



Dr. Stukus: Hello and welcome to Conversations from the World of Allergy, a podcast produced by the American Academy of Allergy, Asthma & Immunology. I'm your host Dave Stukus. I'm a board certified allergist and immunologist and serve as a social media medical editor for the Academy. Our podcast series will use different formats to interview thought leaders from the world of allergy and immunology. This podcast is not intended to provide any individual medical advice to our listeners. We do hope that our conversations provide evidence-based information. Any questions pertaining to one's own health should always be discussed with their personal physician. The Find an Allergist <http://allergist.aaaai.org/find/> search engine on the academy website is a useful tool to locate a listing of board-certified allergists in your area. Finally, use of this audio program is subject to the American Academy of Allergy, Asthma & Immunology terms of use agreement which you can find at <http://www.AAAAI.org>. Today's edition of our "Conversations from the World of Allergy" podcast series has been accredited for continuing medical education credit. The American Academy of Allergy, Asthma & Immunology is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Information about credit claiming for this and other episodes can be found at <https://education.aaaai.org/podcasts/podcasts>. Credit-claiming will be available for one year from the episode's original release date. We are pleased to welcome Dr. Michael Schatz, who is our first repeat guest on our podcast series, and he's a professor of medicine at the University of California San Diego, and practicing allergist at Kaiser Permanente San Diego Medical Center, where he served as the chief of allergy for over a decade. Dr. Schatz is a past president of the American Academy of Allergy, Asthma & Immunology and serves as the principal investigator for the Vaccines and Medications in Pregnancy Surveillance System. Dr. Schatz has a long and accomplished career as a clinician and researcher with a particular area of expertise surrounding asthma and allergic conditions during pregnancy, which is the topic that we will be discussing today. Dr. Schatz, welcome back, and thank you so much for joining us again.

Dr. Schatz: And thank you very much for having me again.

Dr. Stukus: Yeah, well this is going to be a great conversation, and I couldn't imagine a better guest to discuss this important topic, and one that's often misunderstood or poorly understood, both by physicians and patients alike. So I'd like to begin by really talking about the normal changes that occur during pregnancy to a woman's body. Can you take some time and describe some of the normal, expected respiratory changes that occur during this period.

Dr. Schatz: Yes, I'd be happy to. The two that are really most relevant to taking care of respiratory problems during pregnancy are dyspnea of pregnancy and physiologic nasal congestion. So relative to dyspnea of pregnancy, which is thought to be related to the physiologic hyperventilation of pregnancy, this occurs in up to 75 percent of women. So it's really common, and it starts early in the pregnancy, usually in the first or second trimester. But what helps differentiate it from other causes of shortness of

breath is that it's not associated with chest tightness or wheezing or cough or airway obstruction, so that helps differentiate it from the dyspnea associated with asthma. Certainly many people in that regard who have asthma have it prior to pregnancy, but some women will develop asthma or other respiratory problems during pregnancy for the first time, and then the question is, "Well, is it this dyspnea of pregnancy, which is really common, or is it asthma?" And as I say, some of these signs of asthma-- chest tightness, wheezing, cough, or airway obstruction-- would point you in the direction of asthma, and the absence of those would make the dyspnea of pregnancy more likely. Relative to the nasal congestion that, again, is physiologic, it certainly can be mild and not reported, but some women develop what's called-- different things-- but pregnancy rhinitis is probably the best term, which is defined as a syndrome of nasal congestion and vasomotor instability, lasting at least six weeks without evidence of allergy or infection, and limited to the gestational period. So these symptoms which are largely congestion tend to be most prominent in the second half of pregnancy and usually disappear within two weeks of delivery. In terms of treatment, one of course tries if possible with non-pharmacologic treatment, and several non-pharmacologic approaches may be useful for women who have substantial pregnancy rhinitis. For example, exercise can be useful. It leads to a physiologic nasal vasoconstriction. Raising the head of the bed at an angle of 30 to 45 degrees can help nocturnal nasal congestion. Nasal saline irrigation has been shown to be helpful for pregnancy rhinitis, and finally, an external nasal dilator has also been shown to be effective for patients with pregnancy-related nocturnal nasal congestion.

