Navigating Unchartered Waters: The Management of Autoimmune and Inflammatory Skin Disorders in Pregnant and Breastfeeding Patients

Katharina Shaw, MD, FAAD and Nicole Smith, MD, MPH
Interviewed by Mona Sadeghpour, MD, FAAD

MONA SADEGHPOUR, MD, FAAD: Welcome back to another episode of *Dialogues in Dermatology*. I am Dr. Mona Sadeghpour, board certified dermatologist from Pittsburgh, Pennsylvania. Today, I have the privilege of speaking to two physicians: Dr. Katharina Stephanie Shaw and Dr. Nicole Smith. Dr. Shaw is an attending dermatologist at the University of Pennsylvania. She completed residency training in dermatology and NYU and has an advanced fellowship in rheumatology dermatology at Brigham and Women's Hospital. In addition to treating adult patients with autoimmune connective tissue disease of the skin, she is the founder and codirector of the pediatric rheumatology derm clinic at Children's Hospital of Philadelphia.—

--She has a special interest in sclerosing disorders, cutaneous lupus, dermatomyositis, as well as has numerous publications on epidemiology and advanced treatments for these conditions. Dr. Nicole Smith is a high-risk obstetrician and an Associate Professor of Maternal-Fetal Medicine at Brigham and Women's Hospital in Boston. She is internationally recognized for her expertise in managing complex and high-risk pregnant patients and has a special interest in caring for pregnant and lactating patients with autoimmune disease. Welcome.

KATHARINA SHAW, MD, FAAD: Thanks so much for having us.

NICOLE SMITH, MD, MPH: Thank you.

MONA SADEGHPOUR, MD, FAAD: Dr. Smith, let's start by taking a look at why this is such an important topic and why there has been traditionally a practice gap in treating women who are either thinking about conceiving, pregnant, or breastfeeding.

NICOLE SMITH, MD, MPH: Thank you for giving me the opportunity to talk about this important topic. Historically, I think that our focus has really been on the risk of harm from the treatments that we administer to pregnant people and breastfeeding people. Unfortunately, pregnancy actually is the better part of a year and withholding treatment during that time can have some pretty significant ramifications due to either untreated, treatment for the mom, or due to obstetric complications that are a consequence of it.—

--So I hope that we can start to reframe our paradigm, moving from just risk of harm to balancing the risk of untreated disease to the potential risk of medication exposure.

MONA SADEGHPOUR, MD, FAAD: Thank you, that's very important and something that we should all be aware of. Dr. Shaw, let's start with you now, as well. I'm interested, as well as the audience, about the role of interdisciplinary care as it pertains to the management of patients whose inflammatory skin conditions are requiring systemic medications.

KATHARINA SHAW, MD, FAAD: So I think the perfect way to answer this question is to recognize that I got to know Nicole while I was a rheum derm fellow at the Brigham. At that time, I was taking care of a lot of lupus patients, a lot of dermato patients, and some of them just happened to be pregnant or lactating or thinking about getting pregnant. There were several occasions where I had a flare. I had a patient who had dermato and she was flaring. I had a patient who had lupus and she was flaring and she happened to be pregnant or she was breastfeeding.—

--At that point, I just did what I had to do, which is email Nicole and ask her what she would do in this particular situation. I would give her a couple of medications that I would want to start in this patient and then she would help me risk stratify which medication would be most appropriate, taking into account the benefit to the mom, as well as the potential harm to the fetus.

MONA SADEGHPOUR, MD, FAAD: So Dr. Smith, now we're going to come in from your perspective. Let's say you get an email, you get a consultation request from a dermatologist such as Dr. Shaw. What information regarding that patient is important for you to know on the other side?

