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EDITORIAL COMMENT

Congenital Heart Block in Subsequent Pregnancies of SSA/Ro-Positive Mothers

Cutting Recurrence in Half*

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The study reported by Izmirly et al. (1) in this issue of the *Journal* is a very important multicenter, single-arm, 2-stage clinical trial evaluating an orally administered Toll-like receptor signaling antagonist, hydroxychloroquine (HCQ), in recurrent maternal Sjögren's antibody (SSA/Ro)-mediated congenital heart block. As the authors

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stated, congenital heart block (CHB) has significant morbidity and mortality (17.5%) both before and after birth (1). A recent Italian Registry of isoimmune CHB in pregnancy reported a live birth rate of about 80%, with nearly two-thirds of the children requiring implantation of a pacemaker after birth (2). Attempts to reverse second-degree AV block in utero with dexamethasone or intravenous gamma-globulin have been successful in only about 25% of cases, and even when improvement occurs, regression back to CHB still occurs in about one-half of these cases in infancy and even up to age 10 years (3). Third-degree AV block is considered permanent. Approximately 10% of infants with isoimmune-mediated cardiac disease will develop cardiomyopathy in the first year of life (4). Hence, long-term medical surveillance in these children is important.

The initial incidence of CHB in SSA/Ro-positive pregnancies is reported to be about 2% and may be slightly higher in women with active disease and high antibody titers. Isolated SSB-positive titers do not appear to confer a significant risk for CHB. Jaeggi et al. (5) reported that women with low SSA antibody titers have almost no risk of AV block; however, if a previous pregnancy has been complicated by fetal AV block, the risk is reported to be as high as 18% (1,5). Therefore, prevention strategies are of significant importance.

In this issue, Izmirly et al. (1) demonstrated that when initiated early in pregnancy 400 mg HCQ orally daily resulted in a risk reduction of ~50% in the recurrence of CHB. Several prevention approaches have been attempted over the past decades with limited therapeutic impact, such as regular monitoring of mechanical PR intervals, intravenous immunoglobulin, and the use of fluorinated steroids. These approaches failed to reduce the recurrence of CHB. In 2012, Jill Buyon's group reported in a retrospective analysis that HCQ reduced AV block, but a prospective trial was required to confirm as well as to assess the correct dosing and timing (1,6). Hence, this study, performed by a team with extensive experience, represents a remarkable advance in the treatment of pregnancies at high risk for recurrent congenital heart block.

The study recommends the use of HCQ by completion of 10 weeks' gestation because of HCQ's long half-life of 2 months. The best anti-immunologic effect is then achieved in the most vulnerable phase of the development of CHB (between 18 and 25 weeks' gestational age). However, along with this long half-life, come other disadvantages. For example, HCQ

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would be much less beneficial to the fetus if started after the first trimester or after first-degree AV block.

Thus, in summary, HCQ can be used in pregnancy, and infants can be breastfed because no accumulation is reported in breast milk. However, the following question remains: Can or should HCQ be used prophylactically in all pregnancies in which isoimmunization is found? Although the risk for CHB is high in previously affected CHB pregnancies, it is only 2% in SSA-positive pregnancies and may be almost zero when SSA titers are low (5). Considering these facts, the use of HCQ in a low-risk setting is not necessary unless it is indicated for the mother's health.

Probably the most serious potential maternal and transplacental fetal risk of HCQ is its effects on the QT interval. HCQ blocks the KCNH2-encoded hERG/Kv11.1 potassium channel and can cause QTc prolongation and spontaneous ventricular arrhythmias and induce sudden cardiac arrest due to torsades de pointes ventricular tachycardia (7). These risks may increase when HCQ is combined with other QT-prolonging drugs. Examples of such drugs used during pregnancy include ondansetron, azithromycin, and oxytocin. Other QT-lengthening drugs, such as antihistamines, can be obtained by the pregnant patient over the counter, and many older drugs approved years ago have not been officially tested for QTc-prolonging effects. Considering HCQ may be present in minute amounts for up to 10 months after termination, avoidance or extreme caution in the use of QT-prolonging medications must extend well beyond that of most drugs (8). Women are more susceptible to proarrhythmic QTc prolongation, and women during pregnancy can manifest low magnesium, calcium, and 25-hydroxy vitamin D levels, further potentiating risk. It is known that the use of multiple QT-prolonging medications can have an additive effect on hERG blockade. The U.S. Food and Drug Administration recently issued a warning against the injudicious use of HCQ on an outpatient basis for coronavirus disease-2019 prophylaxis. The Heart Rhythm Society and the Mayo Clinic have published algorithms for monitoring HCQ that included pre-initiation electrocardiograms (7). Finally, the manufacturer recommends monitoring the baseline electrocardiogram, electrolytes (calcium, magnesium, and potassium), and renal and hepatic function. The addition of a second QT-prolonging drug warrants a repeat electrocardiogram.

Although we know HCQ's effects on the QTc of the pregnant patient, what is not known is HCQ's impact on the QTc of the fetus before or with CHB. During sinus rhythm, 2% of normal fetuses will have QTc values of 500 ms (9). In CHB, many fetuses will demonstrate excessive QTc prolongation, sometimes in the range of 690 ms, with T-wave alternans (10,11). QTc is a function of heart rate, and, thus, with lower ventricular rates and occasional bundle branch block, an increase in QTc can be expected (10,12). Hence, treatment of the mother may not be entirely benign for the fetus. Specific tools to monitor the fetus at risk are necessary. Only fetal magnetocardiography is currently approved by the Food and Drug Administration and is capable of demonstrating the QTc and complex novel arrhythmias; therefore, it may be a consideration in this specific setting in patients at high risk (11).

At this time, HCQ is indicated (based on the recommendations of Izmirly et al. [1]) for prophylaxis in patients with a high risk for recurrent fetal CHB because the lifelong risk of morbidity is substantial and probably outweighs the risk of HCQ to either mother or fetus. However, they did not recommend the use of HCQ in the low-risk population of SSA patients, especially those with low titers and no active disease. Even if one were to use it in the patient with active lupus or high SSA titers in the absence of prior fetal heart block, it should primarily be for the mother's benefit and with open discussion of the risks. Given a 50% decrease, it would be necessary to treat 100+ low risk SSA-positive pregnancies with HCQ to prevent just 1 case of congenital AV block.

In summary, HCQ is a highly beneficial drug in the management of women with autoimmune diseases and now has a new role for the prophylaxis of recurrent fetal heart block in which it halved the rate of development. Given the risk for QTc prolongation, if available, fetal magnetocardiography should be considered to risk stratify the fetus. Even with the best treatments available, clinical trials are still needed in order to better define the best treatments for CHB once it develops. We must evaluate modifiable risk factors and correct these before and during the vulnerable stages of pregnancy. Finally, the development of better methods for the early detection of CHB, such as home handheld Doppler daily screening during the most vulnerable time frame in the most vulnerable cases, may allow for early attempts at reversal. We wish to commend the authors on their long-term dedication to improving the management of pregnant women with autoimmune disease.

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