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Pregnancy in Sjögren's Syndrome and neonatal lupus

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Plenty of hormonal and immunological alterations are induced by pregnancy in order to protect the fetus from rejection. These alterations can of course influence the activity of autoimmune diseases and it is well known that pregnancy can ameliorate symptoms in women with rheumatoid arthritis, multiple sclerosis, or thyroiditis. However, disease activity can worsen within 1 year after delivery, providing evidence that pregnancy-related hormones have anti-inflammatory properties. For other diseases, such as systemic lupus erythematosus (SLE), there are contrasting opinions.

Data regarding the impact of pregnancy on Sjögren's Syndrome (SjS) is really scant and this is probably due to the fact that disease onset dates generally into the postmenopausal age. Only a few cases have been published reporting the onset of the disease during pregnancy.

Since the incidence of Sjögren's Syndrome has its peak after childbearing age, and the fact that Sjögren's Syndrome is more common in women than in men remains partly unexplained, reproductive factors might be involved. It could be hypothesized that immunobiologic modifications during pregnancy may be associated with Sjögren's Syndrome development. As far as we know, no other studies, apart from one of our group, have investigated the effect of previous pregnancies on the risk of developing Sjögren's Syndrome. We found that a pre-existent autoimmune disease (which suggests a genetic background predisposing to autoimmunity) and a previous pregnancy (with its associated immunobiologic modifications) enhance the risk of Sjögren's Syndrome.

What is the impact of the disease on pregnancy? We know that infertility, spontaneous abortions and stillbirths are more common in patients with systemic lupus erythematosus and scleroderma than in age matched controls, while again Sjögren's Syndrome is somewhat neglected by researchers and we have very few studies addressing this problem. According to previous studies, Sjögren's Syndrome does not affect the ability to carry and deliver healthy babies, since fertility and parity did not differ from control women. On the contrary, in a study from Finland the risk of fetal loss in primary Sjögren's Syndrome was found to be similar to that in women with systemic lupus erythematosus, but not associated with anti-phospholipid antibodies or antibodies to SS-A/Ro or SS-B/La. However, all these studies refer to pregnancies that occurred before the onset, or at least before the diagnosis, of Sjögren's Syndrome.

One of the most concerning complications for a woman with Sjögren's Syndrome during pregnancy is neonatal lupus.

Neonatal lupus can be considered a perfect model of a passively acquired autoimmune disease linked to the transplacental passage of maternal autoantibodies to the fetus.

The mothers can have SLE, Sjögren's Syndrome or other not well specified autoimmune conditions or they can be completely healthy; the autoantibodies are directed against intracellular proteins called SSA/La and SSA/Ro. Some clinical manifestations in the newborn can be reversible (liver involvement with a mild form of hepatitis, reduction in the number of red or white blood cells or platelets, skin manifestations), along with the disappearance of maternal autoantibodies, others can be irreversible and life-threatening (congenital heart block or cardiomyopathy). A heart block is a disturbance in the transmission of the signal from the heart's upper to lower chambers. This does not mean that the blood flow or blood vessels are blocked. The heart block is congenital (CHB) when diagnosed in utero, at birth or within the neonatal period (0-27 days). CHB without structural abnormalities affects 1:20000 neonates in the general population and it is almost universally associated with maternal autoantibodies, the anti-SSA/SSB, while only 1-4 % of fetuses with a mother positive for anti SSA/SSB develop CHB. This percentage increases to 18% if the mother had a previous pregnancy complicated by neonatal lupus.

The CHB associated with autoantibodies generally appears as a slowness of the heart rate (bradicardya) in the fetus between the 16-18th weeks to the 24th weeks. Heart block is classified according to the level of impairment - first-degree heart block, second-degree heart block or third-degree (complete) heart block and the CHB can actually be considered as a dynamic spectrum of disorders where the disease can start as a mild form, I degree block, which then progresses to a more severe form, complete heart block or III degree block. To date, no regression has been observed from third grade block to II or I degree block while I and even II degree block can be transient. The rarity of a complete CHB may be the consequence of a triple hit: maternal autoantibodies and or other maternal factors, foetal factors, and the in utero environment.

The evidence of a direct pathogenic role of maternal autoantibodies comes from epidemiologic studies but it is also supported by autoptic studies (maternal autoantibodies against SSA and SSB antigens have been detected in affected foetal hearts) and by several animal models. However, the low prevalence of CHB in the presence of such autoantibodies is difficult to explain, so it's hypothesizable that not all the autoantibodies (anti-SSA anti-SSB) are alike and not all cause the disease and at the same time we can hypothesize that other factors (maternal and foetal genetic factors, environmental factors such as hypoxia) influence the risk for CHB and modulate its extent.

Evidence-based guidelines for the management of fetuses identified with CHB, and fetuses with a normal heartbeat but at high risk of developing CHB, are not established and we are still

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following expert-based opinions. The most important advice for a woman with Sjögren's Syndrome who wishes a pregnancy is to consult her physician; if anti-SSA/SSB antibodies are present, a weekly fetal echocardiography will be necessary from the 13-14th weeks of pregnancy to the 24-26th. As far as we know, third grade block is irreversible so there is no need to treat the mother unless she needs a treatment for her disease. Serial echocardiography are suggested to reveal signs of myocarditis or cardiac insufficiency as soon as possible.

As fetuses presenting with third degree block might not benefit from any treatment, there are two critical times to intervene: when a first or second degree block is found; or when signs of myocardial dysfunction alone are present. In such cases, we can consider steroids; the most commonly used are fluorinated steroids as only betamethasone and dexamethasone cross the placenta unmetabolized, while prednisone and prednisolone are inactivated by placental enzymes. In the case of first or second degree block treatment with 4 mg oral dexamethasone daily could be tried. If progression to third-degree block occurs, dexamethasone dose should be tapered to discontinuation. If reversal to normal sinus rhytm or lesser forms of block occurs, the drug might be continued to delivery; however the treatment has to be individualized. The administration of corticosteroids to a mother with anti-SSA/SSB without a previous child with neonatal lupus is not justified while for a woman considered at high risk (if she had a previous child with neonatal lupus, the risk of having a second child with the diseases is about 18%) some options are currently under study: iv high dose immunoglobulins or plasmapheresis. Finally, we have no reason not to recommend breastfeeding to mothers with anti-SSA/SSB.

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