NICOLE SMITH, MD, MPH: The most important information that I can receive is what is the risk if the patient's disease is untreated. So again, is she going to have just skin manifestations? Will she have systemic manifestations? Do we need to worry about other medical complications that will further interact with her pregnancy? The other thing I'd like to know is what is the choice of medications, so that we can risk stratify those. The final thing that I would like to know is how long will it take to induce remission, if we need to restart a medication.—

--So if the patient has already, for example, self-discontinued a medication or another physician has discontinued the medication, how quickly can we induce remission again if we need to start it? Because that also helps us better understand how flexible we can be in starting and stopping the medication.

MONA SADEGHPOUR, MD, FAAD: That's a really important topic, because a lot of times we are seeing patients who are either thinking about conceiving, are currently pregnant, or deciding whether they want to continue breastfeeding. As dermatologists who are seeing these patients, with either atopic dermatitis or psoriasis, until we have the time to be able to speak to experts such as yourself, we need to make the first decision of what are we going to do with this treatment at this time. So I understand that sort of the important thing to remember is to not stop the medication, or do you, until we have a chance to be able to have the consultation. Can you comment on what the derm should do for patients who are on these medications?

NICOLE SMITH, MD, MPH: I think it's important to take one moment to step back and think about placental physiology and fetal development. So organogenesis occurs in the first trimester of

pregnancy. So most organ development is actually complete by 12 to 13 weeks. So the risks that we're talking about with first trimester exposure are different than risks that we're talking about in second and third trimester exposure. There are a short list of medications in dermatology and in medicine in general that are true teratogens.—

--So, for example, methotrexate, we know it causes birth defects. Those are medications that should be immediately discontinued with a positive pregnancy test. But the list of medications that don't cause birth defects is far, far longer. So in those cases, the benefit of continuing medication may outweigh any theoretical or actual risk of continuing. So you have time actually to think about it, use your best resources to read about risks in pregnancy, or consult with a maternal-fetal medicine specialist.

MONA SADEGHPOUR, MD, FAAD: We can probably shift and start talking about some common conditions that we see as dermatologists in our clinic. Dr. Shaw, if I can go back to you and use your expertise to take a look at a potential atopic dermatitis patient who is perhaps flaring. They've been managed with topicals, however now they're at a stage where disease has flared. You either need to slather them all over with sort of a stronger topical steroid class or they need to go to potential systemic steroids or they need to go to biologic. How do we think about that particular patient?

KATHARINA SHAW, MD, FAAD: In this particular context, I think it's important to remember that topical steroids, which historically we've been actually quite wary of in dermatology, are completely safe in pregnancy. There's a lot of chatter in the literature about the body surface area and the potency of the topical steroids. I think one of the biggest things to take away is that that just doesn't matter. Topical steroids are safe in pregnancy. This has since been recapitulated in really nice, systematic reviews.—

--There was a beautiful cohort study published in *JAMA Derm* back in 2021 that have shown that the body surface area doesn't matter, the potency of the topical steroids don't matter, they are not associated with fetal growth restriction or prematurity. When you approach a patient who has severe eczema, sure it would be wonderful if you could treat them with just topical steroids, but oftentimes we are in a situation where topical steroids are not enough. In that situation, we've had this wonderful revolution starting in 2017 with the arrival of dupilumab.—

--Dupilumab has been added to our arsenal as a very effective medication for eczema. Again, dupilumab is one of those medications that I don't think we need to have any reticence about starting and we don't need to feel the urge to discontinue it should a patient get pregnant.

MONA SADEGHPOUR, MD, FAAD: Is that also the case during the phase of lactation, as well?

KATHARINA SHAW, MD, FAAD: Yes, it's completely safe to continue during breastfeeding.

MONA SADEGHPOUR, MD, FAAD: As far as systemic steroids, since we're kind of on the path, can you comment on thinking about the safety of that and duration of use? And if there's anything that needs to be monitored or talked to about with the patient? I'm going to go back to Dr. Smith for this.

