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Antiphospholipid Syndrome and Pregnancy: Pathogenesis to Translation

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The antiphospholipid syndrome (APS) is an autoimmune condition associated with thrombosis (venous or arterial) and adverse pregnancy outcomes. Investigation of APS began with the discovery of autoantibodies in patients with syphilis in 1906, characterized as biologic false-positives due to reactivity with anticardiolipin in 1952, and followed soon after by the identification of “circulating anticoagulants” in women with adverse pregnancy outcomes. In the 1980’s, the association of thrombosis, miscarriages, and lupus anticoagulant was discovered, and the term “antiphospholipid syndrome” was coined.

The diagnosis of APS is based on clinical obstetric and/or thrombotic history and laboratory findings of persistently-positive (on two occasions at least 12 weeks apart) antiphospholipid antibodies (aPL) (Table 1). Antiphospholipid antibodies are a heterogeneous group of autoantibodies directed against a complex antigen consisting of negatively-charged phospholipids and phospholipid binding proteins. The best recognized of these, and the aPL required to make a diagnosis of APS, are lupus anticoagulant (LAC), anticardiolipin antibodies (aCL) and anti-β_2-glycoprotein-I (aβ_2GPI) antibodies.[1] The performance characteristics of the aPL immunoassays for aCL and aβ_2GPI and the widely-recognized inter-laboratory variability in aPL results demands that reliable laboratories identify medium- or high-titer results (Table 1). Furthermore, the specificity of aCL and aβ_2GPI antibodies for APS increases with higher titers and with IgG isotype. The requirement for repeatedly positive results exists because other conditions can result in transiently positive aPL results. The presence of LAC, and in some series aβ_2GPI antibodies, are better predictors of pregnancy morbidity than aCL antibodies.[2,3] “Triple” aPL positivity (LAC, aCL, and aβ2GPI) is of greater clinical significance than double or single aPL positivity.[4]

Antiphospholipid antibodies are detectable in up to 5% of asymptomatic individuals. They are more common in patients with systemic autoimmune diseases, particularly systemic lupus erythematosus (SLE). The frequency of aPL in SLE patients is approximately 30%.[5] The association of aPL with recurrent miscarriage (pregnancy loss <10 weeks gestation) is

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variable and has recently been challenged because of flaws in historic studies, including poor standardization of assays, variability of definitions of aPL positivity, inclusion of women with other causes of recurrent miscarriage.[6] Moreover, recent studies have found no increase in frequency of high aPL in women with recurrent losses at <10 weeks.[7]

Pregnancy complications remain a frequent and challenging problem for patients with APS. The primary treatment for pregnant women with APS is focused on preventing thrombosis, but is only partially successful. Presently, greater than 80% of pregnancies result in a live birth. However, these pregnancies are at increased risk for preeclampsia (particularly early, severe preeclampsia) in 18–40%, intrauterine growth restriction (IUGR) in 5–15%, and preterm delivery, despite drugs, such as heparin and low dose aspirin.[8]

Given that the salient extra placental manifestations of APS are vascular thromboses and that occasional thrombi are present, anticoagulation has been used to prevent pregnancy morbidity. Experimental models have emphasized the role of inflammation rather than thrombosis, and histopathologic findings in placentas from women with APS argue that proinflammatory factors, rather than thrombosis, contribute to injury.[9,10] Although it is clear that the specific antigenic reactivity of aPLs and their targeting to placenta are critical to their effect, pathogenic mechanisms that damage the fetal-maternal unit and cause abnormal placental development are incompletely understood. Indeed, the *in vivo* antigenic targets of LAC, the strongest risk factor of adverse pregnancy outcomes in APS patients, are not known. The heterogeneity of aPL may lead to initiation of different pathways of injury. It is not known to what extent impaired fetal growth or fetal demise depends on aPL-initiated inflammation, aPL-triggered modulation of trophoblast or endothelial cell function, or aPL-mediated thrombosis. This review describes the pathogenic mechanisms of pregnancy complications in APS and approaches that can be brought to the clinic to prevent adverse pregnancy outcomes.

Normal placental development

The human placenta is covered by a single multinucleated cell, the syncytiotrophoblast. Shortly after implantation, mononuclear trophoblasts (cytotrophoblasts) invade from the placenta into the uterine decidua differentiating into extravillous trophoblasts. Some extravillous trophoblasts go on to invade the uterine spiral arteries, which supply blood to the decidua by digesting the muscular walls and replacing the endothelial cells that line these vessels. This invasion remodels the spiral arteries into non-vasoactive large-bore conduits.[11] By mid-gestation, the spiral arteries are remodeled through the depth of the decidua and a third of the depth of their myometrial segments (Figure 1). This remodeling allows the large and uninterrupted blood supply required during the second half of pregnancy when fetal demand is greatest. However, during the initial invasion of the spiral arteries, trophoblasts form loosely cohesive plugs in the lumen of the spiral arteries.[12] These plugs temporarily block the passage of maternal RBCs, allowing early development to occur in the absence of oxidative stress, but the plugs have channels that allow the movement of plasma to the placenta.[13] Therefore, aPL can access the syncytiotrophoblast and extravillous trophoblasts throughout the course of gestation (Figures 1 and 2).

