REVIEW ARTICLE

Diagnosis and management of obstetrical antiphospholipid syndrome: where do we stand?

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KEY WORDS

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ABSTRACT

Obstetrical antiphospholipid syndrome (APS) is defined by obstetrical complications and the presence of antiphospholipid antibodies (aPL). Although the incidence of APS is still poorly known, this thrombophilia is now recognized as one of the most common acquired causes of recurrent fetal loss. The diagnosis of APS during pregnancy can be challenging because of its various clinical features. Mothers with APS have an increased risk of thrombosis, thrombopenia, and specific pregnancy-related complications such as preeclampsia, eclampsia, and hemolysis elevated liver enzyme and low-platelet syndrome. aPL can also lead to recurrent, early miscarriages, stillbirths, and to intrauterine growth restriction. Clinicians should be aware of all these characteristics and a thorough differential diagnosis should be performed. Testing for aPL also requires skill due to the difficulty of standardization and interpretation of tests. To know when testing should be performed and when to repeat tests are still a matter of debate. While general management and first-line treatment of APS during pregnancy now have clear guidelines, second-line treatment is still required in 30% of the cases and new strategies are currently in development. In this review, we describe the clinical and biological aspects of obstetrical APS and its current management options. As APS pregnancies can be a real challenge for clinicians, we underline the necessity of multidisciplinary counselling and close follow-up.

Introduction APS is an autoimmune disorder characterized by the presence of antiphospholipid antibodies (aPL) as well as clinical symptoms such as arterial and venous thrombosis and/or pregnancy complications. First determined in 1998, the international classification criteria have been updated in 2006 and are described in TABLE 1.[1] Adverse pregnancy outcomes are various and can lead to high morbidity for both mother and fetus.[2,3]

aPL is a family of 3 types of antibodies that bind to the cell membrane: lupus anticoagulant, anticardiolipin (aCL) antibodies, and anti-β_2-glycoprotein-1 (anti-β_2GP1) antibodies.[4,5] Laboratory tests for the presence of aPL are still a matter of debate. Poor standardization of tests leads indeed to difficulties in interpretation of the results and, therefore, in difficulties in patient's management.[6,7] Research on the specific domains of anti-β_2GP1 antibodies, such as domain I, have been proved to be interesting in case of thrombosis.[8,9]

Present obstetrical first-line treatment for APS combines low-dose aspirin with low-molecular-weight heparin (LMWH) injections during the entire pregnancy and up to 6 weeks postpartum.[10] However, it is inefficient in around 30% of the cases, indicating that the various mechanisms by which the aPL affect the pregnancy are still poorly understood.[11] Presently, no consensus guidelines have been accepted concerning second-line treatments in refractory cases, and they are usually very center-dependent.[12] The emergence of new indications for old medications, such as the use of hydroxychloroquine (HCQ) in the prevention of fetal loss, as well as the development of new strategies give hope for pregnant patients with APS resistant to common treatments.[13-15]

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TABLE 1 Criteria of obstetrical antiphospholipid syndrome.[1] Antiphospholipid syndrome is diagnosed when at least 1 of the following clinical criteria and 1 of the following biological criteria are met

Clinical criteria	Biological criteria
– 3 or more consecutive, spontaneous abortions before the 10th WG, with maternal anatomic or hormonal abnormalities, and paternal and maternal chromosomal causes excluded	– lupus anticoagulant present in plasma on 2 or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis
– 1 or more unexplained deaths of a morphologically normal fetus at or beyond the 10th WG, with normal fetal morphology documented by ultrasound or by direct examination of the fetus	– anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer, on 2 or more occasions, at least 12 weeks apart, measured by standardized ELISA
– 1 or more premature births of a morphologically normal neonate before the 34th WG because of eclampsia or severe preeclampsia or recognized features of placental insufficiency[a]	– anti-β_2-glycoprotein-1 antibody of IgG and/or IgM isotype in serum or plasma (in titer >99th percentile), present on 2 or more occasions, at least 12 weeks apart, measured by standardized ELISA

a placental insufficiency features include: abnormal or nonreassuring fetal surveillance test, abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, oligohydramnios, postnatal birth weight less than the 10th percentile for the gestational age

