Neonatal and Pregnancy Outcome in Primary Antiphospholipid Syndrome: A 10-year Experience in One Medical Center

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Background: Antiphospholipid syndrome (APS) in pregnancy is characterized by the presence of maternal autoantibodies in association with recurrent fetal loss and severe obstetric complications such as prematurity, intrauterine growth retardation, or placental insufficiency. This study aimed to assess the perinatal outcomes in neonates born to mothers with APS.

Methods: The medical records of pregnant women with APS and their offspring were retrospectively collected between January 1997 and July 2007. Maternal and perinatal histories including demographic data, medications, obstetric histories, and neonatal clinical manifestations and laboratory data were analyzed.

Results: Eleven women with a diagnosis of primary APS were included. Eight of these patients had experienced frequent spontaneous abortions (72.7%), and four had unexplained fetal deaths (36.3%). None of them had vascular thrombosis. Specific autoimmune antibodies were detected, including anticardiolipin antibody (n=6), anti-β2 glycoprotein I (n=3), and antiphospholipid antibody (n=7). Among the pregnancies, five had preterm births (45.4%), two had intrauterine growth retardation (18.1%), and one had intrauterine fetal demise (9.1%). Thrombocytopenia was noted in three babies, all of whose mothers had lower platelet counts. One patient with neonatal thrombocytopenia developed intracranial hemorrhage, seen on brain images.

Conclusions: This limited study suggests that neonates born to mothers with primary APS are at risk of prematurity, being small for gestational age, and having thrombocytopenia. Further large, prospective studies are required to better define the perinatal outcomes.
1. Introduction

Antiphospholipid syndrome (APS) is defined as a prothrombotic disorder characterized by repeated vascular thrombosis and recurrent spontaneous pregnancy loss in the presence of circulating antiphospholipid antibodies. It causes significant complications in obstetrics and pregnancy, including maternal thrombosis, fetal growth retardation, prematurity, infertility, and recurrent miscarriage. However, when properly managed, APS represents one of the few treatable causes of pregnancy loss. Various adverse effects on the fetus and newborn baby have been reported, the most common of which are prematurity and its associated complications. Isolated neonatal thrombosis has also been noted, mostly involving arterial vasculature in the brain. There is limited information available concerning the perinatal outcomes of neonates born to mothers with primary APS in Taiwan. This study therefore aimed to explore the perinatal outcomes in neonates born to mothers with APS at a medical center located in northern Taiwan.

2. Patients and Methods

We conducted a retrospective review of the hospital data base at the National Taiwan University Hospital, Taipei, Taiwan, to identify pregnant women diagnosed with APS during the period from January 1997 to July 2007. The diagnosis of APS was made according to the revised International Classification Criteria established in 2006, which are based on both clinical manifestations and laboratory findings. Because there is no specific ICD 9 code for APS, we used several codes to identify possible candidates: 289.8 (other specified diseases of blood and blood-forming organs), 287.3 (autoimmune thrombocytopenia), 795.7 (other nonspecific immunological findings), and 649.3 (coagulation defects complicating pregnancy, childbirth, or the puerperium). Medical records were extensively reviewed after identification of the candidates. Patients who fulfilled the newest criteria for primary APS were included in this study. We excluded patients who had accompanying autoimmune diseases with antiphospholipid antibodies.

Maternal and perinatal histories (i.e., demographic data, medications during pregnancy, and obstetric histories) and neonatal data (i.e., laboratory findings and imaging studies) were obtained from chart records. All patients received screening for autoimmune antibodies, including antiphospholipid antibody, IgG and IgM anticardiolipin, and beta-2-glycoprotein-1 antibody. Maternal hemograms and hemostatic profiles were checked within 24 hours before delivery. Laboratory and imaging studies were performed in the neonates that were admitted to the neonatal intensive care unit or intermediate care ward. Imaging studies, including brain echo and computerized tomography scans were performed when necessary.

3. Results

There were 11 pregnant women fulfilling the criteria for analysis. The age at diagnosis ranged from 22–37 years, with a median age of 32 years. Among their pregnancy morbidities, four patients had unexplained fetal death beyond the 10th week of pregnancy and eight patients had more than three consecutive, spontaneous pregnancy losses. Eight of them had experienced frequent spontaneous abortions. The mean number of miscarriages was 3.1, with an interquartile range of 2.5. None of them had experienced preterm pregnancies due to eclampsia, severe pre-eclampsia or placental insufficiency. No vascular thrombosis events were found among these women. Specific autoimmune antibodies were detected in the mothers, including anticardiolipin antibody (n=6), anti-β2 glycoprotein I (n=3) and antiphospholipid antibody without any specific mention (n=7). Hematological profiles and coagulation tests checked just before delivery showed that four mothers had thrombocytopenia and three had anemia. Medications most commonly taken during pregnancy among the 10 patients with available histories were aspirin (80%), prednisolone (60%), hydroxychloroquine (50%), and low-molecular-weight heparin (40%).