Abnormal placental development in APS

In the major obstetric manifestations of APS including, preeclampsia, IUGR and stillbirths, there is a failure of extravillous trophoblasts to adequately remodel the spiral arteries (Figure 2). The consequence is reduced/interrupted maternal blood flow to the placenta with hypoxic/ischemic injury, inadequate delivery of nutrients to the fetus, and/or high velocity blood flow that may damage the placenta.[13] Antiphospholipid antibodies can reduce the proliferation and invasion of extravillous trophoblasts both *in vitro* and *in vivo*. Inability of trophoblasts to remodel spiral arteries is clinically silent,[14] but the resultant placental mal-perfusion may drive production of the potent antiangiogenic factors soluble fms-like tyrosine kinase-1 (sFlt1, also known as soluble VEGF receptor 1) and soluble endoglin (sEng). sFlt1 sequesters the proangiogenic factors vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), preventing their binding to trophoblast and endothelial cell VEGF receptors, and antagonizing their proangiogenic actions.[15–17] In maternal circulation, excess sFlt1 produces a deficiency of angiogenic factors required for endothelial vascular homeostasis[15] leading to clinical manifestations of preeclampsia.[18–21]

A recent meta-analysis of the histopathologic findings in controlled studies of placentae from aPL-affected pregnancies revealed five features that are associated with aPL: (1) placental infarction, (2) impaired spiral artery remodeling, (3) decidual inflammation, (4) increased syncytial knots, and (5) decreased vasculosyncytial membranes.[10] Of note, placentae of women with aPL rarely show evidence of intravascular or intervillous blood clots.[10] In the sections that follow, pathologic mechanisms for these findings will be described.

Mediators and mechanisms of aPL-induced abnormal placental development (Figure 3)

aPL interactions with trophoblasts

APL recognizing β_2GPI have been shown to be pathologic in obstetric APS, in part, because the antigen is constitutively expressed at the cell surface by all placental trophoblast subpopulations.[22] β_2GPI is also present on maternal decidual endothelial cells. β_2GPI binds human trophoblast and endothelium through the phospholipid binding site in the domain V of the molecule, as well as via various receptors. Thus, the placenta is a major target for β_2GPI-dependent pathogenic aPL binding; and subsequently aPL alter trophoblast function. Although the outer placental syncytiotrophoblast and invading extravillous trophoblast populations both bind aβ_2GPI antibodies, the syncytiotrophoblast internalizes aPL via an LDLR family member, while the extravillous trophoblast maintains aPL on the cell surface.[23,24] As will be described below, this results in distinct responses by the trophoblast subpopulations to aPL.

Impact of aPL on extravillous trophoblast function

Since adverse pregnancy outcomes are established early in gestation and women with APS have aPL prior to implantation, it is important to understand the impact these autoantibodies have on early placentation. Studies using human first trimester extravillous trophoblast cells

have shown that aPL promotes a pro-inflammatory, anti-migratory and anti-angiogenic profile similar to that seen in preeclampsia. These *in vitro* studies demonstrated that aPL recognizing β_2GPI trigger human first trimester extravillous trophoblasts to produce elevated levels of pro-inflammatory cytokines and chemokines; inhibit spontaneous trophoblast migration; increase trophoblast anti-angiogenic sEng secretion; and disrupt trophoblast-endothelial interactions in a model of spiral artery transformation (Figure 3).[25–28]

aPL-induced trophoblast inflammation

APL induce trophoblasts to secrete inflammatory IL-1β and IL-8, via activation of Toll-like receptor 4 (TLR4) and its adapter protein MyD88 (Figure 3); most likely because β_2GPI shares molecular mimicry with LPS.[25] Downstream of MyD88, IL-1β secretion is mediated by the induction of the danger signal, uric acid, which in turn activates the NLRP3 inflammasome to process IL-1β.[29] In parallel, IL-8 production downstream of TLR4 is mediated by the induction of the microRNA, miR-146a-3p, which directly activates the RNA sensing TLR8.[30] Thus, aPL-induced miR-146a-3p and uric acid act as endogenous secondary signals for trophoblast TLR8 and NLRP3 inflammasome activation, to drive trophoblast inflammation.

Reduced trophoblast migration and invasion caused by aPL

The limitation of trophoblast migration by aPL is mediated by the apolipoprotein E receptor 2 (ApoER2; also known as LRP8), a member of the LDLR family, that interacts with dimerized β_2GPI. ApoER2 expressed in human and mouse trophoblasts serves as a target for aβ_2GPI-β_2GPI complexes, and when cross-linked leads to reduced pro-migratory IL-6 and STAT3 activity.[26,31] Complementing these observations, *in vivo* studies also demonstrated a role for ApoER2 in aPL-mediated fetal loss and IUGR.[31]

aPL increase production of dangerous extracellular vesicles from the syncytiotrophoblast