Abbreviations: ELISA – enzyme-linked immunosorbent assay, IgG – immunoglobulin G, IgM – immunoglobulin G, WG – week of gestation

We here describe both clinical and biological assessments of obstetrical APS. We do not deal with pathophysiological mechanisms of obstetrical APS but, on the contrary, we insist on its general management and therapeutic aspects. Finally, we discuss some therapeutic perspectives.

Epidemiology Even if aPL are found in 1% to 5% of the general population, the prevalence of APS is said to be no more than 0.5%. The Euro-Phospholipid project examined a cohort of 1000 patients diagnosed with APS and showed that there was a female-to-male ratio of 5:1. The majority of reported patients affected by APS were Caucasian (98.5%).[16] APS can equally be found alone ("isolated form" or "primary APS") or associated with other diseases, especially autoimmune diseases, systemic lupus erythematosus (SLE) being the main one (TABLE 2).[17]

Clinical aspects: when to think of APS during pregnancy? APS is an entity with various clinical aspects that can be difficult to diagnose, especially during pregnancy. We here describe the general clinical aspects of APS from the perspective of the mother and fetus and also some new considerations of APS regarding infertility and infants born from a mother with APS.

Clinical features for mother and fetus throughout pregnancy Medical complications: thrombosis Pregnancy in itself induces a hypercoagulable state, predisposing to thrombosis and particularly during postpartum period. Pregnant women have indeed a 5- to 6-fold increased risk of venous thrombosis compared with nonpregnant women of the same age.[18]

TABLE 2 Prevalence of primary and secondary antiphospholipid syndrome[17,22]

Associations	% of patients
primary antiphospholipid syndrome	53.1
systemic lupus erythematosus	36.2
lupus-like syndrome	5.0
primary Sjögren's syndrome	2.2
rheumatoid arthritis	1.8
systemic sclerosis	0.7
systemic vasculitis	0.7
dermatomyositis	0.5

According to the Euro-Phospholipid Project, deep-venous thrombosis is the main clinical feature found among APS patients.[16] Moreover, the Nimes Obstetricians and Hematologists APS (NOH-APS) study showed that purely obstetrical APS patients with no history of thromboembolic diseases (n = 517), had an increased risk of thrombosis including deep-venous thrombosis (1.46%), pulmonary embolism (PE, 0.43%), and superficial vein thrombosis (0.44%), despite low-dose aspirin treatment compared with controls (n = 796 with 0.43%, 0.12%, 0.14%, respectively).[19] This suggests that thrombotic mechanisms could be common to both obstetrical and nonobstetrical APS, although many other mechanisms have been proposed for the observed pregnancy complications (not the topic of this review paper). Therefore, general management of APS during pregnancy should also carefully include prevention of thrombosis (see *Management of obstetrical APS*).

Arterial thrombosis can also be associated with APS pregnancies.[20] Main clinical manifestations include strokes, transient ischemic attacks, and amaurosis fugax. In the NOH-APS study, cerebrovascular events were significantly higher in obstetrical APS patients compared with control patients (0.32% vs. 0.09%).[19,20]

Thrombocytopenia Autoimmune thrombocytopenia affects up to 20% to 30% of APS patients. Although it can be difficult to distinguish from idiopathic thrombocytopenia purpura (ITP), platelet count should be assessed prior to conception and throughout pregnancy.[16,20]

Moreover, as LMWH injections can sometimes induce a decrease in platelet count, some authors propose to follow platelet counts the first 3 weeks of treatment but this indication is not compulsory for others.

