias, those associated with APS might also occur in any vascular bed. On the other hand, the most common obstetric manifestation of the APS is RM. Thus, women with aPL are considered at increased risk for both RM and thrombotic events [36].

The above notwithstanding, aPL frequently persists for many years, possibly a lifetime without apparent harm. On the other hand, aPL can be detected in the sera of asymptomatic

subjects, even years before developing a full-blown disease. Thus, an unsolved critical question is what additional factors lead to the sudden development of thrombosis, which occurs only in a minority of patients with these antibodies.

A “two hit hypothesis” has been proposed to explain the clinical observation that thrombotic events do occur only occasionally, despite the persistent presence of aPL. The first hit (aPL) would increase the thrombophilic risk, and a second hit is required so that the clotting takes place [64, 65].

A recent multicenter prospective analysis of 1,000 patients with APS has shown that thrombotic complications are the most common cause of death in APS patients [66, 67]. The mortality rate in this large European cohort of patients with APS during a 5-year study period was 5.3 %, and up to 40 % of the deaths in this cohort were attributed to severe thrombotic events such as myocardial infarction, stroke, and pulmonary embolism [66, 67]. Recent studies suggest that healthy aPL carriers may present with thrombotic events with the same frequency as APS patients [68–70]. Several studies have tried to identify different serologic, genetic, or epidemiological factors that may stratify the thrombotic risk in APS patients and healthy aPL carriers [71–76]. No single predominant risk factor has been identified, although, according to the different studies, possessing a combination of cardiovascular risk factors may increase the occurrence of arterial thrombosis [77], and multiple positivity in tests, exploring the presence of aPL, may be associated with thromboembolic events more frequently than single test positivity [71–73, 78]. Nevertheless, bias cannot be excluded in these studies, and nowadays, we cannot definitely predict which aPL individuals are at risk for thrombosis [74].

Thrombosis Risk in APS-RM Patients

Few studies have investigated the thrombosis risk in the long term in APS-RM patients. The results of these studies are

summarized in Table 1. Only one of these studies investigates the thrombotic risk in APS-RM patients without previous thrombosis [61], while others analyze the thrombotic risk in obstetric APS patients, having not only RM as a diagnostic APS criteria [66, 79–83].

The historic cohort study performed by Silver et al. [80] suggested for the first time that there was a high rate of thrombosis in individuals with aPL, especially associated with pregnancy, showing a 23 % of thrombosis rate among patients with obstetric APS. However, this study evaluated primary and secondary APS and did not provide accurate information about the use of treatment with low-dose aspirin or other anticoagulant drugs. In 2001, two short communications [81, 82] suggested a high incidence of nonpregnancy-related vascular thrombosis in APS patients who present with pregnancy loss as their only manifestation of APS. One of these reports, however, was a retrospective data collection including a total of 65 patients of whom 50 % were receiving aspirin therapy [82], while the second report was a cohort study including 52 women treated with aspirin [81]. Tincani et al. [81] showed the results of a prospective cohort series of primary APS patients, finding a 3.8 % of thrombosis rate among obstetric APS patients treated with low-dose aspirin. Nevertheless, the authors [81] stress that the end point of the study was the observation of major clinical events, while Erkan et al. [82], who found a thrombotic rate of 35.4 %, also considered minor clinical events, such as transient ischemic attacks and cognitive dysfunctions, as thrombotic events.

In 2005, the first case–control study was published, analyzing the long-term thrombosis risk in APS-RM patients, and compared their thrombotic risk with idiopathic RM patients [79]. This study also suggested that a history of RM in APS patients is a risk factor for subsequent thrombosis in the long term. In this report, however, patients with both idiopathic and APS-associated RM presented a similar long-term risk of thrombosis. Nevertheless, in that study,