A common feature of aPL-affected placentae is increased syncytial knots.[10] These are aggregations of nuclei in the syncytiotrophoblast that some workers believe are markers of aged/damaged portions of the syncytiotrophoblast that will be shed from the placenta as large extracellular vesicles called, syncytial nuclear aggregates (SNAs).[32] APL, internalized by the syncytiotrophoblast, disrupt mitochondria triggering aberrant cell death that leads to the shedding of dangerous SNAs that activate the maternal vasculature.[33] Exosomes (small extracellular vesicles) released by aPL-exposed extravillous trophoblasts contain elevated levels of the TLR8-activator, miR146a-3p.[30] Furthermore, uptake of trophoblast-derived vesicles by endothelial cells changes the transcriptome and proteome of the maternal vasculature.[34]

Effect of aPL on syncytiotrophoblast function

The syncytiotrophoblast produces human chorionic gonadotropin (hCG). APL reduce the growth of the syncytiotrophoblast *in vitro* resulting in decreased production of hCG.[35] The ability of aPL to prevent the formation of new syncytiotrophoblast and increase cell death, suggests a reduction in overall functional syncytiotrophoblast leading to reduced

transplacental transport, a concept supported by decreased levels of the cholesterol transporter ABCA1 in APS placentae.[36]

Inflammation at the maternal-fetal interface and maternal vasculature

Mouse models have been instrumental in defining pathogenic mechanisms of aPL-mediated pregnancy complications. Passive transfer of IgG from APS patients with high titers of aPL, or monoclonal human aPL, into pregnant mice results in fetal resorptions and growth restriction, recapitulating obstetric APS in women.[37] Using this model, we determined that aPL localize to placentae and that inflammation, particularly complement activation and recruitment and stimulation of neutrophils, is an essential and causative factor in placental insufficiency, fetal loss and IUGR.[31,38] Activation of complement stimulates infiltrating leukocytes to release TNF-α and sFlt1, which are both associated with impaired placentation and development of preeclampsia.[39–41]

Neutrophils

β_2GPI-specific antibodies recognize β_2GPI bound to the cell surface of neutrophils, and stimulate neutrophil extracellular trap (NETs) formation through ROS- and TLR4-dependent mechanisms.[42] Like SLE, patients with APS show enhanced NET formation, impaired NET clearance, and higher numbers of circulating low density granulocytes that have an increased capacity to produce cytokines and type I IFNs.[42] Increased numbers of NETs are found infiltrating placental intervillous spaces, in association with inflammatory and vascular changes, in patients with SLE and with preeclampsia.[43]

Mouse models confirm a critical role for neutrophils in abnormal placental and fetal development. Pregnant mice treated with aPL show neutrophil infiltration in the placenta, and deleterious effects of aPL on fetal survival and growth are abolished by neutrophil depletion (Figure 3).[38] Similarly, in antibody-independent mouse models of preeclampsia, neutrophils infiltrate the placenta and their depletion improves placental morphology, recovers spiral artery remodeling and rescues pregnancies.[41] In both aPL-dependent and aPL-independent models, recruitment of neutrophils is triggered by complement activation at the maternal/fetal interface, and leads to elevation in local TNF-α levels, reduction of VEGF, and, ultimately, abnormal placentation and fetal death.

Complement activation

Mice deficient in alternative and classical pathway complement components and mice treated with various inhibitors of complement activation are resistant to fetal injury induced by aPL,[37,38] indicating that both pathways contribute to damage (Figure 3). Indeed, the effectiveness of heparin, usually administered at sub-anticoagulant doses may be, in part, because of its capacity to inhibit complement activation. In aPL-treated mice, anticoagulation with hirudin or fondaparinux was not sufficient to prevent pregnancy complications.[44] That complement-mediated injury is a common pathogenic mechanism that drives abnormal placental development is underscored by studies in antibody-independent mouse models of preeclampsia, as well as mouse models of miscarriage, which show that blockade of complement activation rescues pregnancies.[40,41]

Studies in women support the role of complement in pregnancy complications in APS and in non-autoimmune women. Complement fragment C4d, a marker of classical pathway activation, is present in placentae from women with SLE and/or APS and women with preeclampsia.[10,45,46] Inherited hypofunctional variants of complement regulators provide increased risk for preeclampsia in women with SLE and/or aPL.[47] Finally, two studies have shown mild hypocomplementemia in patients with primary APS.[48,49]

TNF-α and other inflammatory mediators downstream of complement activation

TNFα is a mediator that links complement C5a-C5aR interactions and pathogenic aPL to fetal damage (Figure 3). APL, specifically targeted to decidual tissue, cause a rapid increase in decidual and systemic TNF-α levels. C5-deficient mice show no increase in TNF-α and are protected from fetal death, identifying TNF-α as a critical intermediate downstream of C5 activation.[39] That TNF-α is itself pathogenic is suggested by studies showing that miscarriage induced by aPL is less frequent in mice deficient in TNF-α or treated with TNF-α blockade (Figure 3).[39] Furthermore, in antibody-independent models of preeclampsia, complement activation at the maternal-fetal interface leads to increased TNF-α, reduction of VEGF, abnormal placentation and fetal death.[41]. Blockade of complement activation or blockade of TNF-α improves spiral artery remodeling and rescues pregnancies.[41] Evidence that TNF-α contributes to the pathogenesis of adverse pregnancy outcomes in humans includes increased TNF-α in maternal blood and amniotic fluid in preeclamptic patients[50,51] and elevated TNF-α at the fetal-maternal interface in IUGR.[52]

