Prevention of congenital heart block in children of SSA-positive mothers

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The incidence of congenital heart block (CHB) in the offspring of anti-Ro-positive women is ∼1–2%, and the risk of recurrence is 10 times higher in the following pregnancies. Non-fluorinated steroids (prednisone, prednisolone and methylprednisolone) are recommended only for maternal indications, not for prevention of CHB in anti-Ro/SSA-positive women. Fluorinated steroids (dexamethasone or bethametasone) are not metabolized by the placenta and are available to the fetus in an active form. Routine prophylactic therapy with fluorinated steroids is not recommended even in women who previously had children with CHB or skin rash since this therapy has its own side-effects. Intravenous immunoglobulin had been used to prevent the development of CHB in 8 high risk mothers (anti-Ro/SSA positive and previous pregnancy with CHB), and in one case CHB recurred (12.5%). At present, the only sure recommendation that can be made in these women is that in the presence of reliable positivity for anti-Ro/SSA antibodies serial echocardiograms and obstetric sonograms should be performed at least every 2 weeks starting from the 16th week of gestational age: the goal is to detect early fetal abnormalities, such as premature atrial contractions or moderate pericardial effusion, that might precede complete atrioventricular block and that might be a target of preventive therapy. Fluorinated steroids should not be used in the absence of symptoms; in the presence of alarming symptoms, betamethasone seems safer than dexamethasone.

KEY WORDS: Heart block/congenital, Neonatal lupus, Systemic lupus erythematosus, Sjogren's syndrome, Undifferentiated connective tissue disease, Dexamethasone, Betamethasone, Intravenous immunoglobulin, anti-Ro/SSA antibodies, Pregnancy.

Introduction

The incidence of congenital heart block (CHB) in the offspring of anti-Ro-positive women is ∼1–2%, and the risk of recurrence of complete atrioventricular (AV) block is almost 10 times higher in the following pregnancies. Substantial morbidity (∼65% require lifelong pacing) and mortality (∼20%) are associated with CHB [1]. Most of the mothers are asymptomatic at delivery and are identified only by the birth of an affected child.

Pathogenesis

Neonatal lupus is associated with the presence of autoantibodies directed against the ENAs SSA/Ro and SSB/La [1]. These antibodies cross the placenta beginning at ∼16 weeks of gestation and reach the fetal tissues, where: (i) they might induce a *myocarditis*; (ii) they may be *arrhythmogenic*; and (iii) they can interfere with *apoptosis*. The immune-mediated damage of the cardiac conduction system ultimately ends with its substitution with fibrotic tissue.

Anti-Ro/SSA 52 kDa antibodies and antibodies directed against the p200 peptide of the SSA antigen have been linked more stringently to the development of CHB, but the data are not conclusive [1].

Risk of occurrence and pre-conceptional counselling of anti-Ro/SSA-positive mothers

A woman is at risk of delivering a baby affected by complete CHB if she is definitely anti-Ro/SSA positive. If the positivity is uncertain or the titre is very low, we advise confirmation of positivity with standard methods or in reference laboratories. The risk is ∼1–2% of anti-Ro/SSA-positive pregnancies. There are some suggestions that anti-52-kDa Ro/SSA and anti-La/SSB antibodies are more strongly associated with CHB than

anti-60-kDa Ro/SSA alone (at least as tested by immunoblot), but the data are incomplete. Furthermore, the problem of reliability, sensitivity and specificity of the different tests (commercial kits, home made, etc.) is even greater at this level of differentiation of the fine specificities.

Since anti-Ro/SSA antibodies are relatively frequent in women, at least in a rheumatology practice but CHB is very rare, we are faced with the following situation: frequent counselling about a rare disease. In a prospective study, we found that the incidence of CHB in newborns of 100 women already known to be anti-Ro/SSA-positive and with known CTD was 2% (95% CI 0.2%, 7%) [2]. We studied only mothers who had been found to be anti-Ro/SSA positive by counter-immunoelectrophoresis, a method with high specificity and rather low sensitivity, to exclude women with low or dubious titres of anti-Ro/SSA. Our results therefore cannot be extrapolated, for instance, to those with a low positive reaction for anti-Ro/SSA antibodies by ELISA, for which the risk, if any, should even be lower. The CHBs were detected at 22 and 20 weeks. One of the two CHB mothers had primary SS, while the other had UCTD. No case of CHB occurred among 53 SLE mothers. This finding has now been confirmed by other groups: Gladman [3] reported no cases of CHB in 100 live births in 96 women with anti-SSA/Ro and/or anti-SSB/La antibodies and no history of a previous child with neonatal lupus; Cimaz (2003) observed two cases of CHB out of 128 infants (1.6%) [4], Costedoat-Chalumeau one case out of 99 infants (1%) [5], and Gerosa (2007) reported a similar risk [6].