Table 1 Studies analyzing thrombosis risk in APS recurrent miscarriage patients

Authors	Study type	Follow-up (mean years)	Number of patients	Primary APS patients only	Thrombosis <i>n</i> (%)
Silver et al. [80]	Historic cohort	3.2	39	No	9 (23)
Tincani et al. [81]	Prospective cohort	4.8	52	Yes	2 (3.8)
Erkan et al. [69]	Retrospective observational	8.1	65	No	23 (35.4)
Quenby et al. [79]	Retrospective case-control	7.3	141	Yes	6 (4.2)
Ruffatti et al. [84]	Retrospective observational	6.3	53	Yes	8 (15.1)
Cervera et al. [66]	Prospective observational	5	121	No	3 (2.5)
Martínez-Zamora et al. [61]	Retrospective case-control	8	67	Yes	11 (19.3)
Gris et al. [83]	Observational prospective	3.5	517	No	124 (24)

congenital or acquired thrombophilia other than aPL was not excluded in idiopathic RM patients. The results of the study showed that those patients who developed a thrombotic event in this study were found to be heterozygous for the factor V Leiden mutation and homozygous for the prothrombin gene mutation 20210A and were not, in fact, patients with idiopathic RM. Moreover, in this study, patients with one or more fetal deaths beyond 10 weeks gestation were included in the same group as women with three or more miscarriages before 10 weeks gestation. The thrombotic events found in APS-RM patients, in this study, were two pulmonary embolisms, one cerebral venous thrombosis, and three transient ischemic attacks (Table 2).

Ruffati et al. [84] provided the rate of thromboembolic events among women who fulfilled obstetric APS criteria. Sixteen of the 53 patients analyzed had previous thromboembolisms, and only 22 % of the patients had previous spontaneous abortions (72 % had previous fetal deaths). Eight thrombotic events were observed during a 6.3-year follow-up (2.4 % patient/year). They found that the rate of thromboembolic events was significantly higher in the group of women with triple positivity of antiphospholipid antibodies and/or previous thromboembolism. Events were venous in three cases and arterial in the five remaining cases. In the eight patients with thromboembolic events, one was on long-term aspirin; two were on long-term warfarin, and the remaining five were untreated. All these women had previous thromboembolism, late pregnancy loss, and triple antibody positivity.

The results of a prospective analysis of 1,000 patients with APS (the Euro-Phospholipid project), involving 20 tertiary referral university hospitals from 13 European countries [66], also provided data about the risk of thrombotic events in obstetric APS patients. Three out of 121 (2.5 %) women with only obstetric APS manifestations at the beginning of the study, in this series, developed a new

thrombotic event during the 5-year study period (one deep vein thrombosis, one stroke, and one catastrophic APS). The authors provide the data that 23 % of patients analyzed were receiving either anticoagulant or antiaggregant agents, but it was not provided how many patients of the obstetric APS group received these types of treatments. Nevertheless, it was reported that only one of the three patients who presented with a thrombotic event was receiving primary thromboprophylaxis with aspirin before the thrombotic event. It has to be stressed that this study analyzed primary APS patients and APS associated with systemic lupus erythematosus patients.