Dr. Stukus: So it sounds like that there can be both, or either/or, upper and/or lower respiratory sort of manifestations just from any woman becoming pregnant. Do we have an understanding of the potential mechanisms? Does it seem to be more hormonal or is it just the normal physiologic changes that occur during pregnancy as the body adjusts, or is it a combination of the two?

Dr. Schatz: I mean, it's a very good question, and one to which there really isn't a fully satisfactory answer. In terms of the dyspnea of pregnancy, for example, that is felt to be related to the hyperventilation that is largely hormone-mediated. And in terms of the nasal congestion, there certainly are-- or there is blood vessel pooling that happens, again, partly as a result of the hormones, but some fairly extensive studies of pregnancy rhinitis have really not come to a definitive conclusion as to which hormones are doing it. The different studies have shown different levels, different elevations in their patients-- the studies are different in terms of what they're showing. There isn't a consistent change that's been found, because of course not every woman develops this. So it is probably related to hormones, but particularly for the rhinitis of pregnancy, it still remains a mystery.

Dr. Stukus: That's really interesting. Let's shift gears a little bit, because I like how you described the main things that can happen to any woman when they become pregnant. But what about those who already have preexisting asthma or other allergic conditions? What are some of the different ways in which pregnancy can impact those women?

Dr. Schatz: Definitely a very good question, and it's something that women who are thinking about pregnancy wonder about, or certainly during pregnancy experience. Asthma, rhinitis and eczema are the best studied, and in each of those cases the condition can improve, worsen, or stay the same. Interestingly-- and again, it's similar to some of these other changes, even in women who don't have

illnesses-- the reasons for these changes are not generally known. One of the interesting observations is that rhinitis and asthma tend to change together. If the rhinitis gets worse, then the asthma gets worse, and vice versa. But again, even though many physiologic changes occur, and there have been a number of studies trying to address this, it really isn't known. Part of the challenge is that what has to be explained is not only a given change, but why different women change differently.

Dr. Stukus: Do you feel that it's important for women to understand that-- especially if they already have asthma-- that if they are experiencing worsening symptoms that they should discuss with their doctor? And if so, is that being communicated typically through their obstetrician? Or in your experience, how do women come to understand that?

Dr. Schatz: Well, there's no question that it's very heterogeneous. There are certainly women who've already been under the care of an allergist or other specialist first, but certainly the majority of women probably are not. And then it does largely depend on what the obstetrician tells them, and I think more and more obstetricians are recognizing the importance of these respiratory conditions and directing women to people-- to physicians who can help them with it.

Dr. Stukus: That sounds like a very important message to get out there. Now, you mentioned that we don't really have a full understanding necessarily of the mechanisms as to why some women get worse or better, but do we have any clues as to which women with asthma or allergic conditions are at risk to have more severe outcomes? Anybody who would warrant extra precautions or monitoring during pregnancy?

Dr. Schatz: Yes. Again, the most information is for asthma, and it definitely appears that women with more severe asthma need to be more closely monitored, both because, unfortunately, they are actually the ones more likely to worsen during pregnancy beyond their pre-pregnant situation, and they're also the ones who are more likely to suffer the pregnancy complications that seem to be-- that women with asthma are at increased risk for, such as perinatal mortality-- that is, the baby dying before or after birth; preeclampsia, the blood-pressure-associated syndrome during early-- during late pregnancy; prematurity; intrauterine growth retardation-- the baby is underweight; and even possible birth defects. So since all of that is worsened in women with more severe asthma, those are certainly the women who warrant particular attention during pregnancy.

Dr. Stukus: Just so our listeners have a better understanding, how would you define severe asthma for these purposes?

