This conference focused on pregnancy in rheumatic diseases. In antiphospholipid syndrome (APS), thrombotic phenomena, complement system and direct binding of antiphospholipid (aPL) antibodies to the trophoblast can explain the wide obstetrical manifestations. A significant rate of prematurity and intrauterine growth restriction is observed in APS pregnancies. Concerning infant health, short- and long-term outcome for babies born to patients with APS was reported; the pathogenesis of congenital heart block and its management in the first years of a child's life was extensively discussed. Moreover, a specific session analyzed the outcome of systemic lupus erythematosus (SLE), demonstrating frequent clinical relapse during pregnancy. By contrast, rheumatoid arthritis (RA) usually improves, mainly owing to a dramatic change in the cytokines profile. Finally, based on experts' opinions, recommendations for treatment with new antirheumatic drugs in pregnancy were proposed.

The conference, held in Florence April 20–21, 2007, attracted over 500 attendees from 53 different countries. It was co-chaired by Maurizio Cutolo, Marco Matucci Cerinic, Angela Tincani and Pierluigi Meroni. The major topics aimed to analyze the pathogenesis of fetal damage and pregnancy complications in APS, immune modulation of RA during pregnancy, pregnancy outcome in different autoimmune diseases (i.e., SLE and systemic sclerosis [SSc]), the health status of children born to mothers with aPL antibodies or anti-Ro/SSA antibodies and, finally, some recommendations regarding drug treatment during pregnancy in patients affected by rheumatic diseases.

Pathogenesis of placental damage in APS

APS is a clinical disorder, characterized by recurrent thrombosis, fetal losses and circulating aPL antibodies reacting to phospholipid-binding plasma proteins, namely β2-glycoprotein I (β2GPI) and prothrombin. The obstetrical features of APS are represented by the occurrence of miscarriages due to placental insufficiency. During the first session of the conference, different rheumatologists and gynecologists analyzed the role of adaptive and innate immune responses in the pathogenesis of APS-related placental damage, suggesting that thrombotic phenomena alone cannot explain the obstetrical manifestations of the syndrome. Dr Lockshin reported the pivotal role of different complement fractions in inducing vascular disorganization. aPL antibodies target the placental tissues and activate the classical complement cascade. The complement system itself can trigger the endothelium by classical or lectin pathways in order to induce increased vascular permeability through membrane-attack-complex activation, or selective expression of different adhesion molecules and chemokines. This process, in addition to the specific interaction between C5a anaphylotoxin and the C5a-receptor on the endothelial membrane, can promote local production of tissue factor, platelet activation and the massive recruitment of several inflammatory cells.

Two gynecologists (Dr Cetin and Dr Rai) analyzed the mechanisms of fetal losses induced by aPL antibodies and the rationale for treatment with heparin and aspirin. aPLs are involved in placental thrombosis and inflammation, a hallmark of APS, but they could also play a role in the earliest phase of embryonic implantation. They can bind to the trophoblast, impairing its invasiveness, and induce a clear reduction of endothelial heparin-binding epidermal growth factor, a membrane protein involved in cell invasion and trophoblast differentiation. On the maternal side, anti-β2GPI antibodies bind to decidual cells, inducing inflammatory cytokine production. In addition to β2GPI, this binding involves annexin A2 and Toll-like receptor 4. Clinical evidence demonstrates a better prevention from clotting in pregnant APS women treated with aspirin and heparin. Moreover, in vitro experiments demonstrated that the addition of a low dose of heparin can restore trophoblast survival and invasiveness, which was previously blocked by aPL. Based on these findings, Dr Rai suggested that aspirin and heparin treatment reduce trophoblast apoptosis. In fact, heparin demonstrates a wide spectrum of beneficial effects, such as reducing aPL binding and inflammation, reducing complement activity and probably modulating cellular endometrial gene expression.

