Autoimmune diseases and pregnancy

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A B S T R A C T

Autoimmune rheumatic diseases (ARD) occur frequently in women during their child-bearing years and may influence pregnancy outcome and neonatal health. Patients with systemic lupus erythematosus (SLE) can experience a disease flare-up during pregnancy with potential negative effects on the product of conceptus, especially if the disease is active. Therefore SLE, as well as other ARD, need to be treated during pregnancy. Drugs used in pregnant patients need to be carefully evaluated for their possible foetal damage. In this respect a recent consensus report on the use of anti-rheumatic drugs in pregnancy, indicates that corticosteroids, antimalarials and some immunosuppressive drugs can be administered to pregnant patients when needed. Recurrent pregnancy loss is now considered as a treatable clinical condition associated with the presence of circulating antiphospholipid antibodies (aPL) within the SLE (or other autoimmune disease) setting or in otherwise healthy women (antiphospholipid syndrome, APS). Nevertheless APS patients have to be strictly monitored during pregnancy and puerperium because of the high risk of thrombosis recorded also in patients without previous thrombo-embolic events. Patients affected by rheumatoid arthritis (RA) are generally found less symptomatic during gestation, however they need a careful pre-conception counselling because a) the disease is generally treated with drugs (i.e. methotrexate) that are teratogenic, therefore pregnancy must be planned, and b) patients should be informed that the relapses are frequently reported in the three-four months after delivery possibly causing serious problems in the neonate care and consequent depression in the mothers; familiar strategies should be available for the patients to overcome these difficulties. Nowadays, owing to our increasing knowledge of the disease patho-physiological mechanisms and the development of combined medical-obstetric clinics, pregnancy outcome in patients with AD has notably improved.

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Autoimmune rheumatic diseases (ARD) affect women particularly during their child-bearing age. Therefore, a growing interest has been paid to the possible worsening of maternal disease and the possible negative influence of the disease itself and/or the maternal treatment on neonatal outcome. In patients with ARD the risk of spontaneous abortion, repeated foetal loss, intrauterine growth restriction and pre-term births is higher than in the general population, however, over the last years the general improvement in the diagnosis and in the management of these diseases result in a better quality of life and in the planning of a normal family life.[1] Nowadays it is not rare to observe one or more successful pregnancies in these patients, providing that are planned when the diseases are in remission and that they are followed by an *ad hoc* multidisciplinary team, (including rheumatologists and obstetricians) in a third level institution with an active neonatal intensive care unit.

Systemic lupus erythematosus (SLE), that frequently occurs in young females in their child-bearing age, has been recognized as potentially affected by the the immunoendocrine changes observed during pregnancy.[2] In normal pregnancy, the maternal immune system seems to modulate the cytokine pattern to preferential expression of Th2 cytokines, including Gm-CSF, IL-3, IL-4, IL-5, IL-10 and IL-13, that are essentially anti-inflammatory and may be necessary for successful pregnancy in order to prevent rejection of foetal tissues. The Th1/Th2 shift is due to the progressive increase of progesterone and estrogens during pregnancy, which reach their peak-level in the third trimester of gestation. At high levels, estrogens seem mainly to suppress Th1 cytokines and stimulate Th2-mediated immunological responses as well as antibody production. Preferential expression of Th1 cytokines (TNFα, IFNγ and IL-12) might result in abnormal placental and embryonic growth and subsequent foetal

loss.[3] For this reason Th1 mediated disease, like rheumatoid arthritis (RA), tend to improve and Th2-mediated disease, like SLE, tend to worsen during pregnancy.[4]

Systemic lupus erythematosus

Pregnancy in SLE women is considered at high risk because there are potential adverse events including flares of disease activity, maternal thrombosis and miscarriages in patients with aPL, toxicity of drugs used in order to control the disease and neonatal lupus in babies born to mothers with anti-Ro antibodies.[5]

