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Management of fetal congenital heart block in pregnancies with anti-Ro antibodies

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ABSTRACT

Anti-Ro antibodies are detected frequently in the general population, but more so in patients with autoimmune conditions as Sjögren's syndrome and systemic lupus erythematous (SLE). During pregnancy, anti-Ro antibodies can cross the placenta by hijacking physiological mechanisms and can have deleterious effects on the fetus. Administration of hydroxychloroquine (HCQ) to pregnant women with documented anti-Ro antibodies has been shown to prevent congenital heart block (CHB). Serial fetal ultrasound scans and echocardiograms are controversial in pregnant women with anti-Ro antibodies. When complete CHB is diagnosed, this is irreversible and can lead to fetal heart failure, hydrops, and death. After delivery, babies with complete CHB require pacemaker. In the presence of maternal anti-Ro antibodies, there is a high risk of recurrence of CHB for future pregnancies, if there is a previously affected child. Adequate counselling and prophylactic treatment with HCQ should be encouraged.

Keywords: fetus, pregnancy, congenital heart block, anti-Ro antibodies

INTRODUCTION

Autoimmune disorders are among the most frequent conditions encountered in women of reproductive age and they can have severe consequences during pregnancy (1). Anti-Ro antibodies are abnormal autoantibodies directed against the Ro52 and Ro60 antigens in human cells (2). These antibodies are characteristic to Sjögren's syndrome, but they may be found in other autoimmune conditions like systemic lupus erythematous (SLE) and other connective tissue disorders (3). Also, notably, they are frequent in the general population and during pregnancy, with incidence studies giving figures as high as 1 in 200 pregnant women (4). Anti-Ro antibodies are relevant in pregnancy as they can be associated with fetal cardiac block (congenital heart block, CHB), cardiac fibroelastosis, heart failure and neonatal lupus. During pregnancy, maternal IgG antibodies physiologically cross the placenta after 14-16 weeks and concentrate into the fetal circulation, peaking in the third trimester. Some abnormal autoantibodies hijack this physiological mechanism and pass to the fetus, causing disease (5). It is the case of maternal anti-Ro autoantibodies that in 2% of carriers cause fetal CHB and in up to 15% are associated with neonatal lupus (6).

METHODS USED IN THE DIAGNOSIS OF FETAL CONGENITAL HEART BLOCK

Fetal cardiac rhythm abnormalities can be diagnosed in pregnancy with the use of ultrasound (7). The technique not only helps in assessing the cardiac rhythm but also the structure and function of the fetal heart. By power-Doppler imaging with the occasion of every fetal ultrasound evaluation in pregnancy, the obstetrician checks the fetal heart rate (FHR), which should be between 110-140 beats per minute. Abnormalities of the FHR, if persistent, raise suspicion of rhythm disturbances and a specialized fetal exam, usually in the hands of a maternal-fetal medicine specialist, is required. A fetal echocardiography (EChO) is offered anytime a structural cardiac or rhythm anomalies are suspected in the fetus. Assessment of cardiac structures, of

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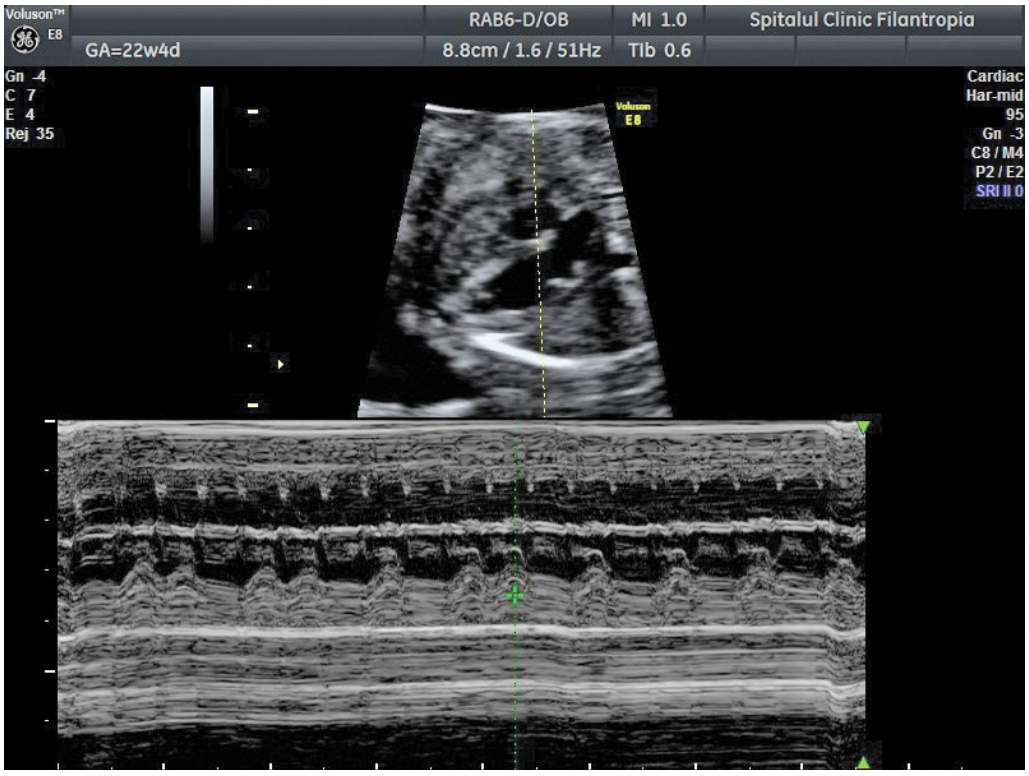

