Transcript

Pregnancy and Rheumatic Diseases: Improving Patient Outcomes and Alleviating Lactation Concerns

FACULTY

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INTRODUCTION

The following transcript was developed from a webcast featuring Megan Clowse, MD, and William Mencia, MD, that was filmed at the 2017 American College of Rheumatology annual meeting.

DR. MENCIA: Hello, and welcome to the Duke Clinical Practice Today series. I'm Dr. William Mencia, and I'm joined today by Dr. Megan Clowse, who is the associate professor of rheumatology and immunology at Duke. We're here at the American College of Rheumatology (ACR) annual conference in San Diego, and you're presenting several abstracts here at the conference.

Your work is so critically important to so many young women who have rheumatic disease. Can you tell us a little bit more about your research?

DR. CLOWSE: Absolutely. My overarching goal is to enable women with rheumatic disease to have the families and the children that they want to have. In order to do that, we take a pretty broad approach to our research to both try to find answers about how women should be managing their pregnancy and managing their rheumatic disease during pregnancy, but we've also been focusing more recently on things like, are patients actually taking the medication that we think they should be taking? Why are they, and why aren't they? We've been focusing on how patients perceive the risk of the medications in pregnancy—how that impacts their decisions to take medicines. We've been also focusing on: are there better ways that doctors can measure disease activity and make good decisions with their patients? So, we are really trying to take a kind of "all angles" approach to how to improve the actual day-to-day management of rheumatic disease in pregnancy, really across the whole country.

DR. MENCIA: That's wonderful. Let's get into the abstracts. One of your abstracts specifically has to do with looking at the relationship between hydroxychloroquine and pregnancy. What did you find?

DR. CLOWSE: This was a study where we looked at blood samples that we've been collecting over

the last 3 years from women who were pregnant with rheumatic disease who were taking hydroxychloroquine. And our main question was: do hydroxychloroquine levels change during pregnancy, and is that important? We know that, as a woman gets more and more pregnant, her physiology changes. She gains weight, she adds an extra person, she gets a lot more blood, and she gets a lot more fat, which affects the storage of drugs. So, that was our primary question.

We measured hydroxychloroquine levels in all of these patients throughout their pregnancy. What we found was, interestingly, that it did appear that the level seemed to decrease to some extent in some women over the trimesters. So, it was a little higher in the first trimester and a little bit lower in the third. Then, there was a significant jump back up for almost everybody after delivery, implying that there probably was some change in the level with pregnancy.

The other thing that we found, however, which was perhaps surprising or just confirming what our belief was, is that about 20% to 25% of the patients had extraordinarily low levels of hydroxychloroquine at some point during their pregnancy, implying to us that they probably weren't taking the medicine at the time, even though they told me that they were taking it when they came in that day to see me.

So we have a patient group of women with lupus who are at various points in their reproductive health history. We'd asked them—before we did the study—how many women do you think don't take their hydroxychloroquine at all but tell the doctor that they're taking it when they're pregnant? They estimated that 20% didn't take it all and told their doctor they were taking it, 30% probably took it sometimes, and about 50% took it all the time. We're actually surprised that we found almost the exact same number were not taking it when they first showed up to see me. Though, after our first visit or two, their level often did go up. I think I was able to convince them to take it, but before that, they hadn't been convinced.

DR. MENCIA: So lower levels may end up causing premature delivery. What about patients who are complying? Do you see premature delivery in that patient population?

DR. CLOWSE: Yes, so in terms of the pregnancy outcomes difference, we didn't see a difference when the level decreased sort of modestly, like the overall decrease. It wasn't really a difference in outcomes for those women. The group that had the different outcomes and the group that had the higher rate of preterm delivery were the women who weren't actually taking hydroxychloroquine (100% of lupus patients with hydroxychloroquine levels < 100 ng/mL delivered prematurely [n = 4] vs 24% of individuals with hydroxychloroquine levels ≥ 100 ng/mL delivered prematurely [n = 21]; *P* = .01). It looked like, as long as you were taking it on schedule—so you had some good, reasonable, measurable dose—that that seemed to be sufficient. But the women who weren't taking it at all actually had a very high rate of preterm delivery.

DR. MENCIA: So following up with those patients to make sure that they are adhering and taking their medication is crucial. But going back to the group that *was* compliant with their therapy—what would you do to the dose even if you're showing lower levels?