Risk of recurrence

Few prospective studies exist on this issue; the percentage seems to comprise between 10% and 20%, and therefore substantially higher than in the first pregnancy [1, 7]. In a nation-wide study from Finland, the risk of recurrence of CHB was 17% (8 of 47), and data from the Research Registry for Neonatal Lupus including 105 affected mothers showed that 19% of pregnancies immediately subsequent to the birth of a child with CHB resulted in a second child with CHB [1]. It is also important to underline that women who have had a prior pregnancy of a child with the bona fide skin rash of neonatal lupus also have about a 19% risk of having a subsequent pregnancy with CHB [1].

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Prevention of CHB

Non-fluorinated steroids

Non-fluorinated steroids are recommended only for maternal indications, and prednisone, prednisolone and methylprednisolone should be preferred [8]. They are not indicated for prophylaxis of CHB in anti-Ro/SSA-positive women, even if they had in the past infants affected by neonatal lupus (CHB or skin rash). These steroids (at least in low and moderate doses) do not prevent the development of CHB [1]. This might be anticipated since prednisone given to the mother does not cross the placenta and is not active in the fetus and levels of anti-Ro and anti-La antibodies remain relatively constant during steroid therapy.

Shinohara [9] has reported that pre-natal maintenance therapy with prednisolone started before 16 weeks' gestation might reduce the risk of developing CHB, but this article is heavily biased by the retrospective setting. In fact, it is now recognized that the majority of women bearing children with CHB do not have recognized SLE and are often asymptomatic at the time of delivery, so they are not pre-treated with steroids: these women would not have been identified had the fetal abnormality not occurred (retrospective diagnosis). Furthermore, that study included too few cases to see a real benefit from steroids, and there are cases of CHB in infants born to mothers who did take steroids.

Fluorinated steroids

Fluorinated steroids are not metabolized by the placenta and are available to the fetus in an active form [8]. Routine prophylactic therapy with fluorinated steroids is not recommended [1, 7]; in fact, the risk is too low to justify treatment with dexamethasone or betamethasone for all pregnant women who are anti-Ro/SSA positive, since this therapy has its own side-effects. Even in women who previously had children with CHB or neonatal lupus skin rash side-effects profile had been shown to be unacceptable [10].

Maternal risks of these steroids are similar to any glucocorticoid, but for these indications they are usually used at high dosages (at least 4 mg dexamethasone daily) and include infection, osteoporosis, osteonecrosis and diabetes. Fetal risks include intrauterine growth restriction and oligohydramnios [8].

Intravenous immunoglobulin

At present the most pressing issue in CHB is the management of a pregnancy subsequent to the birth of an affected child (recurrence rate is ∼16%).

Kaaja and Julkunen [7] used intravenous immunoglobulin (IVIG) and corticosteroid to prevent the development of CHB in eight high-risk mothers (anti-Ro/SSA-positive and previous pregnancy with CHB) [11]. During the pregnancy following the one that resulted in the birth of an infant with CHB, women were treated with IVIG 1 g/kg at 14 and 18 weeks of gestation. Prednisone was started at 14 week of gestation at a dosage of 40 mg daily, which was tapered to 20 mg daily at 16 weeks and 10 mg daily at 24 weeks; prednisone was continued at this latter dosage for the remainder of the pregnancy. One woman underwent the IVIG infusions but refused to take prednisone. Seven of the eight women gave birth to a healthy child without CHB. The woman who delivered a child with CHB was the one who did not receive corticosteroids. A reduction in anti-Ro/SSA titres was observed in six of the eight women. Notably, the overall risk of recurrence was similar to the expected one: $1/8 = 12.5\%$ [11]. The potential mechanisms by which IVIG could prevent the tissue damage are increased elimination of maternal anti-Ro and anti-La (idiotype–anti-idiotype regulation), decrease in transplacental transport of antibodies and modulation of inhibitory signalling on macrophages with consequent reduction of inflammatory response and fibrosis. New evidence showing the potential usefulness of IVIG to prevent CHB was reported by Tran et al. [12]. In a murine model, maternal administration of IVIG inhibited the transfer of anti-Ro/La across the placenta and their susbequent deposition in the fetal heart, most likely by non-specific blockade of placental Fc receptors.

