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### Providing Patients with Answers After Recurrent Pregnancy Loss

Announcer: Welcome to ReachMD. This medical industry feature, titled "Providing Patients with Answers After Recurrent Pregnancy Loss" is sponsored by ReproSource. Here's your host, Dr. Amy Mackey.

Dr. Mackey: Pregnancy loss is a devastating but, unfortunately, familiar reality faced by numerous couples. Upwards of 15-25% of pregnancies end in miscarriage every year. Studies looking at the emotional impact on couples indicate that couples want answers, if they are available. As clinicians, we're often posed with difficult questions as to why this happens recurrently for some couples, and how we can better help them find answers.

This is ReachMD and I'm Dr. Amy Mackey. Joining me to discuss the primary causes of miscarriage and the testing options available for fetal and parental evaluation is Dr. William Kutteh from Fertility Associates of Memphis. Dr. Kutteh, welcome to the program.

Dr. Kutteh: Thanks, it's great to be here.

Dr. Mackey: So, Dr. Kutteh, let's start with an overview of recurrent pregnancy loss. Can you explain how this is currently defined?

Dr. Kutteh: The American Society of Reproductive Medicine in 2012, and in a recent American College of OB/GYN bulletin, define recurrent pregnancy loss as two or more losses. I think everybody now agrees that after two losses, it's reasonable to begin this workup, and we have found in our experiences that most insurance companies recognize that.

Dr. Mackey: And given the high incidence of pregnancy loss, with an estimated 500,000 miscarriages occurring every year, do we know what the most frequent causes are?

Dr. Kutteh: When you look at the testing that is currently recommended on parents, you have genetic abnormalities in one and rarely in both of the parents, and these are typically balanced translocations. You have abnormalities in the uterus itself and these can be either congenital abnormalities from birth, such as a uterine septum, or they can be acquired abnormalities such as scar tissue in the uterus, polyps, or fibroids that are actually interfering with the endometrial cavity. There can be autoimmune abnormalities such as anticardiolipin antibodies and lupus coagulant, and there can be certain hormonal imbalances relating to the thyroid gland, progesterone production, and imbalances in the glucose metabolism.

Dr. Mackey: And with these testing, how frequently do you find abnormal results?

Dr. Kutteh: Two studies that we perform, the first one in over 1,000 women with recurrent pregnancy loss, demonstrated that whether the couple had had two losses, three losses, or four or more consecutive losses, the abnormalities were detected in about 45% of couples. That means that more than half of the couples would not have an explanation for their pregnancy loss.

Dr. Mackey: And does that include testing fetal tissue as well or is that just parental evaluation?

Dr. Kutteh: Well, that's a great question. We just published another paper in *Human Reproduction* in 2018, based on a proposed change in testing method that we had made in 2013, and in this proposal, we suggested that maybe we should be doing the first step, we should be testing the fetal tissue for genetic abnormalities, because we've known for many years that more than half of the miscarriages result from genetic abnormalities in the baby. And then, based on the results of the genetic testing on the miscarriage tissue, if it came back normal, then immediately the clinician would default to perform the recommended workup by ASRM. If it came back abnormal, the clinician would be able to give the patient an immediate explanation and let them know that we know why they lost the pregnancy, that the pregnancy was not going to be a normal child, and that it was a great thing that their body recognized this. It is unfortunate that this ended as a miscarriage, but in the larger scheme of things, this is the way reproduction works. And then the third category, which is the

smallest category, is when that miscarriage tissue came back as an unbalanced translocation. This should immediately alert the clinician to bring those parents in because one of them, undoubtedly, has a balanced translocation. The other, I think, interesting finding that we've observed is that it transforms the way the couple feels about their miscarriage. There's always the feeling of loss and feeling of grief over a failed pregnancy, but as we all know, patients often try to blame themselves for the loss. Did we, you know, I had a glass of wine or I ran up the stairs or many things that people want to think of that could've caused it. I forgot to take my medicine or my vitamin at the right time, and they want to blame themselves for the loss, but when we're able to inform the patient that none of those things matter and that instead of feeling that your body has failed in some way or your uterus has failed in some way, the transformative feeling is now my body recognized this was not going to be the normal, healthy baby that we all want, and not the baby that my doctor wanted me to have, and for whatever reasons, this was not a normal pregnancy. Thank God that my body recognized this and stopped supporting this pregnancy and allowed this pregnancy to fail in a way that we call a miscarriage. And you can almost sense the feeling of relief that many patients have when they realize it wasn't something they did or they should've done or they shouldn't have done, and that it doesn't mean that something is wrong with their body. It doesn't mean that their body failed. So, I think the secondary benefit, when you have an explanation, is not only saying why that loss was but for the emotional health and well-being of that couple.

Dr. Mackey: For those just joining us, this is ReachMD. I'm Dr. Amy Mackey and today I'm speaking with Dr. William Kutteh about recurrent pregnancy loss. So, we were just talking about some of the factors that lead to pregnancy loss, can you talk a little bit more about the evaluation and the tools that we have to evaluate patients who've had two or more unexplained losses?