FIGURE 1. Echocardiography of the fetal heart at 22 weeks of pregnancy in a mother with anti-Ro antibodies. M-mode. The beam record sequential contraction of the atrial and ventricular walls and this is displayed in the image. There is grade 2 intermittent fetal atrioventricular (AV) block

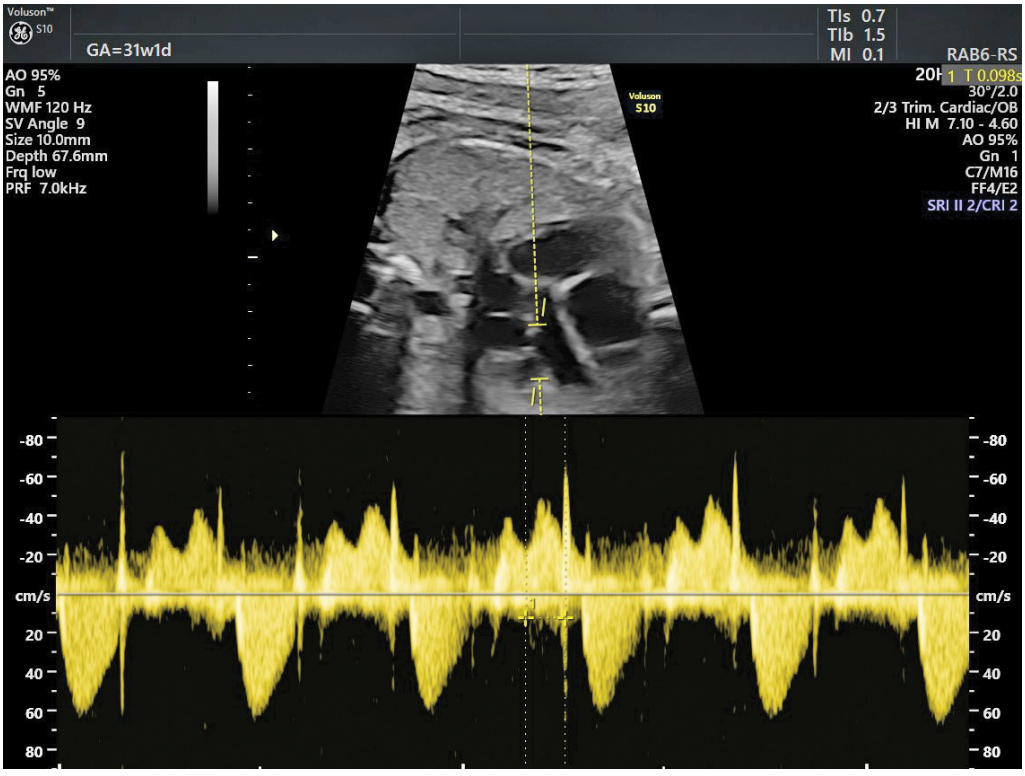

FIGURE 2. Fetal ultrasound power-Doppler measuring the PR interval as part of a strategy of detecting grade 1 fetal AV block

flow and appearance of the valves, of cardiac contractility and of rhythm are performed. The sequence of fetal cardiac conduction of the electric impulse is investigated using M-mode imaging. In M-mode imaging, the ultrasound probe records and graphically displays the sequential contraction of

the atrial and ventricular free walls (7). If there is abnormal conduction at the atrioventricular (AV) node, this will be evident on the recording (Figure 1).

Another mean of investigating AV conduction in utero is by using power-Doppler with the recording gate at the level of both mitral and aortic valves in order to detect their sequential opening. The PR interval (in seconds), equivalent to the PR interval on the surface electrocardiogram (8), can be measured (Figure 2). These methods are frequently employed when evaluating pregnant women with anti-Ro antibodies.