C5a also triggers fetal damage through induction of tissue factor (TF) (Figure 3). APL increase TF in neutrophils which enhances oxidative burst and, thus, provides a mechanism for trophoblast injury and pregnancy loss.[53] Finally, complement activation products, particularly C5a, may cause an imbalance of angiogenic factors required for normal pregnancy by triggering release of anti-angiogenic factors (sFlt1).[40]

IFN-α and maternal vascular vulnerability

Interferon (IFN)-α is a potent antiangiogenic and vasculopathic factor that causes down-regulation of pro-angiogenic molecules and decreases hematopoietic progenitor cells involved in vascular remodeling both of which lead to impaired vasculogenesis.[54,55] IFN-α plays a central role in the pathogenesis of SLE.[56] SLE patients destined to develop preeclampsia are more likely to have increased circulating IFN-α before the onset of clinical symptoms compared to normotensive women, whereas in non-autoimmune patients, preeclampsia is not associated with elevated IFN-α.[57] *In vitro* and *in vivo* studies suggest that elevated IFN-α contributes to the pathogenesis of preeclampsia by sensitizing maternal endothelium to the antiangiogenic effects of sFlt1 and by inhibiting transcription of proangiogenic VEGF necessary for homeostasis in some vascular beds. Endothelial cell-trophoblast interactions are impaired in the presence of elevated IFN-α, a potential basis for inadequate spiral artery remodeling, and the resultant placental and angiogenic dysfunction of preeclampsia. Elevated IFN-α may identify lupus patients at increased risk for placenta-mediated pregnancy complications. Indeed, the increased frequency of preeclampsia in patients who have active SLE early in pregnancy, particularly active nephritis,[58,59] may be related to vasculopathic effects of elevated IFN-α present in many such patients.

Prediction of adverse pregnancy outcomes in APS and SLE

Biomarkers altered early in pregnancy are needed to identify, counsel and manage APS patients at high risk of adverse pregnancy outcomes. The **PROMISSE** Study (**P**redictors of p**R**egnancy **O**utcome: bio**M**arkers **I**n antiphospholipid antibody **S**yndrome and **S**ystemic Lupus **E**rythematosus) is the largest multi-center, multi-ethnic and multi-racial study to prospectively assess clinical and laboratory predictors of adverse pregnancy outcomes in SLE and/or APS women with inactive or mild/moderate activity at conception. Using data and samples from PROMISSE, we have evaluated molecules related to pathways of aPL-induced injury as biomarkers for placental insufficiency and poor pregnancy outcomes.

Antiangiogenic factors

In the maternal circulation, excess sFlt1 produces a deficiency of angiogenic factors required for vascular homeostasis. Prospective studies in otherwise healthy women demonstrate angiogenic dysregulation up to 5 weeks before clinical manifestations of preeclampsia[19]. An imbalance between circulating antiangiogenic and proangiogenic proteins is also associated with IUGR and fetal death[60] in non-autoimmune patients. By 12–15 weeks, sFlt1, PlGF, and sEng levels were markedly altered in patients with SLE and/or aPL destined for severe adverse pregnancy outcomes: early preeclampsia, fetal/neonatal death, or indicated pre-term delivery before 30 weeks.[61] At 16–19 weeks, SLE and/or aPL patients with both PlGF in lowest quartile and sFlt1 in highest quartile had over 30 fold increased risk of severe adverse outcomes, and if LAC or history of high blood pressure was also present the rate was 94%. Importantly, circulating angiogenic factors measured during early gestation have a high negative predictive value in ruling out the development of severe adverse outcomes.[61]

Complement activation

Complement activation is prevalent and may function as a source of procoagulant and inflammatory cell activation in APS patients.[48] In non-autoimmune patients, activation of the alternative pathway of complement, evidence by increased circulating levels of Bb fragment, is associated with preeclampsia and preterm birth.[62] In pregnant patients with SLE and/or aPL, elevated levels of complement activation fragments and smaller increases in C3 level than those that typically occur in normal pregnancies predict adverse outcomes.[63]

Uric acid

Until recently, elevation in serum uric acid in patients with pregnancy complications, such as preeclampsia, was thought to be a marker of renal dysfunction. However, new evidence suggests that the placenta may contribute to the increase in circulating uric acid. In vitro studies reveal that aPL increase trophoblast uric acid production.[29] In women with aPL and adverse pregnancy outcomes, serum uric acid levels mid-gestation were significantly higher than those without adverse outcomes.[29] In women with mild-moderate SLE, increased levels of uric acid at mid-gestation correlated with preterm birth.[64]

Exosomal miR-146a-3p

In patients with aPL and adverse pregnancy outcomes, circulating exosomes contained higher levels of the TLR8 activator, miR-146a-3p, than those of healthy controls. Exosomes

from patients with SLE and poor pregnancy outcomes, but without aPL, also contained higher miR-146a-3p compared to healthy controls. Thus, both APS and SLE may be associated with this TLR8-activating miR during pregnancy and the source may be the placenta.[30]

