INTRODUCTION

Miscarriage is defined as any pregnancy loss that occur before 20 weeks gestational age which is approximately up to the 5th month (the formal medical term for a miscarriage is spontaneous abortion ***(El-Gharib, 2001).***

Miscarriage is the most frequent complication of pregnancy with an incidence ranging between 8% and 25% depending on the population studies and the data collection method ***(Regan and Rai, 2000).***

Many factors are considered potentially liable to cause miscarriage: chromosomal abnormalities, uterine abnormalities, hormonal imbalances, coagulation defects, and infectious and immunological causes. In general, however, it is considered that chromosomal abnormalities are strongly prevalent before the 8^{th} week of gestation and that a high percentage of the miscarriages occurring after the 8^{th} week of gestation may have immunological causes ***(Shoenfeld and Blank, 2004).***

Annexin A5, a potent anticoagulant, was isolated and cloned from human umbilical cord arteries and placentae in the mid 1980s ***(Maurer-Fogy et al., 1988)***. It is an intracellular protein that is abundant in umbilical vein endothelial cells (4,000 ng/mg total protein); however,the plasma concentration of annexin A5 is extremely low (0-5 ng/ml***) (Flaherty et al.,1990).*** In contrast, placentae are rich in annexin A5 (250 mg/10 kg placenta***) (Romisch and Heimburger, 1990)***. Annexin A5 localizes to the microvillar surface of the villous syncytiotrophoblast because it binds to the phosphatidylserine (PS) expressed on the external leaflet of the trophoblast membrane ***(Rote et al., 1998).*** Annexin A5 was shown to act as an inhibitor of phospholipids-dependent blood coagulation reaction because of its high affinity for negatively charged

phospholipids, for example, PS ***(Tait et al., 1989).*** Calcium-dependant annexin A5 functions as a competitive inhibitor for the binding of coagulation factors to membrane-exposed PS ***(Raynal and Pollard , 1994)***, it can function as a modulator of phospholipase A2 (PLA2) activity ***(Pepinsky et al., 1988),*** and it prevents membrane dependant proinflamation reactions ***(Reutelingsperger and van Heerde , 1997).***

It has been postulated that annexin A5 forms an antithrombotic shield around the procoagulant anionic phospholipids PS on the trophoblast surface, which precludes trophoblast participation in phospholipids-dependent coagulation reactions ***(Vogt and Rote, 1997).***

Anti-phospholipid antibodies (APA) are a heterogeneous group of autoantibodies, the persistent presence at medium-high levels of which is associated with the occurrence of thromboembolic events and fetal loss. Those APA most commonly used in clinical practice are utilized in tests for anticardiolipin antibodies (ACA) and lupus anticoagulant (LA), which constitute one of the criteria for classification of primary anti-phospholipid syndrome and systemic lupus erythematosus (SLE). However, the demonstration that one of the main target antigens of APA actually consists of β2-glycoprotein I (β2GPI), a plasma protein involved in coagulation processes, has shifted researchers' attention to the study of other antibodies directed toward coagulation proteins, some of which, like prothrombin and annexin A5, act as phospholipid cofactors. It is now generally believed that it is not phospholipids, but rather phospholipid-binding proteins or phospholipid-protein complexes, that constitute the real target of APA ***(Bizzaro et al., 2005a).*** However, these antibodies present an unusual characteristic that is of great interest in the obstetric field: of the various anti-phospholipid and anti-cofactor antibodies, anti-annexin A5 antibodies proved to be the greatest, if not the only, risk

factor associated with recurrent miscarriages (RM) in women with SLE and in women without autoimmune disease or other risk factors ***(Matsubayashi et al., 2001).*** The antibodies thus seem able to interfere with the pro- or anticoagulant reactions that occur in the cell membranes and the vascular endothelium cells and to be responsible for the high incidence of thrombotic events in anti-phospholipid syndrome (APS) patients ***(Simmelink et al., 2001).***

These antibodies against annexin A5 are also known to induce apoptosis in human umbilical vein endothelial cells (HUVEC) ***(Nakamura et al., 1998).***

In addition, monoclonal antibodies against annexin A5 block intertrophoblastic fusion, suggesting another possible mechanism whereby these antibodies may induce miscarriage ***(Rote et al., 2002; Rand et al., 2005).***

Thus the location and function of annexin A5 make antibodies directed against it potentially pathophysiologically relevant to RM by thrombotic mechanisms, altered placentation and induction of apoptosis ***(Arnold et al., 2001).***