Dr. Kutteh: Using the algorithm, if you had a couple who've had pregnancy miscarriage tissue that returned as normal, and you've ruled out maternal-cell contamination, you've got to remember that unless you're using 24-chromosome microarray, you're going to have a high rate of maternal-cell contamination. But, let's assume for the moment that's been done and you have a normal miscarriage tissue, then you should be sure that you've evaluated the uterine cavity, either by saline infusion three-day sonohysterography or hysteroscopy. You should be certain that you have performed good quality testing for autoimmune abnormalities, such as anticardiolipin antibodies and a lupus anticoagulant, and your patient should have a thorough hormonal evaluation, including thyroid abnormalities, testing for prediabetes or diabetic conditions, and ruling out a luteal-phase deficiency. Current guidelines also include genetic testing on the parents. That would be a standard banding karyotype.

Dr. Mackey: And traditionally, thrombophilia workups have been advocated. Do you find that that's still the recommendation?

Dr. Kutteh: Well, the current guidelines, both from the American College of OB/GYN and the American Society of Reproductive Medicine, do not recommend thrombophilia testing with the exception of two cases. Number one, the patient herself has had a prior thromboembolic event. Number two is that there's been a very strong family history of thromboembolic events. In both those cases, yes, we recommend testing of the patient for thrombophilia. Otherwise, testing is not recommended.

Dr. Mackey: And then so in one of your recent papers, you had an algorithm that discusses the approach that you've just been talking about. Can you go into a little more detail about the algorithm you proposed in that paper?

Dr. Kutteh: Yes. We, and others, proposed in 2013 the algorithm that said after second loss, the clinician should obtain fetal tissue, either by D&C or if the patient collects the tissue, she can bring it in. But, after the second loss, have 24-chromosome microarray testing performed on the fetal tissue. We actually tested this algorithm with the next 100 patients who'd had two or more losses to figure out if it was really valid. Up till this paper was published in 2018, people had just proposed this as a hypothetical algorithm, but we actually proved that if you do the 24-chromosome microarray testing on the miscarriage tissue, and follow that up in the patients that had a normal fetal tissue result, perform the ASRM workup for pregnancy loss, that the combined abnormalities from genetic testing on the miscarriage tissue and the ASRM workup would allow the clinician to provide an explanation, either definitive or probable, for the miscarriage in 95 out of 100 patients that we actually tested.

Dr. Mackey: That's pretty remarkable. Can you talk a little bit more about the genetic testing that helps you reach that 95%?

Dr. Kutteh: Sure. We've been using, for several years, a 24-chromosome microarray testing that is a different method from the traditional chromosome banding, and it eliminates the need to have viable tissue. It allows you to make sure that you don't have maternal-cell contamination by doing a comparative test with the mother's DNA, and it provides us with a diagnosis in over 90% of the samples that we have submitted.

Dr. Mackey: That's amazing. So, you also had mentioned that you could take tissue that was brought from home. Can you talk a little bit more practically about how you instruct patients to do that for our clinicians?

Dr. Kutteh: Not all patients desire to have an operative intervention and in those patients who choose to wait for natural or spontaneous passage, or a second group of patients who choose to have the miscarriage induced with medications, we provide them with a sterile container – it's a dry container – and ask them to wear just a pantyliner, and should they pass any tissue or blood clots, we ask them to

place that into the container. If it happens in the middle of the night, we ask them to put it in the refrigerator and bring it into the office the next morning. We then, in our office lab, tease out from that blood clot the actual tissue, submit that for 24-chromosome microarray. Now, in that case, we only get about 65% results compared to the 90% when we do an operative D&C.

Dr. Mackey: Alright, well that's certainly helpful for us clinicians to understand how to counsel patients about the availability in testing and the results they could expect. So, thank you for that. Before we wrap up, are there any takeaway thoughts you'd like to leave our audience with today?

Dr. Kutteh: Yes. I think the greatest joy as a physician is to be able to provide an answer to your patient when they come to you with a problem. In this case, recurrent miscarriage. And by adding this tool, which is microarray testing on the fetal tissue, we're able to almost double the number of couples that we can give an answer to, rather than leaving the office with well, I'm sorry you had a miscarriage and we don't know what happened, we're able to provide them with an explanation. The other point is that we did a cost analysis in our paper that we published in 2018, and by performing the 24-chromosome microarray first, we actually reduced the overall cost to the healthcare system by 50%, and, at the same time, doubled the number of couples that had an explanation for their loss. So, we would encourage clinicians to offer this to their patients in able to provide them with an answer for their loss.

Dr. Mackey: Well, that's a great way to round out our discussion. And I'd like to thank my guest, Dr. William Kutteh, for helping us improve our ability to provide comfort and guidance for patients trying to conceive. Dr. Kutteh, it was great speaking with you today.

Dr. Kutteh: Thank you, very much.

Announcer: The preceding program was sponsored by ReproSource. This is ReachMD. Be part of the knowledge.