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Neonates from mother with autoimmune disease

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A B S T R A C T

Autoimmune diseases (AD) have a higher prevalence in women, particularly during their childbearing age. A growing interest is being paid to the possible consequences of maternal disease and associated treatment on the fetus and newborn infant. If maternal disease is characterized by the presence of IgG isotype autoantibodies, these can cross the placenta with possible antibody-mediated damage to the fetus. In addition, immunosuppressive and other drugs administered to the mothers during pregnancy might affect the fetal and neonatal immune system development. Finally, mothers disease and/or treatment could be related to neuropsychological alteration reported in some of their children.

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Neonatal lupus erythematosus

Neonatal lupus erythematosus (NLE) is a model of passively acquired autoimmune disease (AD) in which mother's autoantibodies with anti-Ro/SS-A and anti-La/SS-B specificities cross the placenta and may damage the fetus. The most common and serious cardiac manifestation is the autoimmune-associated congenital heart block (CHB), which typically begins in utero during the second or third trimester. In some cases, CHB begins as first- or second-degree block and then progresses to third-degree block. Complete CHB, once established, appears to be irreversible and carries a significant morbidity and mortality.[1,2] The frequency of third-degree block in an offspring of a mother who has anti-SSA/Ro antibodies is estimated at 1–2%.[3] Early-onset cardiomyopathy can occur together with complete CHB in fetus or at birth, however, delayed dilated cardiomyopathy has been also reported.[4-6]

Other cardiac features include congenital malformations, less advanced degrees of block and conduction abnormalities.[7-9]

While the precise pathogenic mechanism of antibody-mediated injury remains unknown, it is clear that the antibodies alone are insufficient to cause disease and fetal factors are likely contributory. *In vivo* and in vitro evidence supports a pathologic cascade involving apoptosis of cardiocytes, surface translocation of Ro and La antigens, binding of maternal autoantibodies, secretion of profibrosing factors (e.g., TGFβ) from the scavenging macrophages and modulation of cardiac fibroblasts to a myofibroflast scarring phenotype.[10]

Cutaneous transient manifestations of neonatal lupus erythematosus usually appear as erythematous and often annular lesions with a predilection for the eyes, face and scalp, frequently photosensitive. The risk of cutaneous lesions is unknown. In most cases, the rash follows ultraviolet light exposure, the mean age of detection is six weeks, and the duration up to 22 weeks. All infants had facial involvement (mainly periorbital region), followed by the scalp, trunk, extremities, neck and intertriginous areas. It is not clear whether topic treatment may improve the outcome of skin lesions.[11]

Less frequently documented features include hepatobiliary disease and Hematologic abnormalities, both associated with maternal anti-SSA/Ro-SSB/La antibodies and generally self-limited; hepatic and hematologic involvement are grouped under the heading of neonatal lupus syndromes.[12,13] It is uncommon for children with neonatal lupus to show the full

expression of disease; rather they have only one or two organ systems involved. To date, complete CHB is irreversible. In contrast, the noncardiac manifestations are transient, resolving at about six months of life coincident with the disappearance of maternal autoantibodies from the neonatal circulation.

Neonatal autoimmune thrombocytopenia

Immune thrombocytopenic purpura (ITP) accounts for about 3% of thrombocytopenia in women at the time of delivery.[14] Transplacental passage of maternal platelet autoantibodies can induce moderate or severe autoimmune thrombocytopenia in the fetus or the newborn in about 10% of cases, and thrombocytopenia can occur as early as 20 weeks of gestation.[1,15]

Although pregnancy is not discouraged in women with pre-existing ITP, maternal and fetal complications can occur, and additional monitoring and therapy may be needed. There may be marked disparities between the maternal and fetal platelet counts. No antenatal measures reliably predict neonatal status, and maternal response to intervention does not guarantee a favourable neonatal outcome. Only previous neonatal outcome provides a useful predictor of the neonatal platelet count in the subsequent pregnancy.[16]

Although 10% of infants born to women with ITP are born with platelet counts below $50x10^9$/L and counts often decrease during the first few days of life, only 4% are born with counts below $20x10^9$/L.[17]

Consequently, the risk of intracranial hemorrhage or other major bleeding complications is less than 1%; this risk is higher than that among the infants of healthy women.[18] The risk is increased if alloantibodies are also present (~10%).[19] There are no studies showing that the risk of intracranial hemorrhage is reduced by the use of cesarean section and current practice is not to alter the mode of delivery.[20] Although the fetal platelet count may be accurately determined by percutaneous umbilical vein sampling, most authors agree that the risk associated with the procedure outweighs the risk of intracranial hemorrhage due to ITP.[14] All neonates of mothers with AD should have a cord blood platelet count determined at birth and again at 24 hours.[21] In thrombocytopenic neonates, the platelet count should be repeated daily for the next three to four days, as platelet counts are commonly at their nadir during this time before rising spontaneously by day seven in most cases.[22]