Dr. Schatz: Well, and there are some standard definitions. I actually think that the simplest is that if women are on a combination of inhaled steroids and long-acting beta agonists and not under control and, again, felt to be taking their medicines, which is its own issue in general and during pregnancy-- but certainly women who are taking full doses of inhaled steroids and long-acting beta agonists and not controlled, for the purposes of what we're talking about have severe enough asthma to really be followed more carefully. I think other characteristics would certainly be women who have exacerbations-- either emergency room visits, hospitalizations, or oral steroid courses-- certainly two of those or more in the past

year would I think be another risk factor that would identify the patient who needs to be more carefully followed.

Dr. Stukus: That's great, and it sounds like overall anybody with asthma, if they're thinking about becoming pregnant or if they recently discover that they are pregnant, that's something they should discuss with their asthma specialty and primary care provider. And along those lines, before we scare any woman out there who has asthma from becoming pregnant, what kind of tips or advice do you have specifically for women who have asthma prior to or during pregnancy? Anything they can do to try to optimize their health?

Dr. Schatz: And there's no question that that's an ideal time to consider pregnancy and asthma or other allergies-- that is, before the woman is pregnant. So ideally, therapy and control would be optimized prior to pregnancy, including optimal avoidance measures, medicines and immunotherapy if indicated. Most medicines for asthma and allergy are considered safe, but some have more reassuring information than others, and switching to those is ideally done prior to pregnancy. I think the other important message is to understand that even though women with asthma who have more severe asthma are likely to worsen, it's not totally predictable what's going to happen to asthma or rhinitis during pregnancy. So I think another message to the woman before she's pregnant is that she needs to be monitored closely, monitor herself closely, so that any change in course that does occur, particularly worsening, can be met with an adequate change in therapy.

Dr. Stukus: You touched upon this, about the issue of medications, and I know that's a common concern. As a general rule, can women continue to safely use their asthma and allergy medications during pregnancy, or will this cause harm to the baby?

Dr. Schatz: And that's such an important question for everybody who takes care of pregnant women or is a pregnant woman. We definitely don't have as much information about the safety of any medicine during pregnancy as we would like, but for most asthma and allergy medicines, at least based on the data available, the risk of the uncontrolled condition is greater than the risk of appropriate medications, and that message is probably the most important message relative to treatment that women and their care providers need to understand. And so those medicines include inhaled albuterol, inhaled steroids, long-acting beta agonist medicines, montelukast, omalizumab, intranasal steroids, most antihistamines, and even prednisone when indicated-- the benefits outweigh the risks. So again, we'd like more information, but even based on what's known, those medicines when indicated would appear to be less risky than the uncontrolled symptoms.

Dr. Stukus: And then the follow-up question would be: Are the same medications deemed safe to use during pregnancy also safe to use during breastfeeding, after the baby is delivered?

Dr. Schatz: Yes, and of course women are interested in that question, and it turns out that the answer is yes, because the baby actually gets less medication through breastmilk than through the placenta. So the general rule is definitely that medicines considered safe or appropriate to use during pregnancy can also be considered safe or appropriate to use during breastfeeding.

Dr. Stukus: You touched upon this a little bit and I'd like to really get your input more on these various pregnancy class designations that's attributed to medications. Can you describe what that is and what it means?

Dr. Schatz: Yes. The pregnancy class designations are well known and have been used to try to-- for both, again, women and their caregivers, to figure out what type of medicine to use. However, those classes have now been eliminated by the FDA because they were felt to be an oversimplification and in some cases misleading. Even though that's the case, the academy did a survey in the past year asking about the new label compared to these pregnancy class designations, and many people are still using these as a way to determine what to use during pregnancy. So I will go into detail about what they meant. So Class A meant that both animal studies and, quote, "adequate and controlled human studies"-- that's how the FDA defined it-- were reassuring. So animal studies reassuring, human studies reassuring, but actually no asthma or allergy medicine qualified for that designation. There were two ways in which a drug could get a Class B rating. Class B generally meant that animal studies were reassuring but that adequate and controlled human data were insufficient for the drug to get a Class A rating. Budesonide was the only medication that was Class B due to the second criteria. Human studies were considered adequate by the FDA even though animal studies showed possible adverse effect. Most drugs were Class C, meaning that animal studies were not reassuring, and that sufficient human data, at least as submitted to the FDA, did not exist. Class D meant that human data were concerning, but the benefits of use may still outweigh the risks in certain circumstances. No category D asthma and allergy medications were identified among currently available medications. And finally, Class X meant that the human data suggested that the drug was absolutely contraindicated during pregnancy; the benefits would never outweigh the risks. No asthma or allergy medications were labeled as Class X either. As I mentioned, this letter designation has now been eliminated by the FDA and replaced by a Pregnancy and Lactation section in the prescribing information, which provides much more descriptive information. The data available are described. The risks of the untreated disease are considered, and it's meant to give the provider more helpful information, not oversimplified information, and to really aid in the decision-making process. Again, our feedback from our members with the survey is that there needs to be increased education about really how to use this new label, and of course not all of the drugs have the new label yet, but they will.