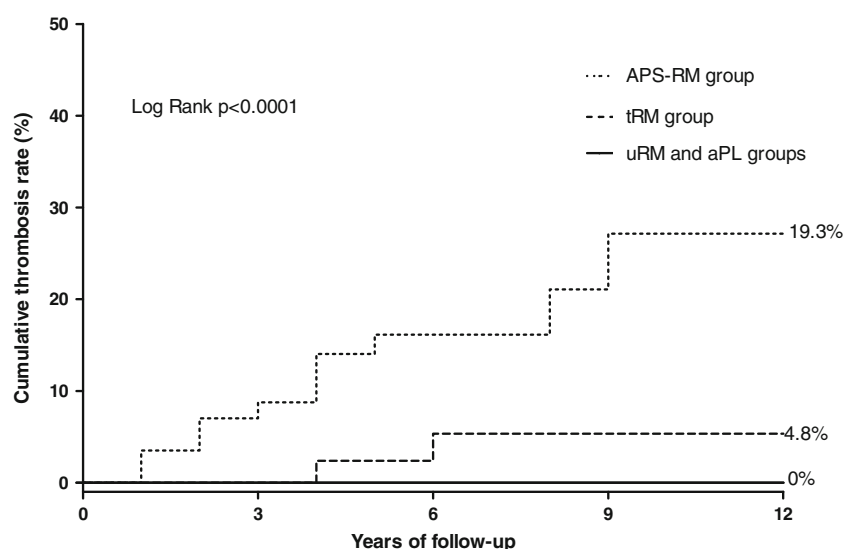
A recent study performed by our group [61], investigating whether patients with primary APS as the only etiological factor for RM and without previous thrombosis are at increased risk of thrombosis later in life, has added new relevant information to this issue from a clinical point of view. It is a case-control study showing that patients with RM associated with the presence of aPL have an increased long-term risk of thrombosis. This study used appropriate control patients (patients with idiopathic RM, patients with RM and thrombophilic genetic disorders, as previously described, and healthy positive aPL patients without obstetric or thrombotic complications). There was statistically significant difference in the rate of thrombosis in the APS group compared with the three control groups (19.3 % in APS-RM patients, 4.8 % in RM patients with other thrombophilias, and 0 % in idiopathic RM patients and healthy aPL carriers) (Fig. 1). Patients in the APS group had 25.6 thrombotic events per 1,000 patient-years (95 % confidence interval (CI), 12.8–45.9) while the corresponding figure in the genetic thrombophilia group was 7.1 thrombotic events per 1,000 patient-years (95 % CI, 0.8–25.5). The odds ratio (OR) of thrombosis in relation to the presence or absence of aPL in patients with RM was 15.06 ($p<0.0001$). This was still true when only patients with thrombophilic disorders other than aPL were considered (OR, 4.8; 95 % CI, 1–22.8) ($p<0.05$). Accordingly, the OR was even higher when the APS-RM group was compared with the idiopathic RM group alone (OR, 42.8; 95 % CI, 2.5–742) ($p<0.0001$). It is of note that 71.4 % APS patients with RM, who were diagnosed with arterial thrombosis, had concomitant thrombosis risk factors (hypertension, hypercholesterolemia, and smoking). Interestingly enough, only 19.3 % of patients in the APS-RM group and no woman among the healthy aPL positive group developed a thrombotic event in the long term, despite aPL and their isotype distribution being similar in aPL-positive patients developing thrombosis or not and irrespective of being RM or healthy controls. Moreover, the occurrence of thrombotic events among women with RM treated with low-dose aspirin was not different than in patients who did not receive this treatment (OR, 2.9; 95 % CI, 0.5–15.1). However, the latter cannot be definitely concluded in this study, given the low number of subjects treated with low-dose

Table 2 Thrombotic events in the long term in patients having RM as the only criteria for APS

Type of thrombotic event	Martínez-Zamora et al. [61]	Quenby et al. [79]
Patients with thrombotic event	11 (19.3)	6 (4.2)
Cerebral arterial infarction	4	0
Deep vein thrombosis	2	0
Pulmonary embolism	2	2
Ischemic infarction	2	0
Cerebellar arterial infarction	1	0
Transient ischemic attack	0	3
Cerebral venous thrombosis	0	1

Criteria for APS include having no previous fetal losses or thrombosis. Values are *n* (%)

Fig. 1 Kaplan–Meier curves of 12-year cumulative incidence of thrombotic events in the four groups studied. APS-RM group, antiphospholipid syndrome patients with recurrent miscarriage; uRM group, patients with recurrent miscarriage without antiphospholipid antibodies or other known thrombophilias; tRM group, patients with recurrent miscarriage without aPL, but with other known thrombophilias; aPL group, patients with positive tests for aPL without pregnancy or thrombotic morbidity



aspirin and the fact that the treatment was arbitrarily administered according to physician's criteria. The type of thrombotic events found in this study is shown in Table 2.

Another recent study [83] evaluated the incidence of thrombosis in the purely obstetric form of APS (consecutive spontaneous abortions before the 10th week of gestation or one fetal death at or beyond the 10th week of gestation), compared to women carrying other thrombophilia and women with negative thrombophilia screening results, but also having consecutive spontaneous abortions or fetal deaths. This study that includes the largest series of patients (517) also found that the annual rates of deep venous thrombosis (1.46 %), pulmonary embolism (0.43 %), superficial vein thrombosis (0.44 %), and cerebrovascular events (0.32 %) were significantly higher in APS patients. In this study, lupus anticoagulant was a risk factor for proximal and distal deep venous thrombosis and superficial vein thrombosis, and women in the upper quartile of lupus anticoagulant activity had the highest risk. The authors concluded that, despite data suggesting that aPL may induce pregnancy loss through nonthrombotic mechanisms, women with purely obstetric APS are at risk for thrombotic complications.