NICOLE SMITH, MD, MPH: Historically, the concern around systemic steroids are related to case-control studies that were done in the 1980s, suggesting a possible association with cleft lip and palate. That association has not been reaffirmed in the 30 years since that time. So based just on epidemiologic literature, that is no longer a concern that we maintain. We often mention it to patients because they might find it online but we don't believe that the association exists.—

--In addition, the placenta is truly a phenomenal organ, which does many things to keep babies safe. The one thing that it does is deactivate glucocorticoids at the maternal-fetal interface. So the only steroids that freely cross the placental are actually betamethasone and dexamethasone.

All the remainder of systemic steroids are decreased such that the fetal exposure is no more than 10 percent of the maternal exposure. So we actually take little pause in utilization of systemic steroids for that reason.

MONA SADEGHPOUR, MD, FAAD: That's great news. So prednisone, okay. However, dexamethasone and betamethasone, not okay. So let's go on to the next disease state and talk about the beloved psoriasis, which we obviously hear a lot about. Exciting times for psoriasis, it's been for a very long time. New treatments have emerged and continue to emerge and obviously these include the biologic group. If you can, Dr. Shaw, comment to us, and obviously this is a small talk, we're not going to be able to get everything, but give us a framework for how to think about using biologics during pregnancy.

KATHARINA SHAW, MD, FAAD: When you have a pregnant patient or a patient who is thinking about getting pregnant and she has psoriasis, I think you have to meet her where her goals are, in the context of the severity of her disease. So there are going to be many patients who are very risk-averse and you can assure them about the mechanisms of placental transfer. You can talk to them about the transit of IgG in the third versus the first trimester and they won't hear you, and that's okay.—

--So I think it's always important to kind of understand a patient's goals as they proceed through pregnancy. I say that because there are ways that we can manage a patient with psoriasis that isn't a biologic. There are topicals that are available to us, as we mentioned before, and then we can even rely on phototherapy. There's some literature to suggest that folate will decrease with phototherapy use, so there are some recommendations to suggest that you should check folate acid levels while someone is getting phototherapy. But overall, there is a way to manage most of the time a psoriasis patient without having to go to a biologic therapy.—

--That being said, and I've learned this from Nicole, we are increasingly using biologics, not just in psoriasis but in a lot of autoinflammatory conditions. So there is emerging safety data to essentially say that there have been no adverse events in pregnancy with a biologic to date. If you have a patient who is extremely severe, their psoriasis affects their daily quality of life, I think you can approach them with a lot of confidence and say it's okay to continue your biologic during pregnancy and lactation.

MONA SADEGHPOUR, MD, FAAD: Actually, this question can really be to any of you, but I'll ask Dr. Smith, since she probably gets approached with this question all the time. What do you do in the case of a patient whose inflammatory burden does really require systemic treatment, however in the pregnant state they absolutely refuse because they're fine, they've either had prior losses or beliefs that prevents them mentally to be able to commit to that?

NICOLE SMITH, MD, MPH: The best that we can do is just to watch them closely. Again, if it's a disease that has systemic ramifications, for me better understanding what the pathophysiology of those manifestations are, so that I know where I have to watch and what potential obstetric consequences there may be from untreated disease.

MONA SADEGHPOUR, MD, FAAD: On that same note, there may be many patients who may either falsely or truly believe that rather than getting on these systemic medications or traditional Western medicine, they want to use alternative medicines, such as supplements or herbals or over-the-counters as a therapeutic modality to manage their disease and they come and ask us for those or recommendations. How do we guide that conversation?

NICOLE SMITH, MD, MPH: I think it's important to consider that if a natural remedy or an herbal remedy is effective, it probably is biologically active in some way. I am not necessarily able to judge the safety of that biologic activity in pregnancy because it's not likely to be something that's been studied and certainly not something that's FDA regulated. So even if I'm able to identify what

the biologically active metabolite is, if it's not regulated and measured within the particular product that they're using, what I usually share with people is that I truly am unable to tell them if there is any risk associated with using it.—

--But again, I think that people need to take caution because just because something was made by nature instead of through pharma doesn't necessarily mean that it doesn't carry risk. If it's working, it's clearly doing something.