Ultrasonography of the head should be performed to rule out intracranial hemorrhage in infants with thrombocytopenia. As most babies found to have an intracranial hemorrhage secondary to maternal autoimmune disorders have had platelet counts $> 30x10^9$/L, it is common practice to treat any neonate with platelets counts below this level with intravenous immunoglobulin (IVIG) regardless of whether or not there is evidence of bleeding.[14] There is no clear evidence that this approach is of benefit or that the threshold level of $30x10^9$/L is appropriate; however, IVIG at a dose of 1 g/kg/day for two consecutive days or 0.5 g/kg/day for four days is usually effective in raising the platelet count. It is not uncommon for a second course of IVIG to be required two to three weeks after birth if the platelet count again falls below $20\text{-}30x10^9$/L because of persistence of the maternal platelet antibodies.[23]

High dose corticosteroids should be considered for neonates with platelet counts of less than $30x10^9$/L at birth. Single donor irradiated platelet transfusions should be considered in the face of life-threatening hemorrhage or for severe thrombocytopenia (platelet counts $< 20x10^9$/L).[24] The neonatal thrombocytopenia usually resolves within four to six weeks, after clearing of the passively acquired maternal autoantibodies. Immune thrombocytopenic purpura is not a contraindication to breast-feeding.[25]

Antiphospholipid syndromes

Antiphospholipid syndrome (APS) is a complex disease that can be classified as an autoimmune-mediated clotting disorder. This syndrome, described as primary or within systemic lupus erythematosus (SLE) or other AD, is a prothrombotic state characterized by the presence of antiphospholipid antibodies (aPL).[26,27] It is now clear that the true antigenic targets of aPL are not the phospholipids *per se*, but plasma proteins bound to an anionic (not necessarily phospholipid) surface. Among them, β2-glycoprotein I (β2GPI) and several other proteins involved in the regulation of blood coagulation, have been described.[28-30]

Anti-β2GPI antibodies are strongly associated with thrombosis and other APS features, and their presence has been included recently in the laboratory classification criteria of APS.[31] Women with aPL may present several pregnancy complications, while if adequately treated the pregnancy outcome improve substantially.[32] However, some questions remain unanswered regarding the persistence of aPL after birth in infants from mothers with aPL-positive AD and the potential pathogenetic role of aPL. The transplacental transfer of aPL is not necessarily associated with aPL-related clinical manifestations in newborns. Several studies on the outcome of infants born from mothers with APS have shown consistently that, apart from prematurity and the related complications, these neonates had no other clinical manifestations.[33] However, a few cases of thrombotic complications in neonates born to mothers with either aPL or clinical and biological APS have been reported.[33]

In our case control study, infants born from moth-

ers with aPL-positive AD were prospectively evaluated for anticardiolipin and anti-β2 glycoprotein I antibodies and results were compared with those obtained from two age-matched control groups.[34] This study confirmed that aCL and anti-β2GPI antibodies can be found at birth in about 30% of neonates from APS mothers. The reduced transplacental passage of aPL may be the consequence of the binding of these antibodies to the placental β2GPI. At 12 months of life all infants were negative for aCL, whereas many infants from the study and the control group were positive for anti-β2GPI. Growth and neurological development were normal in all infants and no thrombotic complication was observed. The negativity of anticardiolipin in all infants at 12 months suggests that anticardiolipin detection is the best assay to evaluate the disappearance of maternal aPL and to estimate the potential risk of thrombosis associated with these antibodies. The high rate of anti-β2GPI positivity in all three groups of infants may indicate that the synthesis of this antibody is stimulated by nonspecific factors, such as infections, vactinations, or nutritional exposure to β2GPI. [35]

Immunosuppressive medications and the neonatal immune system development

All medications used to treat the autoimmune disease cross the placenta therefore, if continued throughout pregnancy, the fetus is inevitably exposed to the potential effects of immunosuppression.[36] Few studies on the disregulation of the fetal-neonatal developing immune system have been conducted in infants from mothers with AD and most of the published studies come from transplanted patients. Usually drug dosages are different in the two conditions, being higher for transplanted patients.