The majority of maternal flares recorded in pregnancy are mild, including haematologic, articular and dermatologic manifestations and they only require a minor treatment adjustments.[6] Renal flares during pregnancy are the most frightening complications with a significant risk of poor maternal and fetal outcomes. Their diagnosis can be also complicated because of the high incidence of preeclampsia in SLE pregnancy.[7] The indication therefore is to continue to treat SLE during pregnancy. In this respect, for active disease, with organ involvement, non fluorinated glucocorticoids, or some immunosuppressive drugs can be used without foetal damage, namely azathioprine and cyclosporine-A.[8] Antimalarial, particularly hydroxicloroquine (HCQ) is given to control minor manifestation like cutaneous or articular disease. The use of these drugs in pregnancy has been debated for a long time because of old reports of auditory and retinal toxicity in fetuses exposed to these drugs in utero. However more recent data, reporting the long term follow-up of children exposed to HCQ in utero, support the safety of this treatment.[9,10] On the other hand the withdrawal of the drug because of pregnancy was shown to expose the woman to SLE flares and does not prevent foetal exposusure because of the very long half-life of antimalarials.[8] Finally heparin and low dose aspirin are currently used to prevent thromboembolic complications and pregnancy losses in patients with SLE and antiphospholipid syndrome (APS).[12]

Antiphospholipid antibodies are a heterogeneous family of autoantibodies that exibit a broad range of target specifities and affinities, recognizing various combinations of phospholipids and phospholipids binding proteins. In the clinical practice the aPL are detected by lupus anticoagulant, anticardiolipin or anti-β2GPπ antibodies assays.[13] According to various reports, they are found in 30 to 80% of patients with SLE and at a lesser extent in several other ARD or in otherwise healthy subjects.[14] Independently from their clinical setting, they are related to repeated spontaneous pregnancy losses within the embryonic (<10 weeks of gestation) and foetal period (10 or more weeks of gestation). The pathogenic role of aPL was clearly shown in mouse experimental animals that, when infused with aPL during pregnancy, develop placental insufficiency and foetal resorbtions equivalent to miscarriages in humans.[15] Intraplacental trombosis is one of the pathological mechanisms involved, while a direct effect on trophoblast cells and induction of complement mediated placental injury has been also described. It has been recently suggested that abnormalities of early trophoblast invasion, by impairing its differentiation, maturation and decreased human chorionic gonadotropin production, may be the primary pathological mechanism in the first trimester pregnancy losses.[16] In addition, the demonstration of the presence of β2GPI on the trophoblast cell membranes explains the aPL placental trophism, β2GPI being one of the most important antigenic targets for aPL.[17] Other pregnancy complications among women who have antiphospholipid syndrome (APS) include intrauterine growth restriction (IUGR), placental insufficiency and pre-eclampsia.[6]

Several clinical trials have concluded that a combination of heparin and low dose of aspirin could significantly improve pregnancy outcome in women with APS by over 70%. The use of antiaggregant/anticoagulant agents prevents thrombosis in the uteroplacental circulation improving maternal and fetal outcome and reduce or eliminate the maternal thrombotic risk during pregnancy and in puerperium. In fact an increased risk of thrombosis was observed also in patients with aPL but without previous thromboembolic events. Heparin, in addition to its anticoagulant activity, might also act by inhibition of complement system, antagonize trophoblast apoptosis and reverse the diminished trophoblast invasion caused by aPL, improving outcome in APS pregnancy.[18] Despite treatment with heparin, recurrent pregnancy losses occur in 20-30% of cases and the best approach to such cases in subsequent pregnancies is unknown. Some trials recommend to add to anticoagulation treatment low-dose aspirin and an immunomodulatory agent such as glucocorticoids, immunoglobulin or hydroxychloroquine.[7]

Anti Ro/SS-A and/or anti La/SS-B autoantibodies are known to have an high prevalence in SLE patients, as well as in other ARD and they are linked to the occurrence of the Neonatal Lupus Syndrome.[19] Neonatal Lupus is defined as a complex syndrome due to the direct effect of maternal anti Ro/SS-A and/or anti La/SS-B autoantibodies that, if of IgG isotype, can cross the placenta with possible damage to the fetus independently from maternal disease. Neonatal Lupus can be characterized by photosensitive rash, hematologic abnormalities, consisting of trombocytopenia, neutropenia or anemia, recorded in about 27% of cases and liver function abnormalities in about 10%. All

these aspects are typically transient, resolving at about six months of life when maternal autoantibodies disappear from the neonatal circulation.[20-22] On the contrary, another manifestation of neonatal lupus, the congenital complete heart block (CHB), when occurring, gives permanent alteration of the heart conduction tissue.