Potential targets to prevent obstetric APS

Antithrombotic therapies

Despite the administration of conventional antithrombotic treatment (heparin alone, or in combination with low-dose aspirin) pregnant women with APS continue to experience adverse outcomes. Although aspirin does not alter the effects of aPL on trophoblast function *in vitro*, there may be some clinical benefits.[63,65] Stable analogs of aspirin-triggered lipoxins (ATL) that resolve inflammation may have potential clinical use. The ATL, 15-epi-lipoxin A4, *in vitro* reversed inhibitory effects of aPL and sera from APS patients on trophoblast migration and trophoblast-endothelial cell interactions.[28]

The use of heparin stemmed from the notion that obstetric APS is a pro-thrombotic disorder, but heparin certainly influences other pathways related to pregnancy.[25,44] Clinical and experimental studies have produced contradictory results regarding the effectiveness of LMWH in preventing aPL-associated adverse pregnancy outcomes, and in being able to reverse the detrimental effects of aPL on trophoblast function *in vitro*.[66,67] Moreover, heparin promotes placental release of anti-angiogenic sFlt1.[27,68] Even with LMWH administered early in pregnancy, the incidence of late-gestation complications, such as preeclampsia, placental insufficiency, and IUGR, remains high. A recent meta-analysis of trials using low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications found no benefit.[69]

Inhibition of aPL binding (Table 2)

APL can react with epitopes in all five domains of β_2GPI, although there is particular interest in antibodies directed against domains I and V. The immunodominant domain of β_2GPI is domain I (D1). Binding of β_2GPI to human trophoblast and endothelium is through the phospholipid-binding site in domain V. The current view holds that β_2GPI binds to exposed anionic phospholipids (or to other receptors) on the cell surface and undergoes a conformational change that permits binding of the antibodies to a cryptic epitope, resulting in dimerization of the antigen and stabilization of the complex. Alternatively, adhesion of β_2GPI to the cell surface may increase the antigen density, thereby favouring binding of low avidity aPL. Blockade of β_2GPI binding to trophoblasts or blockade of aβ_2GPI binding to β_2GPI are theoretical targets to prevent adverse pregnancy outcomes. A synthetic peptide, TIFI, shares a similar sequence with the β_2GPI phospholipid-binding site and displaces β_2GPI from the cell surfaces, thus inhibiting aPL binding. Repeated infusions of TIFI in pregnant mice protected them from complications induced by administration of human aPL.[70] Recombinant D1 peptides, or recombinant mutant D1 with enhanced aPL binding properties, block aPL binding and inhibit aPL-induced pathogenicity.[71] Similarly, a monoclonal antibody (1N11) blocks the interaction of β2GPI with apoER2, thereby attenuating aPL-related pregnancy complications in mice.[72] Finally, a non-complement-

activating monoclonal aPL reactive with D1 (MBB2ΔCH2) competes with anti-β_2GPI antibodies from APS patients preventing in vitro pathogenic effects of aPL and rescuing mouse models of obstetric APS.[73]

Blockade of inflammatory mediators (Table 2)

Given the apparent role of placental miR-146a-3p mediated TLR8 activation and uric acid driven inflammasome activation in the placenta in response to aPL,[29,30] inhibition of these pathways may be beneficial.

Chloroquine is a TLR7/8 inhibitor and is used safely during pregnancy, even in the first trimester, primarily as an anti-malarial treatment.[74,75] Hydroxychloroquine is used clinically to treat patients with lupus and APS and to try to prevent congenital heart block in at risk pregnancies.[75] Chloroquine has been shown to inhibit the internalization of aPL into the syncytiotrophoblast and consequent production of dangerous SNAs.[23] Hydroxychloroquine has also been found to reverse the effects of aPL on annexin A5 and coagulation on the surface of trophoblasts, and it prevents the effects of aPL on trophoblast migration, hCG secretion and fusion.[35,76,77]

Allopurinol is a xanthine oxidase inhibitor and prevents NLRP3 inflammasome activation by inhibiting production of uric acid.[78] Studies in the placenta have focused on the ability of allopurinol to reduce oxidative stress;[79] however, its ability to reduce inflammation in pregnancy has not been addressed. Allopurinol is also safe to use during pregnancy, and by crossing the placenta may also provide neuroprotection for the developing fetus by preventing oxidative stress.[80] Since placental inflammation has been linked to prenatal brain injury, and IL-1β is a key mediator,[81] preventing placental inflammasome activity may not only protect against adverse pregnancy outcomes, but may also provide protection against inflammation-induced fetal injury.