There were 12 babies born to these 11 mothers, including one pair of twins and one intrauterine fetal demise. Among the 11 surviving infants, six were low birth weight (LBW) (54.5%), five were preterm births (45.4%), and two had intrauterine growth retardation (18.2%). Eight patients were delivered by Cesarean section and three were normal, smooth deliveries. The reasons for Cesarean section included twin pregnancy, fetal distress, chemotherapy for maternal breast cancer, previous uterine surgery, prematurity, and elective scheduling. Among the five preterm babies, two were small for gestational age (SGA). One was symmetric and the other was asymmetric. Five babies were admitted to the neonatal intensive care unit due to prematurity and/or respiratory distress. Regarding neonatal outcomes, two babies had respiratory distress syndrome, three had patent ductus arteriosus, two of whom received surgical ligation, and two had low grade retinopathy of prematurity. Among the five babies with available hematological studies, two had anemia, one had leucopenia and one had prolonged activated partial thromboplastin time. In addition,
thrombocytopenia was noted in three babies, all of whose mothers also had lower platelet counts. One patient with neonatal thrombocytopenia developed intracranial hemorrhage, identified by ultrasound and computerized tomography.

4. Discussion

APS has long been recognized as a cause of miscarriage and infertility, and many clinicians consider APS to be the most common thrombotic disorder causing recurrent miscarriage. In an historical assessment evaluating women with APS, Oshiro et al found that 80% of their patients had suffered from at least one miscarriage. Borrelli et al also reported that 60% of their patients who had habitual unexplained miscarriages harbored APS. In experimental, pregnant animal models, antiphospholipid antibodies have been shown to play a pathogenic role in the development of placental insufficiency and miscarriages. Furthermore, in vitro studies have also shown that antiphospholipid autoantibodies can bind to trophoblast cells to activate the complement cascade that mediates placental injury and causes fetal loss and growth restriction. Untreated primiparae with a high titer of IgG antibodies have around a 28–30% probability of fetal loss, which often occurs in the second trimester. Except for obstetric complications, our study revealed no vascular ischemia in the mothers, although deep venous thrombosis, pulmonary embolism and stroke were not uncommon events during their pregnancies. According to this limited retrospective study, pregnancy need not be discouraged in women with a history of APS, though their pregnancies should be considered to be at risk of preterm birth and/or small for gestational age babies.

Various unfavorable effects of maternal APS on the fetus and newborn baby have been reported. The incidence of prematurity among infants born to mothers with APS has been reported to be around 10–24%, and a high incidence of SGA has also been revealed. Prematurity and SGA may result from insufficient placental vascularization owing to complement activation by antiphospholipid antibodies. Placental damage has been reportedly associated with early embryonic mortality, fetal tissue injury and intrauterine growth restriction. Tincani et al performed a controlled study in patients with matched gestational ages and pregnancy complications to verify if the presence of antiphospholipid antibodies was linked to specific risks for the fetus and neonate. They found no significant difference in the incidence of neonatal complications between the groups. Their results further suggested that the main problem in pregnancies with primary APS seemed to be prematurity, with a rate of up to 18.8%. Neonatal thrombosis involving the brain and other regions have been reported in neonates born to mothers with APS, but the pathogenesis remains unclear. It may be due to transplacental antiphospholipid antibodies or other embryonic vascular accidents.

Thrombocytopenia is frequently present in patients with antiphospholipid bodies, with an incidence ranging from 20–40%. Likewise, a high prevalence of thrombocytopenia was noted in our study: Four of 11 (36.3%) mothers with primary APS had thrombocytopenia. Thrombocytopenia was also noted in three babies, all of whose mothers had lower platelet counts. One of these newborns with thrombocytopenia developed intracranial hemorrhage, but fortunately, the other two babies were asymptomatic. The thrombocytopenia is usually mild, and severe thrombocytopenia is most often seen in patients with catastrophic APS and those with thrombotic thrombocytopenic purpura. Godeau et al reported a higher prevalence of serum platelet antibodies in patients with thrombocytopenia. The pathogenesis of thrombocytopenia is unclear, and the proposed mechanisms include coexisting antibodies to platelet glycoproteins, or antiphospholipid antibodies against platelet membranes. Most of these platelet-specific autoantibodies are IgG antibodies that may cross the placenta to affect babies born to mothers with primary APS.

Some limitations of this retrospective study should be noted. No specific ICD code has been established for APS, so we may have underestimated its true incidence. It is likely that many mothers with APS who received medical treatment and had successful pregnancies and normal deliveries in our hospital were not included. Some medical records used in the retrospective chart review were incomplete, and lacked data such as maternal antibody titers determined during pregnancy. In addition, laboratory tests and imaging studies were only performed in the neonates who were admitted for evaluation. It cannot be concluded that those who were not tested were normal.

The results of this small, retrospective population study, suggest that neonates born to mothers with primary APS are at risk of being preterm, of being SGA babies, and of developing thrombocytopenia after birth. Further prospective studies should be carried out involving larger numbers of patients, in order to clarify the impacts of various maternal autoimmune antibody levels on neonatal outcomes.

References