Pregnancy complications in APS: fetal losses, pre-eclampsia & infertility

Dr Branch reported that more than 80% of women with APS had at least one pregnancy failure, which could be...
categorized into pre-embryonic (from conception to the 5th week of gestation), embryonic (from the 5th to the 9th week of gestation) or fetal losses (occurring after the 10th week of gestation). Moreover, APS women demonstrated the same rate of early miscarriages (before 10 weeks) as general populations, estimated in 12–15% of the cases. By contrast, fetal losses are more frequent, representing approximately 18% of the total pregnancies, compared with 2–3% of cases in the healthy population. Dr Lojacono discussed the correlation between pre-eclampsia and aPL. Early pre-eclampsia is defined as an abnormal response to placentation, characterized by an increase of vascular resistance, platelet aggregation and activation of the clotting cascade. Both pre-eclampsia and APS showed the same histological and pathogenetic picture: platelet, endothelial and complement activation, inhibition of fibrinolysis and the protective function of annexin V and apoptosis of syncytiotrophoblast and cytotrophoblast with severe impairment of invasiveness [3]. According to this hypothesis, some authors reported that approximately 70% of women with recurrent pre-eclampsia presented with aPL antibodies or positive genetic tests for thrombophilia. According to these data, early pre-eclampsia has been included in the new criteria for APS.

Dr Carp reported an updated review of infertility and APS. Although experimental models showed a selective embryonic reabsorption due to aPL antibodies and a decrease of several cytokines that are protective for implantation during APS, case-control studies have demonstrated conflicting results regarding the prevalence of aPL in infertility. From a clinical point of view, approximately 30% of infertile women showed one or more circulating aPL antibodies; however, American gynecologists did not propose aPL antibody analysis within the panel of tests for infertility. Another problem is represented by the possibility of in vitro fertilization in APS patients [4]. Dr Carp and Dr Costa separately reported the higher rate of complications associated with ovarian hyperstimulation in women affected by SLE, as published in a few retrospective papers. They were represented by disease flare (~20%) and thrombotic events. In order to prevent additional thrombotic risks, anti-coagulants are indicated for these patients; they must be stopped 24 h before the oocytes’ removal and restarted approximately 24 h after the procedure.

The use of intravenous immunoglobulins (IVIGs) is more controversial: they could be effective, but they can activate complement and consequently trigger further inflammation.

Health status of babies
Different authors focused on the health status of newborns of women affected by APS. Dr Lashassinne presented data extracted from the European register regarding the early outcome of babies born to mothers affected by APS [5]. Within 73 prospectively-included newborns, the rate of prematurity and intrauterine growth restriction was 17.5%; three babies showed a neonatal infection (cytomegalovirus and toxoplasmosis), while only one child showed a congenital malformation. Although aPLs were detectable in about 50% of children, no cases of thrombotic or autoimmune features were observed during the first months of life. Further clinical evaluations were performed in 46 children over 1 year of age. Behavior abnormalities were detected in three babies: one case of autism (2 years of age), one case of hyperactive behaviour (at 2 years of age, then improved at 3 years) and one case of neurocognitive disorder (diagnosed at 9 months old). In order to screen any future motorial defects in babies born to mothers with APS, Dr Motta (pediatrician) proposed to perform a brain echography at birth and then at 1-, 5- and 8-months of age. Analyzing 54 babies of mothers with different autoimmune diseases, he found an increased incidence of intracranial abnormalities, namely germinal matrix hemorrhages and alterations of cerebral vessels. These alterations were not significantly associated with maternal presence of aPL. However, they were all resolved at 12 months of life and could represent a vascular perinatal abnormality. Moreover, concerning the rate of transmission of aPL from mothers to babies, another oral communication reported the experience of the European register. The rate of transmission ranged from 29% for aPL to 44–46% for lupus anticoagulant and anti-β2GPI antibodies; this autoantibody positivity can be detected until the 24th month of life. In some cases anti-β2GPI can appear from 4–18 months of life, possibly due to weaning, vaccination or concomitant infections.

The long term outcome of children born to mothers with APS was studied through analysis of their neuropsychological status. Different authors reported a learning disability in children of mothers affected by SLE [6]. Based on experimental data demonstrating direct aPL-related damage to the brain of rats, Dr Tincani reported a neuropsychological study conducted in children of APS mothers. Among 15 children, a learning disability concerning reading, calculations and writing was found in 4 cases (26.7%). No differences were detected in prematurity rate and socio–economic status when comparing these babies to the controls. Considering that the prevalence of these defects in the Italian population is 4%, this high rate seemed to be related only to maternal aPL.

