**Episode 10: Bacterial Vaginosis w/Dr. Sara Kim**

Dr. Joe Chappelle: Hello everyone, and welcome back to the OB/GYN Podcast. Today I am very excited to introduce a guest speaker. Dr. Sara Kim is an Ob/Gyn resident at Stony Brook Medical Center in Long Island, New York and shares an interest in research and evidence-based practice. Today, I am fortunate enough to have her on the show to talk with us about one of the most common gynecologic complaints: bacterial vaginosis. I love looking in detail at something that we do every day, and Dr. Kim has really done a great job here. I learned a lot from her episode, and I know that you will too, so without further ado, let’s get started with Episode 10: Bacterial Vaginosis.

Dr. Sara Kim: The vagina, like many parts of the human body contains a mixture of different bacteria that we have come to call the microbiome. Over the last 100 years, we’ve come to understand the many beneficial effects of these bacteria colonizers, and in doing so, I’ve come to see that in many ways, the presence of certain microbes is probably not by chance but exist to confer over our health. They perform important functions in the mouth, stomach, G.I. tract, and importantly for today’s discussion, the vagina. When these complex ecosystems become perturbed and the balance of bacteria shifts, it can cause many undesired effects, ranging from asthma to Chron’s disease. As our understanding about these microbiomes has expanded, we have come to realize and understand the consequences of disruption and how to restore balance.

Our understanding of the vaginal microbiome starts in 1894 with Dr. Albert Döderlein. He was examining the vaginal secretions from healthy women and discovered the presence of a bacillus that occurred in great numbers. He called this bacteria Döderlein’s bacillus, but we later come to know it as lactobacillus. He didn’t know how important that bacteria was to vaginal health, but we are going to spend a good portion of today’s episode talking about its beneficial effects and what happens when it is outnumbered. The next step in understanding happened in 1914, when Dr. Curtis discovered the presence of an anaerobic bacteria called Bacteroides in women with abnormal discharge and postulated that also may be a factor in women with endometritis. Again, he was onto a portion of what causes bacterial vaginosis but would be up to the next person in our story, Dr. Schroeder, to bring it together.

In 1921, he published his categorization of vaginal discharge by Gram stain. His scale went from least pathogenic, which meant that it was mostly composed of lactobacillus, to most pathogenic, where there was no lactobacillus and many Bacteroides. This scale from 1921 would be very similar to the gold standard on microbiological diagnosis many decades later, which we’ll discuss in a moment. But before we get there, let’s talk about the two most famous people in our story, Dr. Gardner and Dukes, who in 1955 understood for the first time that bacterial vaginosis represents a shift in vaginal microflora. They developed clinical criteria for vaginitis that included the presence of a gray, odorous, non-clumpy discharge, a pH between 5.5 and 6, the absence of lactobacilli, and the presence of clue cells on microscopy. This was a major breakthrough in the diagnosis of BV, so let’s take a minute and breakdown each of these criteria down and try to understand it.

The first is simple enough. By excluding clumpy discharge, they are trying to separate yeast infections from bacterial vaginosis. And by including a gray, malodorous discharge, they’re making sure that normal vaginal discharge would be excluded. The pH and the absence of lactobacilli go together. We’ll get into the specific effects of lactobacilli in a minute, but for now, it is enough to know that lactobacilli make lactic acid as a byproduct of their metabolism, and this works to help keep the pH of the vagina low. So, when the number of lactobacilli decreases, it follows that the pH will rise. The pH has remained in our modern-day diagnostic schema, but it is easy to determine with litmus paper. While the presence or absence of lactobacilli has been removed because it is harder to determine and it overlaps with the pH, making it redundant. The last criteria, the presence of clue cells, is looking for the presence of vaginal epithelial cells that are covered in an abundance of bacteria. This finding is rare in women with an intact vaginal microbiome and remains in the clinical criteria we still use today.

As I mentioned, many of the criteria proposed by Gardner and Dukes remain today, and this transition from their work to modern day was performed by Amsel in 1983. He removed the lactobacilli criteria and added the whiff test. The whiff test is where KOH is added to the discharge and if a shift in flora is present, a fishy odor will be given off for reasons we’ll get to in a minute. These small changes resulted in a superior diagnostic test and remains the core of clinical diagnosis today. Gardner and Dukes’ prescient work on a standardized clinical diagnosis schema was a highline of their work. The other part of their work led them down a dead end because they didn’t understand how complex the vagina was from a microbiologic viewpoint.