Congenital heart block has two main causes: one is related to the anti-Ro antibodies, and this is usually found in the presence of a structurally normal fetal heart, and the other is in relation to structural anomalies (Table 1).

TABLE 1. Causes of congenital heart block in the fetal life

Anti-Ro antibodies (usually, the fetal heart structure is otherwise normal; in some cases cardiac fibroelastosis)
Structural abnormalities - Heterotaxia syndromes - Transposition of great arteries - Atrioventricular septal defects - Tetralogy of Fallot
Infections - Coxsackievirus - Cytomegalovirus
Medication - Antiepileptic drugs
Maternal disease - Diabetes - Phenylketonuria

As in the adult population, CHB in the fetus is classified in grade 1, grade 2 and grade 3 or complete AV block.

ANTI-RO IN THE MOTHER AND PRIMARY PROPHYLAXIS OF FETAL CONGENITAL HEART BLOCK

In pregnancies where mothers are known to have anti-Ro antibodies, as for example in women with Sjögren's syndrome or SLE, a method of monitoring every 1-2 weeks by fetal echocardiography has been proposed starting at 16-18 weeks of pregnancy. The rationale behind this approach has been that fetal lesser degrees of block (grade 1 and 2) can be detected and progression to complete irreversible grade 3 block can be stopped by giving drugs as dexamethasone, a corticosteroid that crosses the placenta and can act on the fetus. This approach is controversial since studies have shown that some cases of grade 3 CHB manifest in absence of demonstrated progression and that dexamethasone or even intravenous immunoglobulins (IV Ig) do not prevent progression in all cases. Not to mention that this approach is highly costly for medical systems: it does require a high number of serial specialized scans. An approach that has recently become apparent and has been shown to be efficient is primary prevention of CHB in women with anti-Ro antibodies using hydroxychloroquine (HCQ). Hydroxychloroquine is an antimalarial drug very much used and very efficient in SLE. There is convincing evidence that by giving HCQ to women with anti-Ro antibodies before and during pregnancy, the risk of fetal CHB is significantly decreased. Hydroxychloroquine is safe for use in pregnancy and should be kept in patient that are already taking it in SLE and introduced for those with anti-Ro antibodies (9-11).

CONGENITAL HEART BLOCK GRADE 1 AND 2 DIAGNOSED IN THE FETUS

When CHB of grade 1 or 2 is diagnosed in the fetus, an attempt to prevent progression to irreversible grade 3 CHB should be made. Dexamethasone, a fluorinated steroid that crosses the placenta, has been shown to be effective in some case (12). The maternal dose is usually around 4 mg per day and is given long term, up to delivery usually. As with other steroids, abnormal glucose metabolism is to be expected in the mother and possible need for steroid supplementation at delivery.

CONGENITAL HEART BLOCK GRADE 3 DIAGNOSED IN THE FETUS

When a diagnosis of CHB grade 3 in the fetus has been made, this is usually irreversible and leads to cardiac failure. The management in these cases depends on the gestational age at the time of diagnosis and the subsequent progression to heart failure. If the block is diagnosed towards term (after 33-34 weeks of pregnancy), delivery can be planned. It is to be kept in mind that these babies usually require pacemaker after delivery so the birth should be arranged in a specialized center, where neonatal cardiac interventions can be offered and that the baby should be at least 2000-2500 grams. If the complete CHB is detected earlier in pregnancy, follow-up should be planned with the intent to bring the pregnancy as close as possible to term. About 15% of all cases of complete CHB will progress to severe heart failure, fetal hydrops, and death. No intervention or drug has been proved to be useful in preventing heart failure and fetal death in these cases. Studies have tested the use of dexamethasone, intravenous immunoglobulins, plasmapheresis, even intrauterine placement of pacemaker, however, all attempts

have been found to be ineffective (13-16). In fetuses where the FHR drops severely below 50-60 beats per minute and to prevent hydrops, betamimetics (salbutamol, terbutaline) that cross the placenta can be given to the mother to attempt increasing the FHR.

CONCLUSIONS

Anti-Ro antibodies are frequent in the general population, but more so in patients with Sjögren's syndrome and SLE. During pregnancy, these antibodies can cross the placenta by hijacking physiological mechanisms and can have deleterious effects on the baby. Hydroxychloroquine has been shown to prevent CHB in mothers with anti-Ro antibodies and is recommended in all women where they are documented. Serial fetal echocardiograms are controversial in pregnant women with known antibodies. When complete CHB is diagnosed, this is irreversible and can lead to fetal death. Also, there is a high risk of recurrence for future pregnancies when a mother has a previously affected child and effective counselling and prophylactic treatment with HCQ should be planned.

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