Based on these data, the English group has proposed at the Fourth International Conference on Sex Hormones, Pregnancy and the Rheumatic Diseases, organized by Italian Society of Rheumatology in Stresa, 2004, a protocol for the prevention of CHB development in high-risk pregnant women. This is a prospective, pilot trial of treatment with IVIG to pregnant women with anti-Ro/SSA antibodies and previous pregnancy with CHB. The proposed medication regime is infusion of IVIG 0.4 g/kg given at 12, 15, 18, 21 and 24 weeks of pregnancy in women who agree to take part. IgA deficiency is an exclusion criterion. Primary outcome is the development of third-degree CHB. Enrolment is ongoing.

The incidence of adverse effects with IVIG use ranges between 1% and 15% [13]. The most common side-effect related with the infusion is the association of headache, fever and flushing, typically mild and transient. An anaphylactoid reaction is possible in IgA-deficient patients, but could be avoided by starting IVIG infusion at low rate to achieve desensitization. Pain in the IV site, flushing and hypotension may result from the presence of vasoactive substances. Other less frequent adverse events include renal dysfunction and acute renal failure related to sucrose nephropathy. Underlying renal failure and diabetes predisposes to this complication. In order to minimize the renal effects, all patients should be well hydrated. Reports of thromboembolic events have been associated with IVIG use, including venous and arterial thrombosis.

Possible treatment of early fetal abnormalities

The following suggestions are experimental or based on the experience of some experts in the field, and not tested in a controlled trial. First of all, although there is not yet documentation regarding the reversal of third-degree heart block (presumably fibrosis of conducting system), the potential for diminishing an inflammatory fetal response attacking the cells of the conduction system is plausible. Second, incomplete AV block has been shown to be potentially reversible [14, 15]; moreover progression of second-degree AV block to third-degree AV block has been described, even after birth [1] Third, at first appearance of a fetal bradycardia it can be extremely difficult and time-consuming to differentiate between second-degree (incomplete) and third-degree (complete) AV block [15]. Fourth, until recently the in utero detection of first-degree AV block was not technically feasible, but now the electrocardiogram equivalent of the PR interval can be measured by echocardiography [16]. Using the gated-pulsed Doppler technique, time intervals from the onset of the mitral A wave (atrial systole) to the onset of the aortic pulsed Doppler tracing (ventricular systole) within the same left ventricular cardiac cycle may be measured [16]. This time interval represents the mechanical PR interval. Other methods have also been developed [17], and signs of first-degree heart block may occur in up to one-third of the fetuses of pregnant women with anti-Ro/SSA 52-kDa antibodies [17] (though the definition of what time interval equates with first-degree heart block is not clear). Finally, a very informative case report has been described by Rosenthal [14], who described a woman with a previous pregnancy, complicated by CHB [18]; in the next pregnancy, intensive fetal monitoring revealed at 21 weeks' gestation a decrease in left ventricular function, occasional premature atrial contractions, a moderate pericardial effusion and a biphasic flow in the inferior vena cava. All these abnormalities reverted after dexamethasone 4 mg once daily was given, and a male newborn was delivered at 36 weeks' gestation, with a first-degree AV block present in the ECG. This case report shows that early and treatable abnormalities may be

detected and potentially avert deterioration to complete and permanent block. Unfortunately, it has been reported that one fetus may progress from abnormal AV time interval to complete block in 6 days [17], and we observed a case that in 1 week progressed from a normal echo to a complete heart block with myocarditis (personal unpublished data). Anyway the goal might be to detect early fetal abnormalities, that might precede complete AV block and that might be a target of pre-emptive therapy [1, 7]. In the presence of abnormalities such as these (e.g. premature atrial contractions or moderate pericardial effusion) [18] we give betamethasone to the mother, 4–6 mg daily. This therapy is continued for some weeks, according to the evolution of the clinical features. We acknowledge that this approach is not based on evidence. We prefer betamethasone to dexamethasone, since the possible negative effects seem more linked to dexamethasone than betamethasone [8], and it has been suggested that betamethasone should be preferred when available [8]. Moreover, separate meta-analysis of the data in the Cochrane review show that only betamethasone and not dexamethasone significantly reduces neonatal mortality [8]. Even a recent trial concluded that 'pending a randomized, clinical trial, it may be in the best interests of infants to receive betamethasone, rather than dexamethasone, when possible' [19].

Rheumatology key messages

- Corticosteroids are not recommended to prevent CHB.
- IVIG had been used in high risk mothers but recurrences were observed (12.5%).
- Serial echocardiograms are advised to detect early fetal abnormalities.

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