Dr. Stukus: And are you aware of any resource available for both providers and patients where they can actually look up specific medications to see what the new label shows, or is that still being developed?

Dr. Schatz: Well, at this point it would be a matter of identifying the prescribing information for an individual drug. So just searching for the drug and going to the prescribing information that will take you to this pregnancy label. It has a risk summary, and that's helpful-- a little easier to read than the detailed of the data-- but the detailed data are there as well, and as I say, one of the advantages or one of the new pieces of this is to recognize not only the potential risks of the medicine but the potential risks of the uncontrolled condition.

Dr. Stukus: Now that we've had a nice discussion really detailing some of the changes-- normal changes and problems that can occur for women who have asthma, can you describe the role that allergists can

serve in helping women navigate their health during this time? Particularly for both in general and then particularly for those who are receiving allergy shots or immunotherapy?

Dr. Schatz: Yes. I mean, no question allergists can play an extremely important role for pregnant women with asthma and allergies. Allergists can work with their pregnant patients to provide optimal disease control, education about their conditions, and really reassure their patients that control of their condition is the best way to optimize the health of the baby. Regarding immunotherapy, there are surprisingly few data actually regarding safety during pregnancy for either subcutaneous or sublingual immunotherapy, but the existing data are reassuring, with the exception of the concern regarding anaphylaxis, which obviously can be life-threatening to both the mother and the baby during pregnancy. So these considerations have led to the following recommendations that I think most everybody who has looked at this pretty much agrees with. The first aspect of that is that if a person is already being treated, it can be continued as long as the woman is achieving benefit at a maintenance level or at least an apparent therapeutic dose, not having a tendency-- and not having a tendency for systemic reactions. It's not generally recommended to begin immunotherapy during pregnancy due to the unestablished benefit, the uncertain proclivity for systemic reactions, which may be more likely in the build-up phase, and the latency of the beneficial effects.

Dr. Stukus: Okay, that's really important information I think not only for patients to understand but allergists as well, so thank you for describing that. Now, as we get towards the second part of our conversation today, I'd like to shift gears and discuss the Vaccines and Medications in Pregnancy Surveillance System, and if it's okay with you, I'm going to abbreviate it as VAMPSS from here on out. But can you tell us what VAMPSS is?

Dr. Schatz: Yes, very happy to, because it is something unique that we think can play a very unique and important role in providing the information that can really help clinicians make the best decisions with their patients relative to treating pregnant women with any condition, as I'll mention. So VAMPSS is a collaboration of three complementary research arms coordinated by the American Academy, with the aim of providing post-marketing surveillance of the safety of medicines and vaccines during pregnancy. As you know, most medicines, when they are released, have not been well studied during pregnancy, and there's very good logistic and ethical reasons for that to be the case, but unfortunately one can't make very good predictions about safety based on the animal data that often exists or the chemical structure. Very slight differences in chemical structure can lead to very big risk differences during pregnancy. So one starts with not knowing, and so the only way to get this information or really, at least in general the best way, is this post-marketing surveillance, and that's what VAMPSS is set up to do. The philosophy behind the collaboration is that each type of research methodology has unique strengths and weaknesses, but that by coordinating the three research designs, one type of study's weaknesses can be compensated for by another research arm's strengths.

