Uncomplicating Pregnancies in Lupus and APS

Transcript

Jane Salmon, MD (Guest): Preeclampsia is really one of the most important causes of maternal and fetal mortality in [patients with] lupus. We had to address that.

Meghna Rao (Host): Welcome to *Rheum Advisor on Air*, the official podcast of *Rheumatology Advisor*, one of Haymarket Media's leading publications that focuses on the latest news and research in rheumatology to inform clinical practices. I'm your host, Meghna Rao, the editor of *Rheumatology Advisor*.

In this limited series, we're focusing on some of the exciting and clinically impactful research and sessions that were presented at the all-virtual American College of Rheumatology (ACR) Convergence 2020. We're speaking with experts in the field who will be giving us further insight into some of the trending topics in rheumatology, as presented at this year's ACR annual meeting. So, let's dive in!

Meghna: Pregnancy for patients with antiphospholipid syndrome [(APS)] and lupus has historically been associated with complications, including increased risk of preeclampsia, fetal growth restriction, and fetal death, but outcomes have improved in the last 2 decades. However, identifying, predicting, and preventing the risk for pregnancy complications in this population still remains challenging.

I'm fortunate today to speak with Dr Jane Salmon, the Collette Kean Research Chair at the Hospital for Special Surgery and a professor of medicine in obstetrics and gynecology at Weill Cornell Medicine, New York. Welcome, Dr Salmon!

Dr Salmon: Thank you, and thank you for the opportunity to talk about our work and [the] impact on outcomes of patients with lupus and APS.

Meghna: Of course. First, I wanted to congratulate you on being the recipient of the Rheumatology Research Foundation Sean Ruddy Memorial Lectureship last year.

Dr Salmon: Thank you.

Meghna: Dr Salmon, you have spoken in the past regarding pregnant women with APS, the 44 percent with the condition who experience pregnancy complications, including preterm delivery and miscarriage, due to inflammation in the placenta. So what are some of the predictors or risk factors for adverse pregnancy outcomes in women with APS and lupus?

Dr Salmon: You know, one of the challenges in caring for these patients, as you've said, is being able to identify early in pregnancy or prepregnancy, who is destined for one of these adverse outcomes.

We did a large prospective observational study to try to answer that question. So overall, in the PROMISSE study, where we looked at women with lupus and/or antiphospholipid antibodies, not necessarily antiphospholipid syndrome, about 20% of them had adverse outcomes that one would consider important. Preeclampsia, preterm delivery, fetal death after 10 weeks, and the risk factors that were associated with these adverse outcomes, were ever being on an antihypertensive medicine or currently on an antihypertensive medicine. The women in PROMISSE were not hypertensive at baseline. They needed to be controlled, but if they were on antihypertensives [then] that was a risk factor.

If they had a positive lupus anticoagulant [then] that was a risk factor, and if they had an increase in disease activity, but their disease activity was low, [they] couldn't have active lupus to be in the PROMISSE study, but even slight increases in disease activity increased your risk for an adverse outcome.

And finally, race and ethnicity mattered. Individuals who were non-Hispanic [and] White had a 50% lower chance of having an adverse outcome. If you put together some of these risk factors: if you're lupus anticoagulant-positive or if you're lupus anticoagulant-negative but are non-White or Hispanic, and you're treated with an antihypertensive medication, your adverse outcome rate, this is in [patients with] lupus, was 58%, not the 20[%], it's 58[%], and your likelihood of a fetal or neonatal death was 22%.

If you didn't have any of these risk factors, your likelihood of an adverse outcome was about 7%, which is what the general population's is, so I do believe using clinical variables very early in pregnancy or prepregnancy, you can make some reasonable estimates of the risk [for] a safe pregnancy and reassure women or monitor them very, very carefully.

Another really important point in counseling women is that women should have inactive disease when they contemplate pregnancy. Others have shown that active disease is associated with poor outcomes, with preeclampsia, with fetal death, with maternal flares of lupus.

Meghna: Okay, so I'm wondering, can biomarkers be used to predict outcomes in the pregnant population?

Dr Salmon: Yes, there are biomarkers that we've studied and others have studied that are not clinically available but I think eventually might be. They're not sensitive or specific enough yet to use individually as a clinical test in an emergency room or in a practice, but they give you a sense of what's going on, if you follow them longitudinally.