Nowadays there is not any indication to treat pregnant patient with anti Ro/SS-A to prevent CHB; rather it is important a close monitoring of the patients with serial echocardiography weekly starting from 16 to 25 weeks of gestation in order to allow an early diagnosis. When incomplete CHB is diagnosed *in utero*, the advised treatment of mothers is based on fluorinated corticosteroids that can cross placenta and decrease the inflammation of the fetal heart.

Rheumatoid arthritis

Rheumatoid arthritis is less frequently observed during pregnancy due to its peak onset after the age of 40. With the improvement of the treatments, more patients with RA consider a pregnancy. The disease should be well controlled at the time of conception.[23] Prospective studies have shown in pregnant women with AR an improvement in joint involvement in two thirds to three quarters of pregnancies in the first trimester. Only, 10-20% of women with RA have active arthritis at some stage of pregnancy. There are scant data available, but women with RA do not appear to be at high risk for pre-term birth, pre-eclampsia or IUGR. In the three-four months after delivery there is an high risk of exacerbation of the disease.[24] Reed *et al.* have observed an increased risks for cesarean delivery, prematurity and longer hospitalization at births among infants born to women with RA, may due to the pathophysiologic changes associated with RA or medications used to treat the disease.[25] Also in spondyloarhropathies there is no relevant change in disease activity and the foetal outcome is not impaired.

However, women with RA and spondyloarhropathies need a careful pre-conception counseling because the disease is generally treated with drugs such as methotrexate that are teratogenic, therefore pregnancy must be planned. After delivery, the not rare relapse of AR could cause serious problems in the neonate care for the considerable physical disability and consequent psychological distress. These observations suggest the importance of familiar strategies for the women to overcome these difficulties.

Relatively, low doses of prednisone are usually adequate for RA during gestation; if NSAIDs prove to be necessary, the minimum dose able to control inflammation should be used. Leflunomide must be avoided because teratogenic.[8] A wash out or the drug is also mandatory. Anti TNF should be withdrawal because of the few available data on their safety. However, anti TNF and other biological drugs are not teratogenic.[8]

Sjögren syndrome

Sjögren Syndrome (SS) is a chronic autoimmune disease characterized by a progressive degeneration of exocrine glands. It can occur in patients of all ages, but it affects primarily females during the fourth and fifth decades of life. There are two subsets of the syndrome: patients with systemic autoimmune dysfunction but not defined ARD, referring to primary SS and patients with a defined ARD, classifying as having secondary SS. Reumatoid arthritis is the disorder most frequently associated with SS, but SS can be associated with other rheumatic conditions, including SLE. Antibodies targets of the disease are anti-Ro/SS-A and anti-La/SS-B.[21] In most patients primary SS has a benign course and does not appear to influence the disease course. In the event of secondary SS occurring during pregnancy, treatment focuses on the associated disease. However, patients with both primary and secondary SS must be monitored carefully because there is a risk of neonatal lupus and CHB associated with high morbidity and mortality.[26]

Rare autoimmune rheumatic disease

Undifferentiated connective tissue disease (UCTD) is a pauci-symptomatic condition characterized by clinical manifestations suggestive of connective tissue disease (CTD) but in number and/or combination which is not sufficient to allow the diagnosis of a definite condition. UCTD can remain undifferentiated or evolve into a definite disease after in a variable time, with a frequency ranging from 6 to 51%.[27] All the studies showed that the evolution is more common in the first two-three years after the onset of the symptoms, conversely it is rare after five years.[28] The onset of UCTD usually occurs before the age of 40 and it is relatively common to observe pregnancies in women with this condition.

The occurrence of flares during pregnancy and puerperium of patients with UCTD has bee recently reported; severe flares seem to be rare but they may be linked to the evolution of the disease into SLE. Obstetrical complications and miscarriages can be observed, but their prevalence is low and the majority of the patients can have successful pregnancy.[29,30] Like in SS, neonatal complications are mainly linked to the presence of anti-Ro/SSA antibodies in the mother. In fact, according to a collaborative prospective study of our institution, the risk of delivering an infant with CHB may be higher in mothers with primary SS or UCTD than in those with SLE.[31] In the study by Mosca *et al.*,[29] it is interesting to observe that one patient developed SLE two years after pregnancy but the effective possibili-

ty that pregnancy may cause disease evolution is still an open question.