Cutaneous manifestations Skin conditions are frequent (36.9%) and various among APS patients. The most common is livedo reticularis, affecting around 20% of the patients.[21] It is more commonly found in secondary APS associated with SLE (36%) compared with primary APS (16%), and in women (26%) compared with men (16%).[22]

TABLE 3 Preeclampsia criteria

preeclampsia	– high blood pressure (>140/90 mmHg) associated with proteinuria (300 mg in a 24-h urine sample) after 20 WG or – increase in SBP[a] ≥30 mmHg or in DBP[b] ≥15 mmHg after 20 WG, with edema and/or proteinuria
severe preeclampsia	– presence of preeclampsia as described above and at least 1 of the following criteria: – SBP ≥160 mmHg, or DBP ≥110 mmHg on 2 occasions at least 6 h apart – proteinuria ≥5 g in a 24-h urine sample collected at least 4 h apart – pulmonary edema or cyanosis – oliguria (<400 ml in 24 h) – persistent headaches – epigastric pain and/or impaired liver function – thrombocytopenia – oligohydramnios, decreased fetal growth, or placental abruption

Abbreviations: DBP – diastolic blood pressure, SBP – systolic blood pressure, others – see TABLE 1

Leg ulcers (5.5%), pseudovasculitic lesions (3.9%), digital gangrene (3.3%), cutaneous necrosis (2.1%), and splinter hemorrhages (0.9%) can also be found.[22]

Catastrophic antiphospholipid syndrome Catastrophic APS is a rare condition, defined as a "thrombotic storm", leading to multi-organ failure caused by recurrent thrombosis of large and small vessels and high aPL titers.[23]

Among all precipitating factors (infections being the main ones), which are found in 50% of the cases, 5.6% are caused by obstetric conditions. Patients with preeclampsia and HELLP syndrome are indeed particularly at risk of catastrophic APS.[24] In a small retrospective series of 13 patients with pregnancy-related CAPS, CAPS usually followed HELLP syndrome (n = 12).[25] Therefore, clinicians should be very cautious about this potentially life-threatening condition especially when dealing with HELLP syndrome as CAPS can be lethal in about 50% of the cases.

Obstetrical complications Recurrent fetal loss and stillbirth A retrospective cohort study conducted from 1988 to 2006 on 1719 patients with unexplained recurrent miscarriages showed that there was no clear correlation between the number of preceding miscarriages and the age of the mother with APS diagnosis. However, once all risk factors for miscarriages were excluded, aPL were still responsible for 18% of recurrent miscarriages.[26] Early fetal loss is the most common fetal feature for obstetrical APS and affect around 35% of pregnancies.[22] Although quite uncommon in developed countries, stillbirth can occur in 16.9% of APS pregnancies.[22]

Prematurity and intrauterine growth restriction In the Euro-Phospholipid Project, prematurity affected 10.6% of live births.[22] A study conducted from 1990 to 1991 on 55 pregnant women with fetuses with intrauterine growth restriction (IUGR) defined as below the 10th percentile showed a strong association between fetal growth restriction and the presence of aCL.[27] Moreover, a critical review of the literature analyzed 3 prospective studies that investigated the prevalence of aPL among pregnant women with IUGR. The overall prevalence of aPL was 9.5% (interquartile range [IQR], 1.5–20.5). However, one of the main limitations of these studies was the definition of IUGR (birth weight lower than the 5th or 10th).[27]