DR. CLOWSE: Yes, so we're definitely concerned about the lower level issues. We're doing a lot more analysis on the data; we're doing really in-depth pharmacokinetics and pharmacodynamics analysis on that to see where the drug is going. Is it being metabolized more, or is it being excreted more? What we're actually finding suggests that the drug level in the whole body doesn't change a whole lot; it's actually just lower in the blood. And maybe it's actually more in the tissues, which is sufficient. From a clinical standpoint, we're a little bit less worried on our preliminary next-step studies to tell us that we need to actually adjust the dose. We're not, at this point, recommending changing the dose of the hydroxychloroquine, but rather, emphasizing to women that they should actually take it.

DR. MENCIA: Let's move onto another one of your abstracts. You did a meta-analysis looking at the use of hydroxychloroquine in the first trimester. What did you find?

DR. CLOWSE: This was a study that was an international collaboration. Researchers from across the world sent us their lupus pregnancy cohort data from the last 20 to 30 years, and we divided all the patients into those that were taking hydroxychloroquine as of the first trimester versus those that were not taking hydroxychloroquine, and then we compared their outcomes. What we found was a little surprising in that it didn't make as big a difference in pregnancy outcomes as we thought. So, preterm birth was not different in those taking hydroxychloroquine or not taking hydroxychloroquine (OR, 0.78; 95% CI, 0.47, 1.30). It was almost identical, actually, in the two groups. The places that we did see a difference were in women with lupus nephritis. If they had lupus nephritis, taking the hydroxychloroquine significantly decreased their chances of a pregnancy loss (OR, 0.48; 95% CI, 0.24, 0.94) and also decreased their disease activity.

DR. MENCIA: Let's move onto another one of your abstracts. In this particular study, you were looking at pregnancy and medication-taking habits. Do women have to stop taking their medications? Do they have to suffer through their pregnancy?

DR. CLOWSE: That's a great question. I think that our overall cultural belief is that medications plus pregnancy is bad and that it's always better for women to stop their medications. And what we found with women with rheumatic disease—but also women with other diseases like thyroid problems, epilepsy, or asthma—is that often, the underlying illness is worse for the woman, as well as for the health of her developing fetus, than many of our medications. We certainly see that in rheumatic disease as well. It's most clear in our lupus population, where if we take off their medications and allow them to flare, they will have worse pregnancy outcomes. But we also tend to see that somewhat in our rheumatoid arthritis population. Now we are very good at controlling rheumatoid arthritis in many young women because we have so many great medication options. But stopping those medications in order to get pregnant—or

during a pregnancy—often leads to flares of disease, which can both make it hard to get pregnant (because it probably promotes infertility) and actually decrease the ability of a woman to have a full-term delivery (might cause more preterm births).

Taking medications, we think, is actually important for a lot of women. Fortunately, there are lots of good options to be used in pregnancy. I personally am very comfortable with hydroxychloroquine, as I said before. I'm very comfortable with sulfasalazine in pregnancy for rheumatoid arthritis, in particular. Very comfortable with azathioprine for lupus or for arthritis. Very comfortable with tumor necrosis factor (TNF) inhibitors as well. So there are really good options in order to manage disease, but we just have to be bold enough to use them.

DR. MENCIA: Right. Does the same hold true for lactation?

DR. CLOWSE: Actually, it's probably truer for lactation. There's probably even less risk to an infant from a mother taking these medications while she's breastfeeding. There's actually very little transfer of almost all of our rheumatic medications into breast milk. For example, azathioprine transfers well less than 1% of the mother's dose into breast milk. TNF inhibitors transfer very little, if any, into breast milk and are probably digested by the infant's gut, making it not a biologically plausible problem for the infants. Many of our medications are actually quite safe in breastfeeding. But, unfortunately, women don't know that. And doctors don't know that and aren't comfortable with the data. As a result, many women, which we found in this study, are not making decisions with that knowledge. We found that many women were, to be honest, torturing themselves by deciding not to take medications and breastfeeding, stopping breastfeeding to take medications, or just not breastfeeding at all because they needed medications. The guilt that women experience is really quite palpable.

