Physicians should consider HCQ to reduce the risk of recurrent congenital heart block

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New research findings presented at the 2019 ACR/ARP Annual Meeting discovered that hydroxychloroquine (HCQ) significantly reduces the recurrence rate of congenital heart block in subsequent pregnancies of women with anti-SSA/ Ro antibodies, regardless of their health status. (Abstract #1761).

Anti-SSA/Ro antibodies may be present in diseases like Systemic lupus erythematosus, referred to as SLE or lupus, and Sjögren's syndrome. SLE is a chronic (long-term) disease that causes systemic inflammation which affects multiple organs, including the skin, joints, kidneys, brain and the tissue lining the lungs (pleura) and/or heart (pericardium). Approximately 40 percent of women with SLE have anti-SSA/Ro antibodies. Sjögren's syndrome targets the eyes and mouth resulting in extreme dryness, and nearly 100 percent of women with this disease have anti-SSA/Ro antibodies. In healthy women with no symptoms of autoimmune disease, up to one percent can have anti-SSA/Ro antibodies which may first be detected during pregnancy when routine monitoring uncovers congenital heart block. HCQ is an antimalarial drug commonly used to treat SLE and Sjögren's syndrome.

"Congenital heart block affects an estimated two percent of pregnancies among women who have anti-SSA/Ro antibodies who have never been pregnant or have never had an affected child. It appears maternal health accompanying the production of the candidate autoantibodies is not a risk factor for fetal disease, since many mothers whose fetuses develop cardiac injury are asymptomatic and often learn of anti-SSA/Ro

antibodies solely based on disease in their children," said Peter Izmirly, MD, associate professor of medicine at New York University (NYU) School of Medicine and the study's lead author.

Recurrence rates rise tenfold once a mother has had a child with congenital heart block. Advanced block carries substantial mortality and morbidity risks in these children. There are no effective treatments for congenital heart block, so prevention is key. The Prospective Open Label Preventive Approach to Congenital Heart Block with Hydroxychloroquine (PATCH) study, a two-stage, open-label, single-arm phase two clinical trial, evaluated whether HCQ reduces the congenital heart block recurrence rate below the historical 18 percent.

Seventy-four mothers signed consent forms to participate in the trial. All had a previous child with congenital heart block. In addition, 71 percent were white, 48 percent had SLE and/or Sjögren's syndrome, 41 percent had another child with congenital heart block who had died, and three percent had more than one previous child with congenital heart block. Exclusions included: ten due to screening failures, including two miscarriages at less than 12 weeks; seven due to HCQ initiation after 10 weeks of pregnancy; and one due to receiving one mg of dexamethasone at screening. One was lost to follow-up before delivery, leaving 63 pregnancies that could be evaluated with serial fetal echocardiograms at birth or at one year.

The trial included 19 patients in the first stage and 35 in the second, using Simon's optimal approach to allow for early stopping due to absence of treatment efficacy. The protocol required HCQ initiation or maintenance at 400 mg daily by 10 weeks' gestation. Mothers underwent serial echocardiograms, and had blood drawn during each trimester and at delivery for cord blood to measure antibody and HCQ levels.

In the first stage, two out of 19 fetuses had congenital heart block, so the

study proceeded to a second stage. By intention to treat analysis, four out of 54 pregnancies (7.4 percent) resulted in congenital heart block, all at 19 to 20 weeks of pregnancy. Researchers found that three fetuses presented with second-degree heart block, with one reverting to normal sinus rhythm by birth following dexamethasone treatment, and two progressing to third-degree congenital heart block despite dexamethasone and intravenous immunoglobulin (IVIG), with one electively terminated. One fetus presenting with first-degree congenital heart block was treated with prophylactic dexamethasone but despite this progressed to second-degree heart block which reverted to normal sinus rhythm at birth. At two years old, the two children with normal sinus rhythm (second degree in utero) had intermittent second-degree heart block on a Holter monitor.

In the overall study nine mothers were prescribed potentially confounding medications including IVIG and/or dexamethasone after enrollment for lupus flares, cardiac concerns apart from advanced block (APCs, echo brightness, 1st degree block), and/or physician decisions to consider additional prophylaxis. To evaluate HCQ alone, nine additional mothers were enrolled in the trial who only took HCQ, including one whose fetus developed third-degree congenital heart block at 19 weeks. When the researchers included only the pregnancies of women exposed to HCQ alone prior to a confirmed second- or third-degree heart block, four (7.4 percent) out of 54 children developed congenital heart block. In total, five (7.9 percent) out of 63 pregnancies resulted in advanced heart block. Among all participants, the adherence rate for the study was 98 percent based on the HCQ levels in the mothers. No congenital heart block developed in any of the seven mothers who were screened out of the trial because of low dose or delayed start of HCQ.

"Our group has previously reported in a historical cohort that the use of HCQ may be associated with a reduced recurrence rate of congenital heart block, but this is the first prospective study to confirm those

findings," said Dr. Izmirly. "Given the morbidity and mortality associated with the disease and the relative safety of HCQ use during pregnancy, a treating physician should consider using HCQ to reduce the risk of congenital heart block in a mother who has had a previously affected child."

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