Statins have pleotropic anti-inflammatory and anti-thrombotic effects. Although pravastatin did not prevent aPL-mediated changes in human first trimester trophoblast function *in vitro,*[82] statins have been shown to decrease biomarkers of inflammation in APS, reverse markers of angiogenic dysregulation and, as an adjunct to heparin and low-dose aspirin, may attenuate aPL-associated pregnancy complications in patients.[83,84]

Current strategies to block complement mediated injury include inhibition C5 cleavage, blockade of C5a-C5aR interactions and prevention of alternative pathway activation with monoclonal antibodies or small molecules. Eculizumab, a monoclonal antibody that prevents C5 cleavage, has been used in pregnant women with paroxysmal nocturnal hemoglobinuria and patients with catastrophic APS.[85] It has also been suggested that hydroxychloroquine prevents placental abnormalities by inhibiting complement.[86]

TNF-α is a critical effector of abnormal placental development and fetal damage in mouse models, and TNF-α blockade restores angiogenic balance, spiral artery remodeling and rescues pregnancies.[39,41] There is evidence that TNF-α contributes to the pathogenesis of adverse outcomes in humans.[50–52] Importantly, anti-TNF-α agents are available and have proven safe in pregnancy.[87] The IMPACT Study (Improve Pregnancy in APS with

Certolizumab Therapy) is a recently initiated, open label single-stage Phase II trial to evaluate the effect of certolizumab, a TNF-α inhibitor that does not cross the placenta and has been shown to be well tolerated in pregnancy, on reducing the risk of adverse pregnancy outcomes in high risk pregnancies in women with APS.

Conclusions

aPL have emerged as triggers of innate immune inflammatory pathways within trophoblasts and at the maternal-fetal interface. No longer simply pro-thrombotic autoantibodies that activate endothelial cells and platelets, aPL have been discovered to bind trophoblasts and disrupt their normal function. Localized to trophoblasts via β_2GPI, aPL activate membrane receptors and intracellular danger sensors to initiate inflammation, similar to other autoantibodies; but in the case of aPL, the victim is the developing placenta with adverse consequences for the fetus and mother. Elucidation of these injurious pathways has revealed several potential approaches that use therapies that are currently available or that are in development, to prevent the inflammation and trophoblast dysfunction that lead to adverse pregnancy outcomes. That these new therapeutic options are emerging as a result of increased understanding of the mechanisms by which aPL cause disease, highlights the need for high quality mechanistic investigations. As we discover more about the mechanisms of pathogenesis, we will become better at predicting and preventing obstetric APS.

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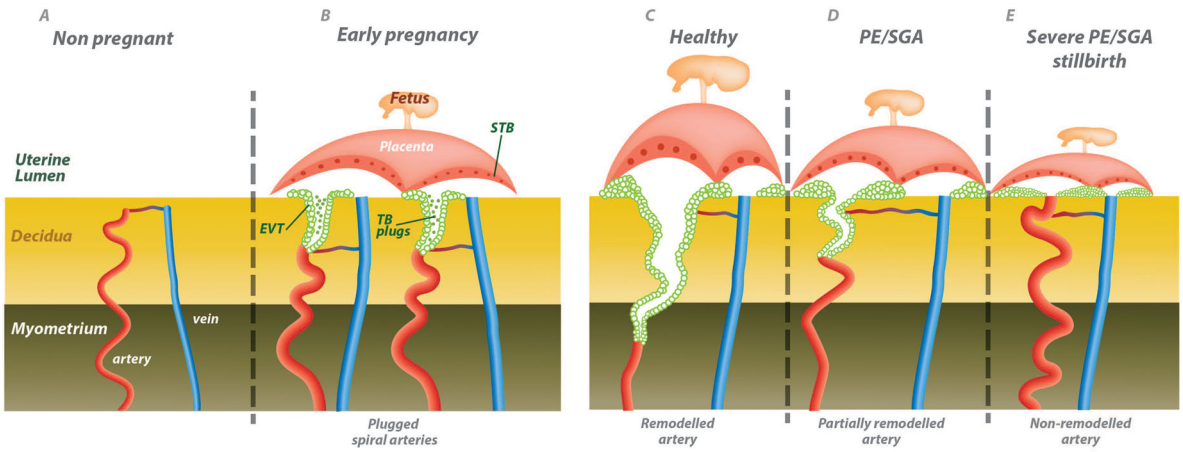

Figure 1. Variations of normal and pathologic remodelling of the spiral arteries

(A) A non-pregnant uterus showing the tightly coiled spiral arteries with musculo-elastic walls that connect, via capillary beds, to the decidual veins, (B) A pregnant uterus in the first trimester where extravillous trophoblasts (EVT; in green) have invaded from the placenta into the spiral arteries and started to remodel the vessels removing the musculo-elastic walls. At this early stage, the invasive trophoblasts form loosely cohesive plugs (TB plugs) that occlude maternal red blood cells but permit the passage of plasma allowing aPL to access the syncytiotrophoblast (STB) and invading cytotrophoblasts. (C) A pregnant uterus at mid-gestation, in a normal pregnancy, with the spiral arteries (there are 30–50 affected arteries) remodelled by invading trophoblasts to 1/3rd of the depth of the myometrium. (D) A uterus at mid-gestation with only partially remodelled spiral arteries that remain tonically active, reducing blood flow to the placenta which leads to preeclampsia (PE) and/or small for gestational age (SGA) fetuses/newborns. (E) A uterus at mid-gestation with very limited remodelling of the spiral arteries with severely reduced volume and increased velocity of blood flow to the placenta, leading to severe placental damage, PE, SGA, and/or stillbirth.