Preeclampsia and eclampsia Preterm delivery is commonly found in 20% of APS pregnancies and mostly owing to complications such as preeclampsia.[22] Preeclampsia is a common disorder that affects 8% of pregnancies. Its definition is purely clinical and described in TABLE 3. APS is considered a risk factor for severe preeclampsia, and studies show an increase in the prevalence of aPL in this specific population.[22] Moreover, in the Euro-Phospholipid Project, 9.5% of pregnant APS were diagnosed with preeclampsia, which was the most common feature found in mothers followed by eclampsia, which complicated 4.4% of pregnancies.[26] In a critical review of the literature conducted in 2013 based on the analysis of 20 papers, aPL was seen in 4% of the cases with preeclampsia, 8% of severe preeclampsia and 16.5% of eclampsia.[28] However, there are many limitations in this review with only 50% of studies implementing the term "severe preeclampsia" and a small sample size (median, 70; IQR 29–163). Moreover, the definition of "severe preeclampsia" was only specified in 50% of the studies. Regarding biological criteria, 60% of all papers were published prior 2000, meaning that anti-β_2GP1 antibodies were not tested since they were not part of the APS definition until 2006. All 3 aPL assays were only performed in 11% of the studies. Moreover, it is now admitted that pregnant patients with a triple antiphospholipid antibody positivity are at a high risk of poor neonatal outcome.[28]

HELLP syndrome HELLP syndrome is a rare condition, the prevalence of which is still hard to estimate. It is usually secondary to preeclampsia, but can occur alone. A critical review of the literature show that only few studies have investigated the role of aPL in HELLP syndrome (n = 4).[29] Among them, the overall prevalence of aPL was 3% (CI 2–14.8) but this might have been misestimated due to the small sample size of patients.

Insights of some new clinical criteria of obstetrical antiphospholipid syndrome The role of aPL in implantation and, therefore, the implications of aPL in infertility is still controversial. A critical assessment of the role of aPL in infertility show that although numerous studies on this subject have already been made, there is still no clear answer

TABLE 4 When to test antiphospholipid antibodies in obstetrics?

– APS patient when planning to get pregnant
– pregnant patient with systemic lupus erythematous other autoimmune diseases
– patient with a history of:
– 2–3 fetal losses <10 WG not due to causes described in TABLE 1
– stillbirth
– prematurity <34 WG, due to preeclampsia or eclampsia or placental insufficiency
– intrauterine growth restriction
– abruptio placentae
– HELLP syndrome

Abbreviations: APS – antiphospholipid syndrome, others – see TABLE 1

about the association between aPL and conception disorders in patients.[30]

Therefore, testing for aPL in patients with a history of infertility or implantation failure (IVF) after in vitro fertilization is presently not recommended.

Biological aspects of antiphospholipid syndrome: when and what to test? To test or not to test? Since aPL are found in 1% to 5% of the general population, there is no indication for aPL testing in asymptomatic pregnant women, especially since aPL assays have a high rate of false-positive results.[31] Testing for aPL should be performed in patients as detailed in TABLE 4. Since the presence of aPL can be transient, once a positive result is found, it should be repeated 12 weeks later to confirm the result and consider a diagnosis of APS.

Which test? Common aPL biological tests are described in TABLE 1. Since detection of lupus anticoagulant depends on clotting times, this test should preferentially be performed when a patient is not under anticoagulants. Based on an enzyme-linked immunosorbent assay tests, only aCL and anti-β_2GP1 IgG and IgM isotypes are currently accepted as diagnostic markers for APS. The correlation between the level of aPL and the severity of clinical symptoms is debatable, and it is disputed whether weak positive aPL titers should be considered.[31]

A meta-analysis on aPL and recurrent fetal loss has showed a strong association between aCL IgG and early or late fetal loss (respectively, OR 3.56, 95% CI 1.48–8.59 and OR 3.57, 95% CI 2.26–5.65) and aCL IgM and late fetal losses only (OR 5.61, 95% CI 1.26–25.03).[32]

APL IgA have been shown to induce thrombosis in a mouse model.[33] However, the pathogenicity of aPL IgA in humans is still unclear. Recently, studies have shown that aCL and anti-β_2GP1 IgA might be potentially interesting for the diagnosis of APS in Afro-Caribbean patients.[34] In this population, aPL IgA in APS secondary to SLE have been associated with an increase in thrombosis.[35]

Other autoantigens have been incriminated in APS pathophysiology[36] Antiphosphatidylethanolamine (aPE), antiphosphatidylserine (aPS), and anti-annexin-V antibodies have been specifically reported to increase pregnancy morbidity, aPE antibodies being associated with an increase in