Another aspect concerning infant health focused on the neonatal lupus syndromes. Dr Clancy reported some pathogenetic mechanisms involved in the most severe feature of neonatal lupus; the congenital heart block (CHB). Maternal, fetal and environmental factors appear to act together: maternal autoantibodies to La/SSB and Ro/SSA can recognize fetal cardiac antigens and activate macrophages with an increasing production of tumor necrosis factor (TNF)-α and transforming growth factor (TGF)-β. This process can induce fibroblast differentiation and activation, with consequent tissue fibrosis and hypoxia. Only 2% of mothers with these autoantibodies can
develop conduction block in utero. In fact, there are also fetal factors involved in the fibrosis of the atrioventricular node. There is a strict correlation between CHB and increased production of TGF-β from the babies, possibly due to a genetic predisposition. TGF-β secreted from macrophages modulates the cross-talk between macrophages and cardiac myofibroblasts, determining at least a differentiation to fibroblasts and fibrosis of the conduction tissue. Environmental factors appear to play a role in this process: children with CHB exhibited higher levels of erythropoietin in cordom flow as a consequence of cardiac hypoxia. Some cardiac tissues appear to enhance their hypoxic response, producing large amounts of growth factors that increase the rate of fibrosis [7]. Dr Brucato reported the importance of correct clinical management of CHB. First, the anti-Ro/SSA-positive mothers are frequently asymptomatic; therefore correct counselling is mandatory in order to avoid incorrect maternal diagnosis. A fetal echocardiography must be performed weekly from the 16th to the 26th week of gestation. If an atrioventricular block is diagnosed, the mother must be treated with oral β-methasone; while β-agonists or IVIG are used only when the cardiac rate is lower than 55 beats/min or in the case of concurrent myocarditis, respectively. Some authors used treatment with IVIG in order to prevent CHB recurrence, usually estimated in 20% of cases [8]. Approximately 18.7% of CHBs occur in mothers without detectable anti-Ro and anti-La antibodies, these conduction blocks are incomplete and transient, but sometimes it is useful to treat them with steroids.

Immune modulation during pregnancy in different autoimmune diseases

Patients affected by SLE frequently experience disease relapse during pregnancy, usually characterized by mild cutaneous and articular features. Renal flares can occur during pregnancy in women with a history of lupus nephritis (~30%), while pregnancy outcome can be predicted by the renal disease activity and proteinuria at conception. On the contrary, SSC does not seem to influence pregnancy outcome, but the cardiovascular modifications occurring during pregnancy can cause several SSC complications. Increase of arthralgias, gastroesophageal reflux and dyspnea are frequently observed, while an increasing risk of ventricular arrhythmias and hypertensive renal crisis must be carefully considered. Different rheumatologists analyzed the mechanisms of RA remission during pregnancy; in approximately 75% of patients, RA improves during pregnancy, mainly owing to a dramatic change in the cytokine profile with a prevalent expression of T-helper (Th)2 lymphocytes, resulting in a non-inflammatory milieu. Some authors found a strict correlation between RA improvement and maternal/fetal human leukocyte antigen (HLA) disparity. During pregnancy placental apoptotic syncytiotrophoblast debris, containing fetal HLA II peptides (different from maternal HLA II), are found in the maternal blood. Maternal dendritic cells can simultaneously present fetal and self-RA-associated antigens to T lymphocytes in the setting of a non-inflammatory environment, this process can explain fetal tolerance and RA improvement [9]. Dr Cutolo explained how the change in sex hormones profile during pregnancy can increase TH2-mediated cytokines and consequently the immune response, which is responsible for clinical improvement of disease. In addition, regulatory T lymphocytes, usually inhibited in RA by elevated levels of TNF-α, can play a role during pregnancy, suppressing autoreactive T lymphocytes and inducing a tolerogenic milieu [10].