Dr. Stukus: So it sounds like a wonderful collaboration. What led to the development of VAMPSS in the first place?

Dr. Schatz: Well, again, this of course is an area that I and others have been interested in for a long time, and we actually looked at how one could move forward in terms of getting more information, and there was a conference held looking at what types of systems were out there to get this information, and that's where it became clear that there was no one system that was perfect, that there each, as I say, had advantages and disadvantages, and the idea of combining them then could give the most comprehensive approach. Another part of VAMPSS that we find is very important is an independent advisory committee to be able to look at the information that's collected and provided this independent perspective, and this committee consists of obstetricians, of pediatricians, of pulmonologists, of a consumer representative, and an independent biostatistician. So that's another piece of this to try to really get the very best information from this system.

Dr. Stukus: That sounds great. You mentioned the research component of it. Are there specific questions that VAMPSS was designed to try and answer?

Dr. Schatz: Yes. I mean, VAMPSS was largely designed to answer the question of: Compared to unexposed women with the same condition or without any underlying illness, does exposure to the medicine or vaccine of interest increase the risk of pregnancy or infant complications? The most common of which I mentioned before-- preeclampsia, fetal or infant death, prematurity, intrauterine growth restriction, and infant birth defects-- and I could go, if you like, into the three research arms that try to get that information.

Dr. Stukus: Oh, I think that would be wonderful to learn about. Absolutely, please.

Dr. Schatz: Yeah. So one research arm is a prospective cohort arm. That's similar to the typical pregnancy registry in which women who are taking a medicine are enrolled while they're pregnant and interviewed while they're pregnant for various exposures and potential confounders; and then pregnancy outcomes are measured after delivery. The pregnant registry or the cohort arm of VAMPSS has some advantages compared to the typical pregnancy registry, because our prospective cohort arm includes two types of controls. Many of the registries out there just get information on exposed women and then perhaps try to compare those results to a general population, not nearly as good as having concurrent controls, either with no medical illness or with the same medical condition but without exposure to the drug of interest. So the prospective cohort arm of VAMPSS is very important, and has some advantages. The second research arm is a case control arm. In that research design, infants with specific birth defects are identified, and exposures during pregnancy are compared in their mothers to maternal exposures in control infants without specific birth defects. This methodology has the highest power to evaluate specific birth defects, and it's really the only methodology we know of that really has the power for specific birth defects. And although one will often see studies that report total birth defects in one group versus another-- and one needs to look at that, and of course total birth defects is the aggregate of individual defects. When a drug causes a problem, it's much more likely to cause a specific defect. It doesn't usually increase the rate of total malformations. So this becomes very important to see if a given medicine or other exposure increases the risk of specific birth defects, which the case control study is powered to answer. The third and newest arm is a retrospective database arm, which uses a large Medicaid database and large commercial database to assess pregnancy outcomes in a very large number of

exposed compared to unexposed pregnant women. So it's like the prospective cohort study, but it uses a database-- a retrospective database. So it has some of the advantages of the prospective cohort arm-- that is, according to the records that identifies exposures during pregnancy-- can look at multiple outcomes, and some of the advantages of the case control arm, in the sense that it's large enough to address at least some specific birth defects. But because patients are interviewed in the database study, certain confounders that one can only get by talking to the patient are not assessed in that arm as they are in the other two arms, and the database study is generally still only powered to evaluate groups of specific birth defects rather than individual birth defects as the case control arm can do. But again, we feel that by combining all these are these research arms, we can most comprehensively assess the safety of medicines and vaccines during pregnancy.

Dr. Stukus: Wow. That's amazing, and it sounds like a treasure trove of much needed and valuable data that's being collected. I'm sure this is a question you get from probably every single participant: How will the information be used?

Dr. Schatz: Yes, it is definitely an important question. The information will be used really to provide guidelines for the management of medical illnesses during pregnancy. Medicines with reassuring safety data can be recommended while medicines which appear to increase the risk of adverse outcomes would not be recommended, unless their unique benefits appear to outweigh the risks.