MONA SADEGHPOUR, MD, FAAD: I wish we could record that sound bite and post it on social media for many skin influencers out there. I appreciate that and that's really a point well taken. This has been really tremendously helpful and I think one of the things we should probably talk about is a therapeutic modality that is a little bit controversial. So we've talked about topical steroids and systemic steroids and biologics. But let's focus on rituximab, which may actually become relevant if you have a patient such as one with pemphigus, where we really have good evidence that rituximab should be the first line therapy and due to a variety of reasons should really be the one that we can reach out to, however there is conflicting evidence that it should not be used. How do we think about that and can you bring us up to date with what's going on in that particular situation?

KATHARINA SHAW, MD, FAAD: I know Nicole and I are both very passionate about this particular question and this particular medication. It's very common actually to have a woman of childbearing potential come in with pemphigus, it's not that rare of a disease. One of the challenges is when we consider rituximab, to your point it's now considered first line therapy for pemphigus because we know that the earlier you start rituximab in a pemphigus patient, the higher likelihood there is that disease remission will be achieved.—

--So there is an imperative to treat and to treat early. But in a patient who is thinking about getting pregnant or is in the early stages of pregnancy, if we go to our derm literature, including the most

recent review that was published in our *Journal of the American Academy of Dermatology*, if you look up rituximab, it says rituximab is contraindicated. And not only is it contraindicated, it's listed as being contraindicated for 12 months prior to conception. So that's very challenging.—

--Nicole and I have had several conversations about this and perhaps I'll let her weigh in on more of the primary literature to support the use of rituximab in this particular setting. But I think this is a perfect example of how we as dermatologists, we owe it to our patients to not stop at just one literature review that tells us that a medication is contraindicated or not compatible with pregnancy. When there is a medication that has the potential to transform a patient's life with a particular disease state, it behooves us to take the next step and see whether that medication truly is contraindicated or not. Nicole, can you comment on rituximab use in pregnancy?

NICOLE SMITH, MD, MPH: First, I would just reiterate everything that you said. The greatest harm that we can do is to prematurely discontinue a medication that we know to be efficacious for a patient. Rituximab is a tricky one, because if you go to some of the high level reviews they would suggest that there is a potential for fetal harm. But once you start digging down deeper into it, rituximab has been used widely for a very long period of time, for a variety of diseases during pregnancy.—

--So we have some good experience with it. The only potential harm that has been documented is B cell depletion in newborns for up to six months after the last administration of the medication. Typically for a patient who is taking rituximab, or frankly for any biologic during pregnancy, I do recommend that those pregnant people speak to their pediatrician in advance. Give the pediatrician time to also look up the medication and think about what the potential consequences might be and talk to them about their vaccination schedule.—

--So as long as we're thoughtful about the infant vaccination schedule, we have not had any other evidence of increased infections or increased harm in newborns related to rituximab use, or

frankly to other biologic use. So it tends to be a medication that I would say if it is the only medication that's effective for the patient, I would 100 percent support its use during pregnancy.

MONA SADEGHPOUR, MD, FAAD: That's phenomenal insight. It's great, which is why you can't always just blindly follow the letter of what you're reading and you really do have to put on your thinking cap and do some more research.

NICOLE SMITH, MD, MPH: I would add to that that I think it is completely understandable that clinicians find it difficult to actually find this data, because it's not available. This really granular pregnancy level safety data is not available in most of the references that most clinicians, including myself, are using on a day to day basis. I use a reference called REPROTOX, which for me is the single source of truth in terms of pregnancy-related safety data and really goes into all of the animal studies, all of the clinical human experience. But I understand that that's not easily accessible to everyone, so it is a complicated situation.

MONA SADEGHPOUR, MD, FAAD: So this nicely transitions into the next question I have for you, Dr. Smith, which is thinking about safety during lactation. So let's think about a patient who has successfully completed treatment during pregnancy and is now potentially receiving or reading some conflicting information about safety of that particular medication during lactation. Can you talk to us about resources or places that clinicians can go to be able to get further guidance on a particular medication's safety during lactation?