Cimaz *et al.* studied the immune function in nine children born from mothers treated with immunosuppressants for connective tissue diseases. Complete blood count, IgA, IgG, IgM, IgG subclasses and lymphocyte subpopulations were determined in all cases. Moreover, serum levels of anti-HBsAg were also evaluated. The same evaluation was done in 14 babies from mothers with similar diseases who had not been treated. None of the parameters tested resulted significantly different between the two groups and all children responded satisfactorily to hepatitis B vaccination.[37]

The same group of researchers, in a recent study, evaluated the immune function in eight children born by mothers with AD who received immunosuppressants during pregnancy (cyclosporine A or dexamethasone) and in six babies from mothers with similar diseases, but who did not receive any treatment. Cytokine production of interleukin-2 and interferon-γ in peripheral blood mononuclear cells stimulated by phorbol-myristate-acetate and ionomycin were measured. The results suggest that the immunosuppressive drugs given for AD during pregnancy do not induce significant immunosuppression in babies.[38]

Airò *et al.* evaluated the response to Clostridium tetani toxoid vaccination in 26 babies born from mothers with AD. In this study, babies were divided into three groups according to treatment: no immunosuppressive drug (group 1: n = 6), treatment with hydroxychloroquine alone (group 2: n = 3), treatment with glucocorticoids and/or other immunosuppressant agents (group 3: n = 15). Results showed that a sizeable proportion of children born from mothers with AD was not protected, or only partially protected after a normal cycle of anti *C. tetani* toxoid vaccination and a booster was suggested. Indeed, 12% did not have a protective titer of anti C. tetani toxoid IgG (>0.03 UI/mL) and 31% had a partially protective anti C. tetani toxoid IgG (from 0.03 to 0.5 UI/mL). However, no clear relationship with the use of immunosuppressive drugs during pregnancy was observed because the antibody titer was not significantly different among the three groups.[39]

In our ongoing study we are evaluating the immune function of infants from mothers with AD (unpublished data). Children enrolled in the study were divided into two groups: 19 infants from mothers receiving, during pregnancy, steroids alone or in combination with other immunosuppressive agents and 15 infants from mothers receiving low dose aspirin only. In all babies, we evaluated the lymphocyte subpopulations and the *in vitro* production of immunoglobulins at birth, one, six and 12 months of life, respectively. In particular the *in vitro* production of immunoglobulins was studied culturing the infants peripheral blood mononuclear cells in resting and stimulated conditions (culture medium were supplemented with CDw32 L cells, anti-CD40 monoclonal antibody and rhIL-10). IgG, IgA and IgM concentrations in the culture supernatants were determined both in resting and stimulated conditions. Our preliminary results showed that the *in vitro* production of immunoglobulins and the lymphocyte subpopulations were similar in the two studied groups.

These few experiences on the immune function evaluation of children from mothers with AD seem to show that prenatal exposure to immunosuppressive drugs does not have a profound effect on the developing immune system. More data and a longer follow-up are needed to confirm these observations.

Neurological outcome of children from mothers with autoimmune disease

Limited data are available on the long-term observation of children from mothers who suffered of AD

during pregnancy. Some literature has suggested that children of women with SLE are significantly more likely to have neurodevelopmental dysfunctions, as learning disabilities (LD) or attention deficit.[40-42] Support for a relationship between the presence of maternal antibodies and LD in offspring is found in a study showing that serum level of the anti-Ro/SSA antibody in mothers of dyslexic children were 20 times higher then those of mothers of children without dislexia.[43]

In our previous study 47 children (23 male and 24 female) from mothers with SLE during pregnancy were evaluated to assess their neuropsychological development.[44] The tests applied were related to the children's ages: Griffiths scale up to four years, Wechsler Preschool and Primary Scale of Intelligence (WPPSI) test from four to six years of age, Wechsler Intelligence Scale for Children Revised (WISC-R) test from six years onwards; finally, specific tests for the diagnosis of LD between the ages of seven and 13. Intelligence levels were always normal (mean IQ score 106.32; median 104; SD 9.05). Fourteen children were specifically studied for LD and three reported scores lower than normal, but only two (who were brothers) were defined dyslexic. Antiphospholipid antibodies were positive in the mothers of the three children with impaired LD tests. Other maternal autoantibodies or drugs administered during pregnancy did not seem to be related to LD. In conclusion, we confirmed that children of patients with SLE have normal intelligence but an increased rate of LD, particularly if male. Our data seems to relate the occurrence of these problems to the presence of aPL in the mothers during pregnancy, but this relationship needs to be investigated further possibly including children of patients with primary APS.

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