So certainly, evidence of complement activation plays a role in pregnancy complications in APS and lupus. So, complements, split products in the circulation, are associated with a worse outcome, as they are increasing through pregnancy, if they do.

In addition, there are factors called antiangiogenic factors. Those are factors made by a stressed, hypoxic, poorly developing placenta, and those factors, when they get into the maternal circulation, are toxic to the maternal endothelium and drive the clinical

features of preeclampsia we see, hypertension, proteinuria, seizures; and one can measure those factors way before there's any clinical evidence for preeclampsia or vasculopathy, but one can look at the relative pro- and antiangiogenic factors in the circulation, and predict likelihood of a severe adverse outcome.

But finally, if you're careful [and] look longitudinally, changes in total C3 are something to look at. They're not strong predictors, but through pregnancy, C3 typically increases because it's like an acute phase reactant and it's also driven by the pregnancy hormones. So normally, C3 should go up in pregnancy; if a patient's C3 doesn't go up, it suggests that it's being consumed. Though we don't have typical clinical assays to look at complement split products to document consumption, if you see a woman whose C3 is even falling (there [are] a wide range of C3s, so you need [to look at] the woman's baseline) or if it's not going up through pregnancy, you might also worry about an impending adverse outcome.

So, another nonclinically available, but I think provocative, approach to predict outcome would be looking at the gene expression profile of the leukocytes in the blood of a patient.

Meghna: Interesting! Dr Salmon, are there any therapies or potential therapies that can reduce placental abnormalities in patients with APS and lupus, and possibly prevent or lower the risk for severe pregnancy complications?

Dr Salmon: God, we really wish there were! I think the therapies we have are not adequate, because in the subset of women I mentioned, 58% of them are going to get into trouble.

[W]omen with APS or with [the] lupus anticoagulant, almost all of them in PROMISSE were on aspirin, were on low-molecular weight heparin, if that was indicated based on history of previous APS, so I don't think they're adequate. But I think the standard of care [is] certainly putting any [patient with] lupus on a baby aspirin because that's used in women at risk for preeclampsia in general, and seems to decrease the risk.

Someone with APS, you would give them prophylactic doses of low-molecular weight heparin if they've had thrombosis or if they're on Coumadin for APS, you'd switch them to therapeutic doses. There [are] some data arguing that hydroxychloroquine may play a role; it's certainly safe in pregnancy. We're looking at some, I think, interesting biologics and target disease in our animal models, so I think there's a chance that we'll have some new therapies coming up soon.

Meghna: Sure. [I] had a chance to look at the IMPACT trial that is assessing the use of a TNF [(tumor necrosis factor)] blocker in pregnant women with APS, and it seems very promising, and I will look forward to seeing the results.

Dr Salmon: Yes, the IMPACT trial is something we're very involved in right now, and that's a single arm, phase 2, open-label study using certolizumab, which is a TNF inhibitor that does not cross the placenta and doesn't get into the baby. It seems to be relatively safe in pregnancy and we're administering it early in pregnancy to these individuals that I've described, really high-risk individuals with lupus anticoagulant. All

those patients are on standard of care therapy, which is aspirin and low-molecular weight heparin because they must have APS.

Meghna: Sure. Now, just taking [a] step back, tell us about the research in mouse models that you conducted that aimed to determine the cause of pregnancy outcomes, such as fetal loss and fetal growth restriction, in women with APS.

Dr Salmon: Thank you, you're asking me to tell you about years and years of work! That was really exciting, and I think for me, the ability to translate the mouse studies to patients, it's really every investigator's dream.

So, in order to think about what could be causing pregnancy complications in women with antiphospholipid antibodies and to try to be agnostic in the mediators, it's not just thrombosis, because if it were just thrombosis, anticoagulation would be more effective, and it just isn't good enough.

We created a mouse model where you passively transfer antiphospholipid antibodies into pregnant mice, and we were able to recapitulate the human disease, which was lots of miscarriages. Mice have 6 [to] 10 pups, and about 30[%] or 40% of them died in utero when the mouse was exposed to APS, and they also, the ones who would have survived, were growth-restricted. So that was very much like what [patients with] APS get. And we were able to give aPL [(antiphospholipid)] antibodies to mice that were knocked out in a whole range of genes to determine which genes are essential to get the pathologies.