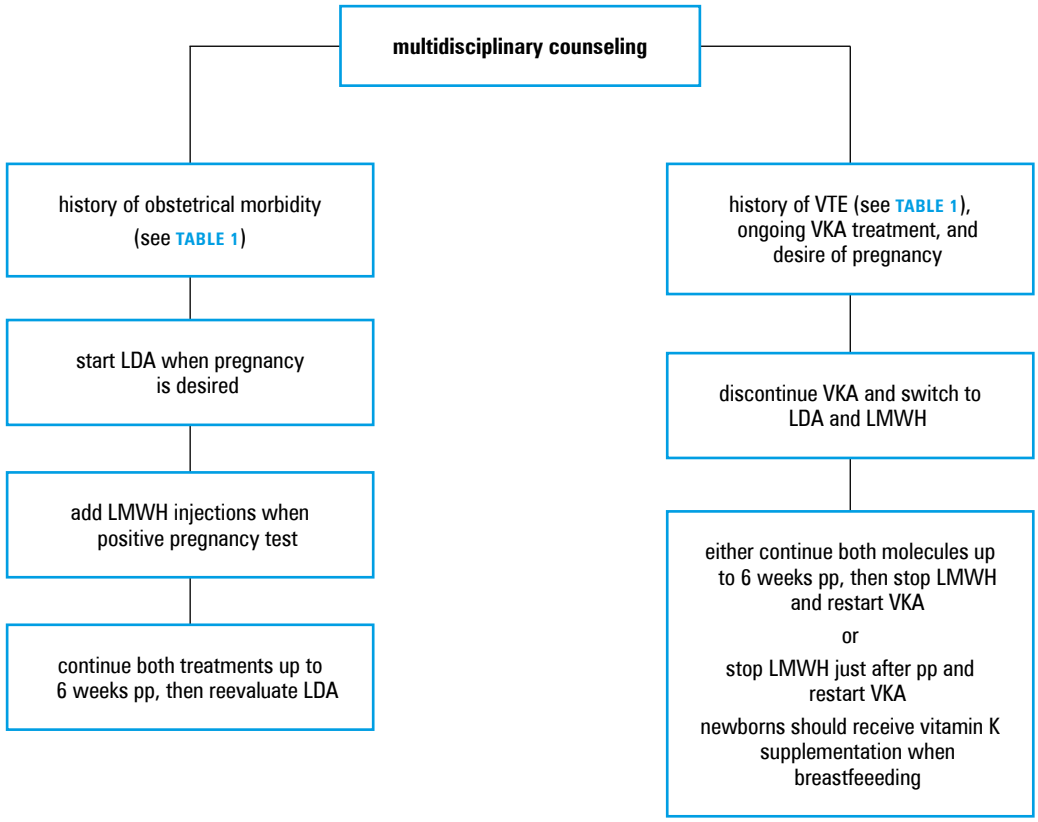

FIGURE 1 Obstetrical antiphospholipid syndrome first-line management[41]
Abbreviations: LDA – low-dose aspirin, LMWH – low-molecular-weight heparin, pp – postpartum, VKA – vitamin K antagonist, VTE – venous thromboembolism

TABLE 5 Obstetrical antiphospholipid syndrome second-line treatment[12]