In conclusion, these studies suggest that a history of RM associated with aPL is a risk factor for subsequent thrombosis in the long term. Moreover, thrombosis in APS patients with RM is frequently associated with concomitant cardiovascular risk factors.

Long-Term Thromboprophylaxis in APS-RM Patients

Nowadays, there is no way to predict when or which healthy aPL patients will develop thrombosis. However, the presence of circulating aPL, rather than thrombophilic genetic defects in patients with RM, is a determinant of thrombotic events later in life, especially among these APS patients with RM

having cardiovascular risk factors [61]. Several studies suggest that aPL-positive individuals should be risk-stratified according to traditional cardiovascular risk factors, which can be responsible for triggering acute thrombosis. It may seem that treatment and/or prevention of these thrombosis risk factors could be an important intervention to reduce arterial thrombosis as previously suggested [69]. Thus, there is support to the two hit hypothesis [64, 65], where aPL (which would be the “first hit”) increases the thrombophilic risk, and the clotting takes place in the presence of another thrombophilic condition (i.e., RM associated with traditional cardiovascular risk factors or not, acting as the “second hit”). This would explain previous epidemiologic studies suggesting that a woman's reproductive history may indicate future cardiovascular risk [58]. On the other hand, it is to note that, as for other autoimmune diseases, the etiopathogenesis of APS is also apparently multifactorial involving responses of both adaptative and innate immunity, being supported by a genetic background and triggered by environmental factors. In other words, genetically determined and environmental factors (second hits) may cooperate with aPL (first hit) in favoring thrombotic events [65]. Therefore, whether an individual will develop a thrombotic event will depend on the concomitant presence of additional factors that may increase the whole thrombotic risk. This would explain why up to 80 % of patients with RM associated with aPL did not develop a thrombotic event.

The above discussed facts may have clinical implications. The efficacy of long-term thromboprophylaxis and its associated risk of bleeding is a complex problem in aPL-positive patients who have not developed previous thrombosis or in APS patients with isolated obstetric morbidity. While most authors advocate the use of antithrombotic therapy only in patients with aPL and thromboembolic events, there is no consensus as to whether patients who have not experienced

yet any thrombotic event might also be given prophylaxis. A retrospective observational study has suggested that low-dose aspirin may be effective in the prevention of thrombosis for asymptomatic, persistently aPL-positive individuals who have additional thrombosis risk factors APS [62]. Moreover, a recently published prospective study found that hypertension and lupus anticoagulant were independent risk factors for thrombosis in aPL carriers and therefore recommend the use of thromboprophylaxis in these high-risk subjects [76].

For patients with RM and aPL, this issue cannot be solved by the scanty, incomplete, and contradictory data resulting from the studies previously reported in the literature. Therefore, further studies are warranted to assess the efficacy and risks of long-term thromboprophylaxis with low-dose aspirin and/or heparin in patients with RM associated with aPL.

Unexplained RM and Risk of Thromboembolic Events

As previously explained, only two case-control studies analyze the long-term risk of thromboembolic events in unexplained RM patients [61, 79]. Compared to APS-RM patients and/or RM patients with genetic thrombophilias, idiopathic RM patients do not seem to have a higher risk of thromboembolic events at long term [61, 79]. Nevertheless, previous studies suggested an increased risk of ischemic heart disease in RM patients [58, 60, 75]. It is important to stress that these studies did not search for acquired or genetic thrombophilias among RM patients.

Thus, according to previous studies that suggest a higher long-term risk of arterial events in individuals with RM [57, 58, 60], patients should be advised to avoid traditional cardiovascular risk factors, and physicians should individualize the risk.

Final Comments

There is new relevant information available suggesting the importance of investigating aPL in RM patients, providing the evidence that APS-RM patients may have a high risk of thrombotic events in the long term. Further studies must confirm this data and research must focus on the possibility of stratify and quantify the individual risk of thrombosis among obstetric APS patients and healthy aPL patients. This information is of high interest in order to find out which patients are candidates to chronic thromboprophylaxis.

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