17 Obstetric Antiphospholipid Syndrome

T. Flint Porter, Robert M. Silver, and D. Ware Branch

Introduction

Clinicians first recognized that pregnancy loss was associated with antiphospholipid antibodies (aPL) in the latter third of the last century. The term *antiphospholipid syndrome* (APS) was introduced in 1986 [1] to formalize the association of aPL with pregnancy loss, as well as with thrombotic events. Over a decade of subsequent international laboratory and clinical experience led to the development of an International Consensus Statement on preliminary criteria for definite APS published in 1999 [2]. There is widespread recognition, however, that refining the diagnostic criteria of APS is an ongoing process [3]. In this regard, no area has generated more controversies than obstetric APS, in part because of the substantial differences in patient selection for various studies. The purpose of this chapter is to critically analyze the relationship between aPL and obstetric problems, as well as to outline appropriate management strategies when aPL are found in association with pregnancy loss.

Pathogenesis of Obstetric Problems in APS

The potential complications of pregnancy in women with APS include pregnancy loss (including fetal death and recurrent pre-embryonic and embryonic losses), pre-eclampsia, and placental insufficiency. All have been ascribed to abnormal placental function, probably resulting from maldevelopment of the uteroplacental circulation. Extensive infarction, necrosis, and thrombosis were identified in placentas from failed pregnancies in women with aPL in early reports [4–7]. A large case-control study subsequently confirmed these findings, reporting thrombosis or infarction in 82% of placentas from women with aPL and fetal death [8]. A spiral arterial vasculopathy in decidual vessels also has been linked to aPL-related fetal loss [4, 7]. It must be said, however, that the histological abnormalities seen in APS cases are non-specific. The decidual vasculopathy described in some APS cases, which is characterized by acute atherosis, intimal thickening, fibrinoid necrosis, and an absence of the normal physiologic changes in the spiral arteries, also has been associated with pre-eclampsia and fetal growth restriction [9]. Furthermore, such findings are not always present in gestational tissues of women with APS [10].

How does maldevelopment of the uteroplacental circulation occur in APS? The first investigators in the field assumed that the recognized hypercoagulability of APS was in some way impacting the uteroplacental circulation. Interestingly, initial opinion held that *acute* placental thrombosis in the second or third trimester might be the culprit in APS-related placental insufficiency, or might be the final precipitating event in fetal loss or fetal distress. Numerous possible mechanisms of thrombosis at the level of the maternal decidua and in the intervillous space have been considered. Unfavorable alterations in the prostacyclin–thromboxane pathway [11] and increased tissue factor expression [12, 13] have been implicated. An effect on the protein C pathway is also a possible mechanism, particularly because antigenic and functional levels of protein S decline in normal pregnancy and some pregnant women develop acquired protein C resistance. Recent investigations have shown that aPL disrupt the "antithrombotic shield" on trophoblasts formed by annexin V, a protein with potent anticoagulant activity based on its high affinity binding to anionic phospholipids, which, in turn, displaces coagulation factors from phospholipid surfaces. Importantly, annexin V is very highly expressed by trophoblastic cells, making it a prime candidate for aPL at the level of the placenta. Decreased annexin V has been found on the villi of APS placentas [14], and aPL have been shown to reduce annexin V expression on placental villi and cultured trophoblast [14–16]. Finally, sophisticated techniques have been used to show that monoclonal aPL disrupt the crystal formation of annexin V on phospholipid bilayers [17].

A number of non-thrombotic mechanisms by which aPL might cause placental maldevelopment have also been proposed. Some investigators have found that aPL appear to damage or hamper the normal biology of trophoblasts [18–20]. A particularly attractive candidate mechanism for early pregnancy loss as well as placental insufficiency in later pregnancy is aPL-mediated inhibition of trophoblast invasion [19].

Within the last several years, two lines of experimental evidence suggest a more traditional autoimmune inflammatory role for aPL in the placental damage and maldevelopment. Because aPL also cross-react with oxidized low-density lipoprotein (LDL), a role for oxidant-mediated injury of placental vascular endothelium has been suggested [21]. This is topical because of current interest in oxidative stress as a causative or contributing factor in placental insufficiency, pre-eclampsia, and fetal growth restriction [22]. LDL can be oxidized by trophoblastic cells, as well as other cells present at the maternal–fetal interface [23]. Oxidized LDL itself can inhibit trophoblast invasion in vitro [24]. Inconsistent findings and a lack of direct evidence at the maternal–fetal interface are lingering problems with this concept, at least in terms of adverse fetal outcome. Nonetheless, one can't help but wonder whether aPL might be generated in susceptible individuals by this process of oxidative stress with oxidation of LDL.

Recent work in mice suggests that complement activation is crucial to aPL-related fetal death and fetal growth restriction [25, 26]. This murine model employs passive immunization with polyclonal human aPL IgG or monoclonal aPL and is associated with a substantial rate of fetal death and fetal growth restriction. Local (placental) IgG and C3 deposition are seen with aPL immunization, and there is a robust infiltration with neutrophils. Blocking C3 *convertase* and C5–C5a receptor interactions prevent aPL-mediated pregnancy complications in this model. Also, genetically engineered mice deficient in C3, C4, or C5 and mice depleted of neutrophils are protected. It is worth noting that studies of human placentas from