Dr. Stukus: Well, it sounds to me from everything you've described that this entire VAMPSS was designed really to benefit pregnant women, to learn from them and advance our understanding for future pregnant women. Are there ways in which clinicians and pregnant women can support VAMPSS?

Dr. Schatz: There definitely are. I think one other point I would make about this whole subject is that, again, we're here to provide information and the question is: What is the consequence of not knowing? And we like people to realize that there's two consequences of not having adequate information. The first and the most common is that women and their caregivers are reluctant to use medicines during pregnancy and, again, I think any of us who take care of pregnant women have seen that, even if it actually is safe and would be beneficial for the woman's condition. So probably the most important, quantitatively, piece of information we will provide, that is the most important information quantitatively, will be that reassuring information so that women can feel comfortable. But the second is the less common but obviously important possibility that a medication is actually harmful during pregnancy or the baby, but without appropriate studies that risk remains unidentified. So that is a big reason why we feel this is such an important endeavor.

Dr. Stukus: And how can people support VAMPSS?

Dr. Schatz: Well, the most important way is to support the prospective cohort arm. The prospective cohort arm needs pregnant women who are taking medicines to enter the study, and the study only involves phone interviews and medical record review. So clinicians can recommend the study to their pregnant patients, and then the pregnant patients contact the study. One of our major current projects is the study of the safety of asthma biologics during pregnancy. So we definitely need women who are

taking any of the asthma biologics-- benralizumab, dupilumab, mepolizumab, omalizumab or reslizumab-- as well as comparison women with asthma, especially severe asthma, who are not taking these medicines. So there's a phone number that I want to give to recommend or enroll in the study and a website that the clinicians can give their pregnant patients to call. So the phone number is 866-626-6847. I'll repeat that, 866-626-6847, and the website is <https://mothertobaby.org/ongoing-study/asthma/>. Again, <https://mothertobaby.org/ongoing-study/asthma/>.

Dr. Stukus: That's great. Just to clarify-- it dawned upon me as I listened to you describe this-- I'm not hearing you say that pregnant women are being experimented upon in VAMPSS, but that this is a very different system. Is that correct?

Dr. Schatz: That's correct, and I think that does bring up a very important point. I mentioned that these drugs are not typically studied before they become available because in that case typically either a placebo was used or comparisons, but people are randomly given medicines in those typically preapproval studies, and one would not want to randomly give medicines to pregnant women. So this is definitely not a matter of being experimented on because these are women whose physicians have already decided they need this medicine. It's just a way then of saying, "Okay, people who are already taking this medicine, what can we learn about the safety?" So absolutely I think it's a very important point that the decision to use the medicine is a totally separate decision, but trying to get information from women who are taking medicines is what this system is all about.

Dr. Stukus: Great. That's a very reassuring message to send, so thank you. Well, Dr. Schatz, thank you again for joining us today. I think this was an extremely helpful and important conversation that we had on a topic that frankly a lot of people don't fully understand. So it was great. Is there anything else you'd like to add?

Dr. Schatz: Well, I think I'd only add that managing asthma and allergic disease during pregnancy is particularly challenging due to the concurrent presence of two patients, mother and developing infant. But I do believe that allergists and immunologists are very much up to that challenge, and a combination of optimal patient education, trigger avoidance information, appropriate medication, immunotherapy when indicated, and close follow-up should optimize the health of both the mother and the baby, which is of course everyone's goal.

Dr. Stukus: Well said. Thank you again. We hope you enjoyed listening to today's episode. Information about credit-claiming for this and other episodes can be found at <https://education.aaaai.org/podcasts/podcasts>. Credit-claiming will be available for one year from the episode's original release date. Please visit <http://www.AAAAI.org> for show notes and any pertinent links from today's conversation. If you like the show, please take a moment to subscribe to our podcast through iTunes, Spotify or Google Play so you can receive new episodes in the future. Thank you again for listening.