29 Placental Pathology in Antiphospholipid Syndrome

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Introduction

Autoimmune disease, both organ and non–organ specific is associated with increased fetal wastage and/or infertility [1–3]. Fetal wastage was one of the earliest clinical features recognized as part of antiphospholipid syndrome (APS) [4–6] and even though the pathogenesis of APS fetal loss is not completely understood, it appears to be a consequence of placental failure as fetal abnormalities are rarely found. Failure to complete pregnancy successfully is one of several criteria used to define APS [7] .

Both early recurrent and late unexplained pregnancy failure are now recognized as clinical features of APS. Ware Branch has suggested that fetal wastage should be divided into pre-embryonal, embryonal, and fetal (more than 10 weeks' gestation), and has concluded that more than 70% of fetal wastage (more than 10 weeks' gestation) occurs in women with APS [8]. Fetal wastage in normal women who happen to have antibodies to negatively charged phospholipids is about 10% [9], but women with APS can expect a fetal loss rate of 80% [10]. Many of these women will experience recurrent fetal wastage with some of them never successfully completing pregnancy [11]. Other obstetric problems that occur in patients with APS include prematurity and pre-term delivery (less than 36 weeks' gestation) as well as intrauterine growth restriction (IUGR) and hypertension including pre-eclampsia and toxemia of pregnancy [11–13].

For pregnancy to proceed normally the placenta must be allowed to develop and grow appropriately so that an adequate blood supply is available to support and promote the growth of the developing fetus. Failure of the normal uterine physiological changes to occur and the development of intra-placental pathology will ensure placental insufficiency and the features that accompany a failing placenta, that is, intra-uterine growth retardation, pre-term delivery (prior to 36 weeks' gestation), pre-eclampsia, and toxemia of pregnancy. All of these clinical features occur more frequently in APS than in normal pregnancies [11–13], although a recent study of women with a previous history of pre-eclampsia did not find aPL more frequently in those women who developed recurrent pre-eclampsia in a subsequent pregnancy [14].

These clinical associations as well as the recurrent fetal loss suggest that there may be multiple pathologies that complicate and disrupt pregnancy in patients with

phospholipid antibodies. This chapter will describe the known pathological changes that have been described in the placentas of patients with APS, and will discuss the potential mechanisms that may contribute to this pathology.

Antiphospholipid Syndrome

The basic pathological process found in APS is that of a bland thrombosis in both the arterial and venous systems [15]. Even though this syndrome is almost certainly an antibody mediated process, thrombosis is the primary pathology. Animal studies reproducing human disease using passive immunization with aPL-positive immunoglobulin [16, 17] and active immunization with β_2-glycoprotein I [18, 19] suggest that these antibodies are directly involved in the thrombotic process.

The precise pathogenesis of the thrombotic diathesis associated with aPL remains unknown. It is now known that certain proteins are required as co-factors for the binding of antibody to negatively charged phospholipid and that some of these protein co-factors are natural anticoagulants [20, 21] or components of the coagulation cascade [22]. The recognition that some aPL require a protein co-factor to augment binding to phospholipid antibodies has helped explain some features [20–22]. However, as it is apparent that these antibodies are a family of antibodies [23] and that the required proteins can also vary [20–22], it would seem that one explanation for the thrombotic diathesis probably will not suffice. A full discussion of the potential prothrombotic mechanisms in aPL is presented in other chapters in this book and will not be presented here.

Approximately 50% of patients with APS who have experienced a clinical thrombosis will re-thrombose [24, 25], and several retrospective studies have suggested that the only way to prevent re-thrombosis in APS patients is to treat these patients with high dose, life long anticoagulation [25, 26], although a recent study has suggested that international normalized ratios (INRs) less than 3 may be adequate [27]. Some patients have persistent aPL for many years and yet they only develop clinical thrombotic events when they are exposed to certain pathological or physiological events. This has lead to the concept that a "second hit phenomenon" is needed in these patients. We feel that it is extremely important to identify specific known triggers for specific patients (Table 29.1). One of these known triggers is pregnancy and the postpartum period, a complication which makes pregnancy a rather dangerous time for patients with APS. Some patients only thrombose when they are pregnant, or during the postpartum period [29], whereas others will re-thrombose recurrently. Seventy percent of those that re-thrombose do so on the same side of the vascular tree [25, 26].

Table 29.1. Triggers for thrombosis in antiphospholipid antibody syndrome patients.

Pregnancy and postpartum state
Oral contraceptives
Lupus flares in patients who also have SLE
Infection
Elective surgical procedures
Invasive vascular studies, i.e., cardiac catherization