Intravenous Immunoglobulin in Pregnancy: a Chance for Patients with an Autoimmune Disease

Angela Tincani MD[1], Mirko Scarsi MD[1], Franco Franceschini MD[1] and Roberto Cattaneo MD[1]

[1]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy

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The article by Stojanovich et al. [1] in this issue of *IMAJ* is rather intriguing and prompts a number of comments. Intravenous immunoglobulin can be administered to pregnant women [2]. According to the Food and Drug Administration classification of the risk in pregnancy, IVIG is classified as C, which means "human data are lacking; animal studies show risk or are not done" and, therefore, is potentially dangerous for the fetus. However, it is well known that FDA categories are often not helpful to the clinician for treating patients with active disease during pregnancy. Despite the fact that IVIG can cross the placenta, no fetal adverse effects have been reported in studies performed on patients affected by hematological and autoimmune diseases. In addition, immune system functions were found to be normal in infants born to mothers treated with IVIG for fetal alloimmune thrombocytopenia [3]. Importantly, in clinical practice today, IVIG is the treatment of choice for thrombocytopenia during gestation.

The use of IVIG in pregnant patients with antiphospholipid syndrome was reported to be helpful in several case reports and in small series of patients with repeated unsuccessful pregnancies with or without standard treatment of heparin and low dose aspirin [4]. In addition, IVIG infusion was shown to prevent obstetric complications in APS animal models, possibly preventing the binding of antiphospholipid antibodies to trophoblast. In fact, IVIG prepared from large pools of blood donors may contain anti-idiotypic antibodies to pathogenic antiphospholipid antibodies that can impair their capability to bind beta-2 glycoprotein 1 at the trophobalst level [5], thereby preventing the alterations of placental invasion typical of APS pregnancy complications. In contrast, randomized controlled trials performed in pregnant patients with APS stressed that: a) the rate of live births in patients treated only with IVIG is significantly lower than that of patients on standard treatment [6], and b) IVIG does not appear to confer additional benefits to patients treated with heparin and low dose aspirin [7]. However, although not statistically significant, a lower rate of fetal growth restriction and admission to the neonatal intensive care unit were recorded among the IVIG-treated mothers [7]. Therefore, there is general agreement that IVIG can be considered a rescue treatment for patients with APS-related pregnancy complications despite receiving classical treatment [8].

Another field of application of IVIG in pregnant patients with autoimmune diseases is the prevention of anti-Ro/SS-A associated congenital heart block. This rare event is linked to the transplacental passage of maternal immunoglobulin G anti-Ro/SS-A and/or anti-La/SS-B. The proposed pathogenic events start from binding of antibodies to their antigen carried on the surface of apoptotic fetal cardiocytes, causing pro-inflammatory and profibrotic cytokine production and resulting in damage to the conduction tissue. The occurrence rate of congenital heart block in women with anti-Ro/SS-A and anti-La/SS-B has been estimated at 1–2% [9]. But when a patient already has a child affected by congenital heart block, the recurrence rate is about 20% [10], suggesting therapeutic attempts to reduce it. A relatively small number of these high risk mothers were recently treated with IVIG and corticosteroids during pregnancy, with significant reduction of the recurrence rate. IVIG given to the mothers is able to decrease circulating antibodies in the fetus [11]. This effect has several explanations: a) anti-idiotype regulation as reported above for antiphospholipid antibodies; b) induction of inhibitory Fc receptor; and c) decrease in placental transport of pathogenic antibodies by non-specific blockade of placental Fc receptor, as shown in animal models [11]. Prompted by clinical experience, interesting experimental studies and the rarity of these high risk patients, a collaborative European study was proposed. The protocol consists of five injections of IVIG (0.4/mg/kg) at 12, 15, 18, 21 and 24 weeks of gestation [12] to all anti-Ro-positive women who had a previous affected child. In our unit, one of these patients was treated during her second pregnancy and she delivered a male child without cardiac abnormalities. Obviously, a European registry of treated patients will be necessary to assess the recurrence rate under IVIG treatment.

The reported case can probably be classified as primary APS with lupus-like disease. The occurrence of severe preeclampsia

IVIG = intravenous immunoglobulin
FDA = Food and Drug Administration
APS = antiphospholipid syndrome

conditioning a premature birth (and neonatal death) associated with the presence of antiphospholipid antibodies detected by all the "classical" tests (lupus anticoagulant, anti-cardiolipin and anti-β2 glycoprotein 1 antibodies) allows a formal diagnosis of APS. On the other hand, the detection of antinuclear antibody, anti-DNA, anti-Ro/SS-A and anti-La/SS-B, even in the absence of a full-blown picture of systemic lupus, supports a diagnosis including a wider spectrum of autoimmune manifestations, which is not unusual in these patients.

In our opinion, the sole and mere presence of anti-Ro/SS-A antibodies does not justify dexamethasone administration during pregnancy. First, it is still doubtful that dexamethasone can be helpful; moreover, dexamethasone is potentially linked to a huge number of unwanted effects – both early (miscarriages, late fetal death, growth restriction) and late (neurodevelopmental abnormalities) [13-15]. Since maternal anti-Ro/SS-A antibodies carry a relatively low risk of congenital heart block [9], we only need to monitor its eventual occurrence with serial fetal echocardiography. Only if congenital heart block is diagnosed, can dexa- or, better, beta-methasone administration be justified [2].

In contrast, the use of IVIG in the reported case could have had more than one advantage: theoretically, IVIG could have impaired both the pathogenic antiphospholipid and anti-Ro/SS-A antibodies as discussed earlier. The idea to prescribe low doses of IVIG is certainly interesting, particularly considering the high costs of this treatment. However, it should be demonstrated that they are effective at this low concentration. Unfortunately, the information derived from the paper by Stojanovich et al. [1] is not completely convincing. In fact, there could be a bias in rating pregnancy outcome since the mother was also given low molecular weight heparin and aspirin – the treatment that usually allows successful pregnancies in APS patients. On the other hand, we may argue that low dose IVIG did not impair transplacental passage of anti-Ro/SS-A antibodies, since the baby had cutaneous manifestations of neonatal lupus, indicating that these antibodies reached the fetal circulation. In addition, not much can be derived from observing autoantibody levels during pregnancy. The titers of some autoantibodies (ANA, anti-Ro/SS-A, anti-La/SS-B) seem stable, while others (anti-cardiolipin, anti-β2 glycoprotein 1 and anti-DNA) tend to decrease. Additional confounding effects are provided by hemodilution that occurs during pregnancy and by the administration of dexamethasone which can reduce autoantibody production.

In conclusion, intravenous immunoglobulins are an important resource in the management of pregnant patients with autoimmune syndromes. The possibility of low dose IVIG administration is certainly of great interest, but its efficacy needs to be proven by larger studies.

ANA = antinuclear antibodies

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Correspondence: Dr. A. Tincani, Rheumatology and Clinical Immunology – Spedali Civili, Piazzale Spedali Civili 1, Brescia, 25123 Italy.

Phone: (39-030) 399-5487, Fax: (39-030) 399-5085

email: tincani@bresciareumatologia.it

There is no terror in the bang, only in the anticipation of it

Alfred Hitchcock (1899-1980), prolific U.S. movie director and producer and master of the suspense and thriller genres