We did a study with CreakyJoints. It was an online survey where women with rheumatic disease wrote in and told us lots of things about their reproductive history and their medication use in pregnancy and lactation. But one of the sections was a free box where people could tell us about their decision process and story of breastfeeding, medications, and rheumatoid arthritis. It was pretty heartbreaking, some of the things that people were saying. One woman said that she decided that it was more important for her to be able to hold her baby than breastfeed her baby. And so, she decided to stop breastfeeding and take medications. To be honest, in my care, she would have done both, and she would have been on medications early on after delivery to avoid a flare because we know she's going to flare. So we start medications right away after delivery. Thus, people are able to comfortably and safely breastfeed for as long as they want to.

DR. MENCIA: That's fantastic. Let's take a look at your fourth abstract. Here, you and your colleagues were looking at patient-reported outcomes as a potential measure for higher-risk pregnancies. What did you find?

DR. CLOWSE: In my pregnancy registry, which I've had for about a decade now, I've been collecting patient-reported outcomes. My patients do these huge, long questionnaires, and I finally looked at them this past year. What we found was pretty surprising. We had patients always doing a HAQ, a Health Assessment Questionnaire, which is basically a measurement of disability. And then, we had them doing some global assessments, as well as pain assessments, 0-to-10 kind of things. What we found is that, for women with rheumatoid arthritis, if they had more disability or more pain or more instances of globally reporting their health is poor (especially that their rheumatoid arthritis is poor), then they tended to deliver early. There's actually a clear, statistically significant association with their patient-reported outcomes—saying that they were sick—and their pregnancy outcomes being worse (OR, 5.9; 95% CI, 1.5-23.9). They also matched my assessment; at each visit, I assessed their disease activity with joint counts and so on, and they all matched.

But then, we went to our patients with lupus. Lupus is a really different process; it's a very different disease than rheumatoid arthritis. It's much less straightforward to study and measure, in particular. What we found was that there was really no correlation between the women who felt worse on their surveys, my assessment of their disease activity, and their pregnancy outcomes. What we think is that the part of lupus that really impacts pregnancy outcomes the most is lupus nephritis. So, having active kidney disease when you were pregnant is very, very poor for a pregnancy. It leads to high rates of pregnancy loss, very high rates of preterm birth, and very high rates of preeclampsia.

Lupus nephritis is really—in my mind and in my clinic—the main thing that drives the poor pregnancy outcomes in lupus. But, if you talk to a woman with lupus nephritis, she actually doesn't feel that bad. She doesn't have a lot of joint pain, and she's able to get out of bed in the morning. As long as she doesn't have anasarca and a lot of swelling, she often doesn't feel all that bad. Thus, her patient-reported outcomes are pretty good. She's able to do all the things she wants to, she's not disabled, and her pain is not so bad. What we found from talking to our patients is that, as long as they didn't feel bad, they actually didn't score their lupus as very active, even if they had active lupus nephritis.

Regarding the women with lupus, on the surveys that we gave them, we couldn't tell who was sick, and it didn't seem to impact pregnancy outcomes. But the women with rheumatoid arthritis were great at it. Therefore, we're looking for ways that regular rheumatologists out in the community who don't see lots of pregnant patients can make good decisions that they're confident in about medications and management and pregnancy. What we have shown is that if you ask a woman how her rheumatoid arthritis is doing, she can tell you how her rheumatoid arthritis is doing. If it is active, then you need to do something about it with safe and compatible medications, which we have plenty of. If she tells you that she's feeling okay and her arthritis isn't particularly active, then you probably don't need to be more aggressive. With rheumatoid arthritis, it's a pretty easy message. With lupus, as always, it's a

challenge.

DR. MENCIA: This is really important and fascinating research that you're doing at Duke. Any final thoughts for our learners?

DR. CLOWSE: I know that most rheumatologists don't see a lot of pregnant patients—one or two, maybe three per year—so it's a rare event, and it is a stressful event. It is definitely something that makes doctors nervous, and with good reason. Things change, the rules are different than when their patients are not pregnant; now you're worried about a second person in addition to your patient. But I think that there are pretty simple guidelines that you can follow. For example, the Europeans published a couple of really nice guideline papers in the last year. The ACR is currently working on guidelines. So there are some pretty simple things that you can do that actually impact pregnancy outcomes, as well as quality of life, for our patients. And that's allowing your patients to take the compatible medications and following them progressively through their pregnancy, treating flares when they pop up, and being supportive of women in their decision to have children.

DR. MENCIA: Wonderful. Thank you, Dr. Clowse.

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