In the early days of their research they discovered a bacterium that was present in over 90% of women, which fit their clinical criteria. They called this bacteria *Haemophilus vaginalis* believing it to be of that genus. Later, DNA-based studies would find it to be of a new genus, which was named after Dr. Gardener, and so now we call it *Gardnerella vaginalis*. No matter what you call it, Drs. Gardner and Dukes thought this newly isolated bacterium was a cause of all bacterial vaginosis, but in this case, they were wrong. In their defense, they did design a great study to test their hypothesis. They inoculated asymptomatic women with pure cultures of Gardnerella to see if they would develop BV. Even though they were later able to isolate the bacteria from the discharge of 10 of the 13 women in the trial, only 1 one of these women clinically developed BV.

They were greatly confused by this because they did not understand that there were many different bacteria involved in the process, and that a complete imbalance of the microbiome was needed to affect BV. In that line, they also didn’t know that most of responsible bacteria were anaerobic, and they couldn’t have because the tools needed to culture those bacteria didn’t exist. In fact. It wouldn’t be until the 1970s that anaerobic microbiology advanced to a point where those bacteria could be cultured successfully. After this advancement, it was shown that many anaerobic bacteria, along with Gardnerella, were present in large numbers in women with BV and that Gardnerella alone was probably insufficient to cause the clinical symptoms associated with BV.

With this new information and tools about the vaginal microbiome, a microbiological diagnostic schema was developed by Nugent to provide an objective method of diagnosing BV. He released his criteria in 1991, and it might sound a little familiar, because it is not so different than the 1921 method proposed by Dr. Schroeder. The Nugent score ranges from 0 to 10 and is based on determining the relative concentrations of lactobacillus, Gram-positive rods, Gram-negative variable rods and cocci, which are largely the organisms found to be in abundance in BV. The Nugent score gives a value of 0 to 4 in three categories: number of lactobacillus, number of Gardnerella/Bacteroides and number of curved Gram-negative bacilli. If the score is less than or equal to three, the smear is considered negative for BV. If the score is 4 to 6 with absence of clue cells, the smear is considered indeterminate. If the score in 4 to 6 with presence of clue cells, it is considered to represent the shift towards BV. While a score of greater than or equal to 7 Is positive for BV. While the Nugent scores objectify and standardize how Gram stains are reviewed, it is subject to viewer variability and it is not readily available to clinicians due to the processing time.

As we catch up to modern times, I think we can start talking about how BV actually develops. Well, first off, it is not an infection per se, but as alluded to before, it is more of an alteration of the normal vaginal microbiome resulting in clinical symptoms. So, in order to understand that altered state that leads to symptoms, we need to understand how the vagina works in its normal state. In an unaltered vagina, the vaginal epithelium produces and secrete glycogen, which is a great source of fuel for lactobacilli. These bacteria metabolize the glycogen and produce lactic acid as a byproduct. This substantially decreases the pH of the vaginal fluid. This low pH prevents the growth of most other bacteria and keeps the vagina with relatively low levels of the other bacteria talked about, namely Gardnerella and anaerobes.

When an external force is applied, such as menstruation or antibiotics, amongst many others, the levels of lactobacilli fall, and as the pH rises, these other bacteria outcompete the lactobacilli. As these bacteria increase. the metabolic byproducts increase as well, and it is these acids and amines that are responsible for the vaginal irritation and odor. These amines in particular, react with KOH to give off the characteristic fishy odor associated with the whiff test.

As any gynecologist can tell you, vaginitis is one of the most frequent reasons that women present for care, and the majority of those cases are due to BV. In fact, CDC describes BV as the most common vaginal infection in reproductive-age women. When these women present, we need a quick and reliable way to diagnose what the responsible agent is and treat it. The four clinical components of Amsel’s diagnostic criteria remain the bedrock of modern medical diagnosis. To review, they are one, pH of greater than 4.5, two, homogeneous thin white discharge that coats the vaginal wall, three, presence of clue cells on microscope, and four, fishy odor of the vaginal discharge with the addition of 10% KOH, also known as the whiff test. Having three out of the four is consistent with BV, with a sensitivity and specificity of 92 and 77% respectively when compared against Nugent’s criteria. Most tests for BV are compared to Nugent’s score because it remains the gold standard for BV diagnosis. However, it is time-consuming, costly and still subjective to a degree, and for these reasons, it is seldom used except in cases of recurrent resistant BV or in research settings.