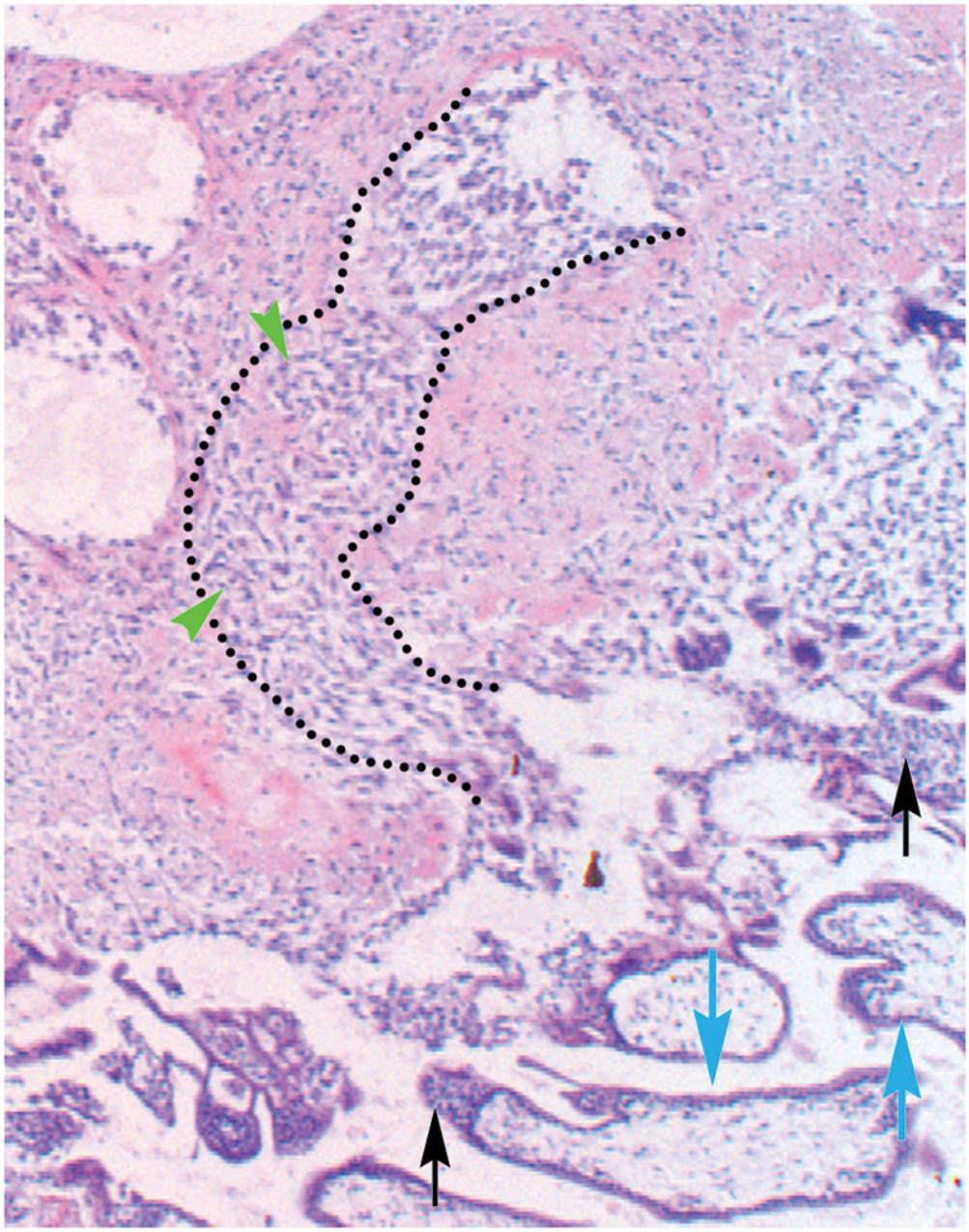

Figure 2.

Haematoxylin and eosin stained photomicrograph of the maternofetal interface/implantation site of a first trimester pregnancy showing a spiral artery (outlined by the dotted lines) that is plugged by trophoblasts (green arrows) that have invaded the artery from the placenta (black arrows). The wall of the artery has been removed by the invading trophoblasts. Villi that make up the body of the placenta and float in the maternal blood are completely covered by the syncytiotrophoblast (blue arrows).