Treatment of pregnant women affected by different autoimmune diseases

Different specialists suggested how to manage immunosuppressive drugs before or during pregnancies in patients affected by RA or SLE. Based on animal data, leflunomide is contraindicated in women of child-bearing age. An American collaborative research group conducted a prospective study analyzing pregnancy outcome of women exposed to this drug [11]. A total of 62 pregnancies in women affected by RA and exposed to leflunomide were compared with 108 pregnancies in untreated RA women. Preterm deliveries in the first group were observed more frequently, but the same rate of major structural malformations in the newborns were seen, with a prevalence of 7.4% in the leflunomide-exposed group and 6.3% in the unexposed group. In any case, a wash out from the drug is strongly recommended before conception. Dr Østensen discussed the management of RA women treated with different immunosuppressive drugs before pregnancy [12]. Anti-TNF-α (infliximab, etanercept and adalimumab) and anti-B lymphocyte (rituximab) drugs cross the placenta at the 14th week of gestation. Approximately 150 cases of infliximab-exposed pregnancies were reported with the same outcome of unexposed women in terms of miscarriages, preterm delivery and congenital malformations. Of 24 adalimumab-exposed pregnancies, there were two miscarriages, one hip dysplasia and 21 healthy newborns, while within 78 etanercept-exposed pregnancies, one woman (treated throughout the pregnancy with etanercept 100 mg/week) delivered a baby with Vater syndrome, featuring multiple gastroenteric, vertebral and kidney malformations. Four cases of pregnant women treated with rituximab were reported, in all babies a low B-lymphocyte count was detected, without the occurrence of particular sequelae. In clinical practice, it is mandatory to stop infliximab, etanercept and adalimumab at conception, while rituximab must be stopped approximately 12 months before pregnancy. Methotrexate must be withdrawn at least three months before conception and mycophenolate-mofetil must be stopped 6 weeks before conception owing to reported hand malformations. Cyclosporine treatment is
permitted during pregnancy, even if some cases of maternal cholestasis and prematurity are reported. No definitive data are available regarding the detection of anti-TNF-α drugs in maternal milk; however, since all the immunoglobulin classes could be present in the milk, lactation is not recommended during treatment.

Difficult cases

The treatment of pregnant patients with APS and previous thrombosis has not been fully clarified. Dr Derksen reported that these patients must be treated with oral anticoagulants in order to avoid the risk of a second thrombotic episode, estimated in 2.4% of patients. Within the first 6 weeks of gestation, oral anticoagulant drugs must be stopped and shifted to unfractioned or low molecular weight heparin (LMWH), and the platelet count needs to be monitored for the first 15 days of treatment. APS women present multiple thrombotic risk factors, so they must be treated with the full heparin dose during their pregnancy until 24 h before programmed delivery. Dr Abbate reported a meta-analysis of the most common side effects attributed to anticoagulants during pregnancy; LMWH demonstrated a high successful pregnancy outcome (~97% of cases), with a very low risk of maternal thrombocytopenia and fetal bleeding. As LMWH is rapidly metabolized, a double-dose regimen is preferred.

Another difficult case, frequently occurring in clinical practice, is represented by the management of patients not fulfilling formal classification criteria of APS. Asymptomatic women with a confirmed positivity for the lupus anticoagulant test should be considered carefully. In fact, based on their desire for a child, their age, cardiovascular and thrombotic risk factors, they could be treated during their first pregnancy with a combination of aspirin and low-dose heparin, as in the case with other APS patients.

Finally, Dr Lockshin and Dr Tincani presented the results obtained from a questionnaire sent to 26 APS specialists (gynecologist, rheumatologists and internists) regarding the management of difficult cases in APS.

The first question concerned the treatment recommendation in APS-women starting a new pregnancy, with persistent lupus anticoagulant test positivity and a mid-pregnancy fetal loss (despite treatment with low-dose aspirin and prophylactic-dose LMWH); most of the interviewed specialists increased the LMWH dose to a therapeutic regimen. If the same patient was at a therapeutic dose of LMWH because of previous thrombosis, most of them continued the same dose of heparin or used IVIG in association with oral corticosteroids.

Most of the authors recommend the use of low-dose aspirin in a pregnant aPL-positive patient, who is asymptomatic, with only one or two early (<10 weeks) miscarriages, or with APS-related features (such as headache, livedo or heart valve disease). By contrast, the use of heparin is recommended only in cases where the aPL-positive patient presents with a history of two early miscarriages or clinical APS features.

Concerning in vitro fertilization procedures, most of the specialists recommend the use of low-dose aspirin for every aPL-positive patient (asymptomatic, affected by APS with vascular events or with pregnancy morbidity). The use of heparin is mandatory only in women with classical APS treated for in vitro fertilization, while no consensus was obtained for heparin treatment in asymptomatic aPL-positive women. Oral contraceptives appear to be generally avoided in patients affected by APS or in women with persistent positivity for aPL. The last question referred to the duration of thrombosis prophylaxis in APS patients after delivery. Most experts agreed that heparin administration should be continued for all the puerperium (4–6 weeks). In fact, this period is known to be particularly at risk for the occurrence of thrombosis, even in patients without previous thrombotic events.

Bibliography


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