NICOLE SMITH, MD, MPH: I'd be happy to share some resources. I think it's also worthwhile considering the reframing of that paradigm of the benefits of lactation as compared to potential harms of medication, rather than simply harm of medication alone. What many people aren't aware of is that not only does breastfeeding confer a decreased risk of childhood asthma, of childhood infections, and of long term risk of type 1 diabetes in children, it also is associated with a reduced risk of breast cancer in the breastfeeding individual, as well as in the child.—

--In addition, there is some very fascinating data that very clearly documents that women who are pregnant and never breastfeed actually have an increased lifelong risk of cardiovascular disease, stroke, and also type 2 diabetes, as compared to women who were pregnant and breastfeed. In fact, if you are pregnant and breastfeed, you can reduce your lifelong risk of cardiovascular disease compared to if you had never been pregnant at all.—

--That's not any kind of questionable data, new data, this is based on a metaanalysis covering over a million women from around the world, really very clearly demonstrating these long term health benefits. So while we tend to think about breastfeeding as a cultural choice, we do also need to inform our patients that it's a medical choice and it's a choice that has consequences to long term health. Certainly, there are a lot of people for whom breastfeeding is not the right choice, for a variety of different reasons, and I don't suggest that we should be telling our patients that they have to breastfeed.—

--The way that I normally frame it is to say, "I would like you to know the same things that I know about the long term health benefits of breastfeeding as you make your choices moving forward." So when we tell women that they can't breastfeed due to medication, we need to take that counseling very seriously, because it isn't just telling them that they're making a cultural choice, you may actually be impacting their lifelong health. So to that end, I would say it's worthwhile going to the best resources.—

--I think the best resource is called LactMed. It is an open access source that's funded by the NIH. I tend to bring it up with patients while I'm in the room with them and we go through the monograph together. It's very easy to read, it's easy to understand, and it clearly outlines what any potential theoretical risks may be. I would say that if you go to LactMed, you will feel much more comfortable with most medications during pregnancy, as compared to synthesized reviews listing safety data for lactation.

MONA SADEGHPOUR, MD, FAAD: That's phenomenal advice and we're going to write that one down and I'm going to put it in my note section. This has been tremendously helpful and I have learned so much, as I'm sure our audience will. I appreciate both of your time for being here and sharing your expertise with us.

KATHARINA SHAW, MD, FAAD: Thank you so much.

NICOLE SMITH, MD, MPH: Thank you so much.

Commentary
Sabrina Shearer, MD, FAAD with Benjamin Stoff, MD, FAAD (ed.)

Many medications have traditionally been withheld during pregnancy and breastfeeding due to theoretical safety concerns. However, in patients with severe autoimmune and inflammatory disorders, undertreatment may lead to significant morbidity in pregnant and nursing patients and their children. In this episode of Dialogues, Dr. Mona Sadeghpour interviews Drs. Katharina Shaw and Nicole Smith to provide an overview of the management of autoimmune and inflammatory skin disorders in pregnant and breastfeeding patients.

5 Key Takeaways from Today's Episode:

1. Topical steroids are likely safe to use in pregnancy at any strength and any body surface area.
2. Many systemic glucocorticoids are deactivated at the maternal-fetal interface. With the exception of betamethasone and dexamethasone, fetal exposure to systemic steroids is less than 10% of the maternal exposure.
3. Some studies suggest that phototherapy may reduce folate levels. Folic acid should be supplemented in women of childbearing age, and levels may be monitored in pregnant women treated with phototherapy.
4. Some immunosuppressive medications, including rituximab and other biologics, are often safe to use during pregnancy, but may reduce immunity in newborns during the first several months of life. Patients should talk to their child's pediatrician about their vaccination schedules prior to delivery.
5. Breastfeeding has been shown to have long lasting positive health impacts for infants and mothers. Databases such as LactMed can provide insight for physicians and patients on the risks and benefits of individual medications during lactation.

Thanks for listening!

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