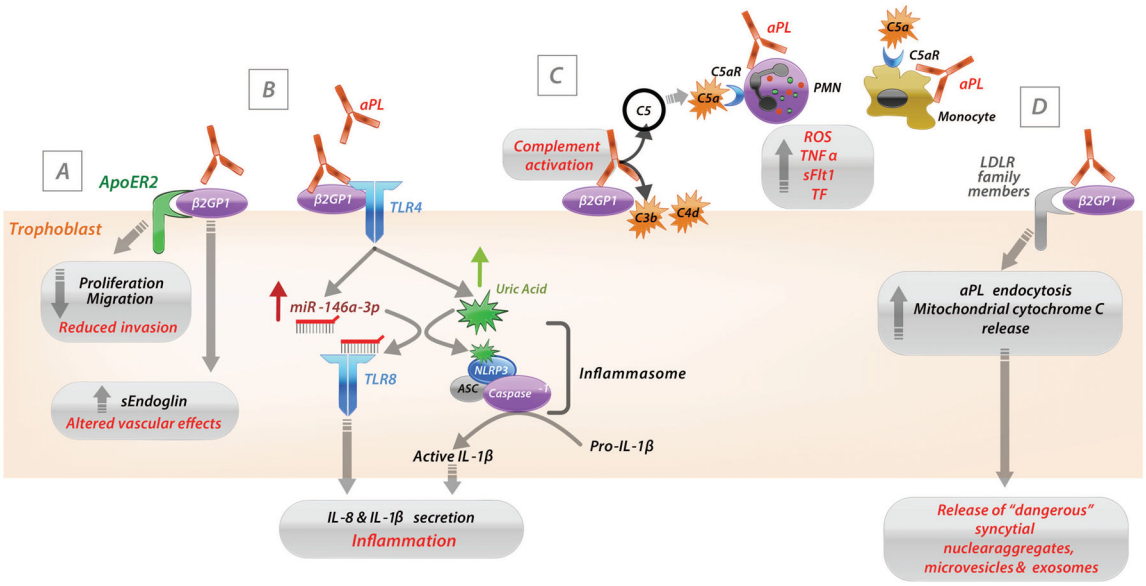

Figure 3. Effect of antiphospholipid antibodies on trophoblast cells

Antiphospholipid antibodies (aPL) recognizing beta$_2$ glycoprotein I (β_2GPI) expressed by the trophoblast: (A) promotes an anti-angiogenic profile and through apolipoprotein E receptor 2 (ApoER2) reduces cell proliferation and migration; (B) triggers secretion of inflammatory cytokines and chemokines by activating toll-like receptor (TLR) and inflammasome pathways; (C) activates complement on the cell surface leading to neutrophil (PMN) and monocyte activation with release of reactive oxygen species (ROS), TNF-α, anti-angiogenic factors (sFlt1) and tissue factor (TF); and (D) become internalized via low density lipoprotein receptor (LDLR) family members and in turn promote mitochondrial disruption and the deportation of "dangerous" syncytial nuclear aggregates and other microvesicles/exosomes.

Table 1

Revised classification criteria for the antiphospholipid syndrome

Antiphospholipid antibody syndrome is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met*
Clinical criteria
1. Vascular thrombosis One or more clinical episodes[Δ] of arterial, venous, or small vessel thrombosis[◊], in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (ie, unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity **a.** One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus; or **b.** One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe preeclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency[§]; or **c.** 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. In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.
Laboratory criteria[¥]
1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies).
2. Anticardiolipin antibody (aCL) of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (ie, >40 GPL or MPL, or > the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA.
3. Anti-beta-2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures.

IgG: immunoglobulin G; ELISA: enzyme-linked immunosorbent assay. aPL: antiphospholipid antibodies.

[Δ]A thrombotic episode in the past could be considered as a clinical criterion, provided that thrombosis is proved by appropriate diagnostic means and that no alternative diagnosis or cause of thrombosis is found.

[◊]Superficial venous thrombosis is not included in the clinical criteria.

[§]Generally accepted features of placental insufficiency include: (i) abnormal or non-reassuring fetal surveillance test(s), eg, a non-reactive non-stress test, suggestive of fetal hypoxemia; (ii) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, eg, absent end-diastolic flow in the umbilical artery; (iii) oligohydramnios, eg, an amniotic fluid index of 5 cm or less; or (iv) a postnatal birth weight less than the 10th percentile for the gestational age.

[¥]Investigators are strongly advised to classify APS patients in studies into one of the following categories: I, more than one laboratory criteria present (any combination); IIa, LA present alone; IIb, aCL antibody present alone; IIc, anti-b2 glycoprotein-I antibody present alone.

From: Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006; 4:295. http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2006.01753.x/abstract.

Table 2

Potential targets and therapies to prevent obstetric APS

Approach	Target	Therapy
Block binding of β_2GPI to trophoblast cell surface	Binding site for domain V of β_2GPI	• TIFI peptide
Block binding of β_2GPI to ApoER2 on trophoblasts	β_2GPI binding site	• 1N11 monoclonal antibody
Block binding of aPL (aβ_2GPI) to β_2GPI	Binding site for domain I of β_2GPI	• Domain I peptides • Anti-domain I monoclonal antibody (MBB2ΔCH2) that fails to activate complement
Block activation of intracellular danger sensing pathways	TLR7/8 Inflammasome	• Hydroxychloroquine • Xanthine oxidase inhibition
Inhibit inflammatory mediators	Complement pathway TNF-α Angiogenic regulation	• Block C5 • Block C5aR • Block alternative pathway activation (factor D, factor B) • Anti-TNF-α monoclonal antibodies or soluble TNF-α receptors • Statins