Drugs	Actions	Side-effects
steroids[43]	prevention of recurrent fetal losses anti-inflammatory	when large doses: – gestational diabetes – infections – pregnancy-induced hypertension – preterm deliveries
HCQ[42]	prevention of lupic flares and cardiac congenital abnormalities prevention of recurrent fetal losses anti-inflammatory anti-aggregant immune-regulator	no side effect has been reported on babies born from mother treated with HCQ[45-47]
IVIg	severe thrombocytopenia in CAPS	urticaria fever interstitial pneumonia no data on pregnant women are available
plasmapheresis[48]	associated with low-dose prednisolone may be effective in refractory obstetrical APS	mild preeclampsia (5.5%) preterm deliveries (22.22%) IUGR (11.11%) thrombocytopenia (5.5%) oligohydramnios and fetal distress (16.6%)
B-cell targeted therapies – rituximab	primary APS CAPS	unknown
anti-TNF-α therapies – infliximab – etanercept – adalimumab	only in vivo studies on pregnant mice, showing that TNF-α activates C5 proinflammatory cascade C5-deficient mice showed a fetal protective effect[49]	unknown (possible infections and autoimmune reactions for mother, no side effects reported on fetus yet)

Abbreviations: CAPS – catastrophic antiphospholipid syndrome, HCQ – hydroxychloroquine, IUGR – intrauterine growth restriction, TNF-α – tumor necrosis factor-α

early fetal loss.[37] Recently, the Global Anti-Phospholipid Syndrome Score was determined as a risk score for thrombosis and fetal loss in SLE patients, taking into account aPS and antiprothrombin (aPS-PT) antibodies as important predictors for aPL clinical complications.[38] Akhter et al.[35] also corroborated this study for anticoagulated SLE patient in whom lupus anticoagulant assays could not be used to predict an increased risk of thrombosis.

Management of obstetrical antiphospholipid syndrome

General considerations Pregnancy is not contraindicated in women with APS. Multidisciplinary counselling with obstetricians, hematologist, general practitioners, and immunologists should be performed to plan the pregnancy and determine the risks for both mother and fetus.[2-3] FIGURE 1 describes the general management of obstetrical APS. All risk factors for thrombosis should be avoided. During pregnancy and postpartum period, close follow-up should be performed with clinical examinations, ultrasound assessments, and determination of the tolerance, the efficacy, and the eventual side effects of treatments.

There is still no indication for treating patients with a history of infertility or implantation failure after IVF and the presence of aPL.[30] However, our general practice shows that aPL can be commonly tested in this context, leading to management problems.

First-line treatment The current recommended therapeutics combine daily LDA beginning when the pregnancy is wanted with injection of LMWH injections to be started once pregnancy test is positive. Danowski et al.[10] recently established guidelines for APS treatment, and showed that there was no difference in managing APS in pregnant women with a history of recurrent early miscarriages or late fetal loss. However, our recent study showed that women with prior fetal losses treated with both molecules during pregnancy had lower early fetal loss rates but higher late complications such as PE compared with control women and APS women with recurrent early miscarriages only, suggesting that pathogenic mechanisms of aPL during pregnancy need to be better understood.[39]

In the absence of treatment, only 20% of pregnancies will develop positively. Treatment with

the recommended therapeutics of APS during pregnancy increases the chance of completing a full-term pregnancy by 70%. The European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS) has shown that this first-line treatment is correctly administered according to actual guidelines in 87.1% of pregnant APS patients.[40] FIGURE 1 summarizes the first-line management of obstetrical APS.[41]

First-line treatment has a few minor side-effects for the mother such as bruises and mild haematomas. Mild pain at LMWH injection sites may also be present.[42] To date, no side effects for the fetus have been reported. For APS patient already under oral anticoagulant (especially those with previous thrombosis history) such as warfarin, they may be switched to full-dose LMWH immediately after pregnancy confirmations because of the risk of teratogenicity of vitamin K antagonist (VKA).[10] VKA could be started again after delivery, as babies should receive oral vitamin K if breastfeeding.