Although UCTD is a mild condition, the risk of flares during pregnancy linked to a possible disease evolution underlines the necessity of careful multidisciplinary monitoring.

Mixed CTD (MCTD) is characterized by overlapping features of classic CTD and the presence of antibodies to ribonucleoprotein.[32] One-quarter of MCTD patients transforms into LES, while one-third progresses to Systemic Sclerosis (SSc). There are few and controversial studies on pregnancy outcome in women with MCTD. According to some authors, pregnancy is linked to the same risks of adverse maternal and foetal otcome reported in SLE.[33] On the contrary, Lundberg *et al.* suggest that patients with high anti-RNP titer have a slight risk of foetal loss or maternal flare; therapeutic recommendations are glucocorticoids in combination with immunosuppressive (no teratogenic) agents.[34]

Progressive systemic sclerosis (SSc) is a CTD disease with inflammation and fibrosis. The mean age of symptom onset is in the early 40s, so half the women with it have the potential to become pregnant. The older literature includes many case reports in which mother and infant had bad outcomes. On the basis of those reports, it is not unusual for physicians to recommend that scleroderma patients avoid pregnancy. More recent studies gave a more optimistic picture.[35] However, about one-third of these patients have exacerbations of Raynaud's phenomenon, arthritis and skin thickening after pregnancy.

The most frightening situation linked to pregnancy in SSc is an increased risk of renal and pulmonary complications.[35] Renal crisis is difficult to diagnose and treat during pregnancy because it is characterized by an acute onset of severe hypertension, often thrombocytopenia and increases of serum creatinine, which mimics preeclampsia, especially in women with diffuse scleroderma for less than 5 years. Angiotensin-converting-enzyme inhibitors must be used urgently in renal crisis because they are the only drugs that will save the lives of mother and infant. These drugs have been associated with feto-neonatal renal insufficiency, but probably the balance between the risk of problems for infants and the risk of serious kidney damage in the mother, in this particular case, is for the use of these drugs.[35] Pregnancy outcome is usually good, but may be characterized by and increased rate of prematurity and small full-term infants because scleroderma induce placentar vascular abnormalities.[36] Women with early diffuse scleroderma should be encouraged to delay pregnancy until their disease has stabilized decreasing the risk of renal crisis, which usually happens 3-5 years from onset of symptoms.

Polymyositis (PM) and dermatomyositis (DM) are the most common forms of idiopatic inflammatory myopathy. There are two peaks in the age group 10-15 yr and 40-60 yr, with only 14% of patients estimated to present during childbearing years (15-30 yr). Pregnancies in this group are uncommon.

According to the few reported data, pregnancy does not seem to be associated to disease flares.[37,38] Pregnancy outcome seems to be greatly improved after the introduction of corticosteroids treatment.[39,40] Seven cases of PM that started 1 to 3 after pregnancy are described, suggesting that the post-partum period may be a trigger to the development of myositis.[41] In the review of Silva *et al.* what is emerging is that foetal prognosis is influenced by the activity of the maternal disease and the age of onset of the disease. Poor foetal outcome is noted in women with new onset of disease during pregnancy or exacerbation during the first trimester of gestation.[37] In patients with childhood onset of PM or DM the percentage of at term births was 70%, in women with adult onset before pregnancy this percentage decreased to 50%, while when the diseases were diagnosed during pregnancy the percentage of living newborns was 38%.

The percentage of at term delivery and foetal loss is respectively of 47% and 33% in patients with active disease.[42] The criteria for the use of steroids should be identical during pregnancy and at the non-pregnant state. In the case of PM-DM flare during gestation, if prednisone is not able to control the disease, immunosuppressive drugs such as cyclosporine or azathioprine should be added to the therapy.[40]

In conclusion, nowadays, owing to our increasing knowledge of the disease pathophysiological mechanisms and the development of combined medical-obstetric clinics, pregnancy outcome in patients with ARD has notably improved. This paper underlines that better maternal and foetal outcomes can be expected if the pregnancy is planned, the rheumatic disease is stable and if appropriate medication adjustments can be made ahead of time.

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