In these studies, we found that complement was a critical mediator, particularly C5A, C5A receptor interactions, that neutrophils were early initiators of disease, and were required to drive pathology. Now, complement inhibition might be a really exciting approach in patients, but that wasn't really available to us.

The other thing we showed is that TNF blockade is effective in the mouse model. C5A receptor triggers TNF release by inflammatory cells, so though it's downstream of complement, we were able to prevent fetal resorptions, fetal death, and growth restriction using TNF blockers in mice deficient in TNF. And I think importantly, all those studies looked at miscarriage and growth restriction. They didn't look at preeclampsia, and preeclampsia is really one of the most important causes of maternal and fetal mortality in [patients with] lupus, we had to address that; and we were able to study a mouse that spontaneously gets preeclampsia. It's not an autoimmune mouse, there are no antiphospholipid antibodies in this mouse, it's a mouse that has mild hypertension, and when she becomes pregnant, she gets much more hypertension, and she gets a phenotype of a preeclamptic woman, or proteinuria, poorly developed placentas, fetal growth restriction, and fetal death. And in that mouse model, we could use complement inhibitors, as well as TNF inhibitors, to rescue the pregnancies.

So we have 2 animal models to support the role of inflammation at the maternal-fetal interface, a role for neutrophil C5A receptors, as well as TNFL [(TNF ligand)]. That's what empowered us to do the IMPACT study.

Meghna: Very interesting! Now, [s]hifting gears a little bit, this was extensively discussed in one of our previous episodes, but Dr Salmon, we have seen that patients

with lupus are significantly affected by racial and ethnic disparities in terms of diagnosis, treatment, and even disease outcomes, but what is the difference across ethnic groups among women with lupus with high risk for pregnancy complications?

Dr Salmon: You know, that was one of the most interesting, and I think surprising, findings of the PROMISSE study.

The 400 [patients with] lupus we followed [-up with], they were seen every month of pregnancy beginning before 12 weeks and at postpartum, and they were seen by a group of 7 or 8 investigators, OBs [(obstetricians)] and rheumatologists who were particularly expert and particularly interested in lupus pregnancies, so [the patients] were followed [-up with] regularly. We couldn't understand why, and they were all on the same kinds of therapies, we couldn't understand why the women who were non-Hispanic [and] White did better. Maybe some of the patients missed visits, but they didn't. We looked at missed visits. Maybe they weren't compliant, but it was an observational study, and the patients had inactive lupus, and almost none of them were on very much in the way of medicine. They couldn't be on high-dose steroids, so compliance, also, wasn't something we were terribly worried about. So, what we found to be most important was – the biggest difference between the races was the personal education, like what percentage of the non-White Hispanic [patients] had education above high school vs the others, and that was different.

Then, we looked at the census data, at the zip codes of the patients who enrolled, because we couldn't ask them about their personal income, whether they lived in a community that, on the average, had low income, less than the 50 percentile in the United States, or a community where the percentage of individuals with a college degree was low. And those 2 elements, which I call socioeconomic characteristics, as well as their personal education level, we clustered together.

Black and Hispanic patients had 2-fold higher rates of adverse outcomes. When you considered socioeconomic factors and put that into the analysis. If the patients didn't have APL, APL is a little different, but in APL-negative [patients with] lupus [and] White non-Hispanic [patients], had 10% adverse outcome rates. The Black [patients] had a 25% outcome rate. The Hispanic [patients] had a 17% outcome rate. And the whole population was pretty big; each of these groups [had] more than 50 patients.

Meghna: Wow, [d]efinitely something we should look forward to in the future, maybe research in that direction.

Dr Salmon: Thank you for letting me talk about the work, and I'm hoping that the completeness of our clinical trial will make a difference to patients. I think we'll learn a lot.

Meghna: Absolutely. It was definitely insightful, and hopeful for women with APS and lupus, who were historically told not to get pregnant. But thank you again for your time, Dr Salmon. It was indeed a pleasure to speak with you.

Dr Salmon: Thank you.

Meghna: Please stay tuned for more episodes in this series. For more information on *Rheumatology Advisor* and this podcast, you can reach out to us at editor@rheumatologyadvisor.com. We, at *Rheumatology Advisor*, look forward to delivering timely, evidence-based news to you. You can also sign up for our free newsletters on the site.