Second-line treatment Second-line treatments for APS pregnancies (or "refractory obstetric APS") are often a combination of first-line treatments with more aggressive therapy. To date, no consensus have been established and these treatments are proposed essentially on a case-by-case basis.[12] Available drugs are described in TABLE 5. Among them, HCQ is the safest one.[43] This molecule is used for the reduction of flares in lupus patients and is also commonly used in secondary APS associated with SLE. It has also been shown to be effective in the prevention of fetal loss and complications, especially in patients with anti-SSA and anti-SSB antibodies.[13-14]

Although high obstetrical morbidities were described in a study, treatment with low dose of prednisolone during first trimester pregnancies (n = 18) in refractory aPL-related pregnancy loss showed a decrease in fetal loss from 30% to 9%.[44]

Since no well-designed trials have been conducted on all the secondary treatments listed in TABLE 5, careful precautions should be taken prior to their administrations.

Special considerations: preventing catastrophic antiphospholipid syndrome The best admitted treatment for CAPS is based on its prevention, therefore, postpartum period should be covered with 6 weeks of anticoagulation.[25] Once CAPS has been diagnosed, despite the lack of good studies on the treatment and the management of this entity, combined aggressive therapies, for example, with anticoagulants, corticosteroids, plasmapheresis, and rituximab are usually admitted as beneficial. Despite this, CAPS is still lethal in 50% of the cases.

Perspectives Immunomodulatory therapies, such as B-cell targeted therapies, anti-cytokines therapies and complement inhibition have shown their potential in vitro and in vivo in APS animal model and also in a few case reports.[15] However, these studies focused on their efficacy on thrombotic APS and CAPS (TABLE 5) rather than pregnancy, so their efficacy and safety during pregnancy still need to be determined and, therefore, clinical trials are required.

Take home messages

1 Obstetrical APS is a complex entity with high morbidity for both mother and fetus.

2 Its diagnosis is based on clinical symptoms and periodic aPL tests that should only be performed according to specific guidelines.

3 Management of obstetrical APS must be multidisciplinary and close follow-ups is required to prevent early complications.

4 New clinical trials should focus on new aPL tests and innovative therapeutic development.

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ARTYKUŁ ORYGINALNY

Rozpoznawanie i leczenie APS u kobiet w ciąży– aktualny stan wiedzy

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SŁOWA KLUCZOWE

ciąża, nawracające poronienia, przeciwciała antyfosfolipidowe, stan przedrzucawkowy, zespół antyfosfolipidowy

STRESZCZENIE

Ciążowy zespół antyfosfolipidowy (*antiphospholipid syndrome* – APS) definiuje występowanie niepowodzeń położniczych i przeciwciał antyfosfolipidowych (*antiphospholipid antibodies* – aPL). Wprawdzie częstość występowania APS jest wciąż słabo poznana, ale tę trombofilię uważa się obecnie za jedną z najczęstszych nabytych przyczyn nawracającej utraty ciąży. Rozpoznanie APS w ciąży może być trudne z powodu różnorodności objawów klinicznych. Matki z APS mają zwiększone ryzyko zakrzepicy, małopłytkowości i swoistych powikłań ciążowych, takich jak stan przedrzucawkowy, rzucawka i zespół HELLP (*hemolysis, elevated liver enzyme, low platelet*). aPL mogą też powodować nawracające wczesne poronienia, urodzenia martwego płodu oraz wewnątrzmaciczne ograniczenie wzrastania płodu. Lekarze powinni znać te wszystkie manifestacje i przeprowadzać dokładną diagnostykę różnicową. Badanie w kierunku aPL wymaga umiejętności wobec trudności ze standaryzacją i interpretacją badania. Nie ustalono ostatecznie, kiedy należy wykonywać badania i je kontrolować. Istnieją jednoznaczne wytyczne dotyczące ogólnego postępowania i leczenia pierwszego rzutu APS w ciąży, ale w 30% przypadków konieczne jest leczenie drugiego rzutu, a nowe metody są w trakcie badań. W niniejszym przeglądzie przedstawiono aspekty kliniczne i biologiczne ciążowego APS oraz dostępne metody leczenia. Ciąża u kobiety z APS może stanowić prawdziwe wyzwanie dla lekarza prowadzącego, dlatego podkreślono konieczność wielospecjalistycznych konsultacji i ścisłego nadzoru.

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