In recent years, other scoring systems have been developed to try and simplify Nugent’s score so that it has more applicability in clinical settings, but Nugent’s score still remains the gold standard. Also new in recent years is molecular-based tests, like the Affirm, which tests for Gardnerella DNA on a vaginal swab. When compared against the gold standard Nugent’s score, it performs well, with a 90% sensitivity and 67% specificity. In the office setting, this is a very convenient method to diagnose BV, but the result is not immediately available, which does limit its usefulness. Additionally, the use of the Affirm or other molecular-based test should definitely be correlated with the clinical picture, because a positive test for Gardnerella does not always mean a woman will have symptoms.

This point about pre-clinical or asymptomatic BV versus symptomatic BV is important to the next part of our discussion. It is tempting to think that if a woman doesn’t have symptoms of BV, then we are treating a test as opposed to the woman. As I said, this is tempting, but maybe wrong. The more we have learned about BV, the more we have come to recognize that even small shifts in the balance of vaginal flora may have serious effects. Keep this in mind as we move into the next section.

So, moving away from diagnosis, let’s focus for a minute on the ramifications of a BV diagnosis. In non-pregnant women, the most common complaints are odor and itching. For most women, these episodes occur rarely and can be treated effectively. For those women with recurrent BV, it can cause significant quality-of-life effects, and we’ll discuss that when we get into treatment. The most significant effect of BV, however, are preterm labor, post-hysterectomy complications and HIV, and so let’s dive into those for a minute.

A simple shift in the vaginal flora may not seem much but can actually have some dire consequences in regards to preterm birth, low birth weight and preterm premature rupture of membranes. Multiple studies have demonstrated quantitively and qualitatively that receiving a diagnosis of BV increases the rate of delivering preterm, which itself is the leading cause of neonatal mortality in the United States. In 1995, Hillier et al. conducted a study that aimed to look at the association between bacterial vaginosis and preterm delivery and low birth weight infants by collecting vaginal swabs of pregnant women. Its conclusion was that microorganisms associated with BV were present in large numbers in women who delivered prematurely. While there is actually and inverse relationship between predominance of lactobacillus and rate of preterm delivery.

It was and remains an interesting finding, but why are BV and preterm delivery correlated? Do the different microbes actually reach the fetus? In 2008, Onderdonk et al. specifically looked at the bacteria present in the placenta of these preterm deliveries and found they were colonized by abundance of Gardnerella and other anaerobic microbes. Other studies have demonstrated the presence of the bacteria have led to an odd regulation of inflammatory markers in the newborn systemically, which have been adversely associated with developmental delays and brain damage. It is not surprising then, that while knowledge of BV has been in existence for a long time, and attempts to characterize the vaginal microflora has existed for decades, that with the additional knowledge of its effects on the fetus, that there has been a newfound focus and significant funding from the NIH to understand the vaginal microbiome, and the consequences of its disruption.

With such efforts to understand the vaginal microflora to prevent preterm birth, one may think, why not just screen everybody and treat a shift in vaginal flora even in asymptomatic pregnant females? In 2003, Tebes et al. did a meta-analysis of all studies between the years 1994 to 2001 to help elucidate whether routine treatment of all pregnant females was effective at decreasing preterm births. Most of the studies in the meta-analysis looked at screening and treating patients who had risk factors for preterm delivery, like history of preterm birth. But there were few studies that looked at low-risk populations as well. The conclusion of this meta-analysis is that routine screening in the general low-risk population is not indicated, and does not decrease the rate of preterm birth, at least in low-risk populations. In high-risk populations, the data is less clear, and there may be a benefit for more aggressive screening and treatment. Current ACOG guidelines recommend treating symptomatic BV, but routine screening is not recommended due to the lack of evidence.

Another area of concern regarding BV is in the postoperative setting, specifically its association with increased post-hysterectomy vaginal cuff cellulitis. A study by Larsson and Carlsson in 2002 specifically looked at this effect. In their study, women with and without preoperative diagnosis of BV were either prescribed one gram of metronidazole to be administered rectally prior to surgery and for six more days following the surgery, or no treatment. They demonstrated the decrease in vaginal cuff infection in women with a preoperative diagnosis of BV who were treated with metronidazole with a decrease in cuff infection from 35.7% to 0%. In women without a preoperative diagnosis of BV who were treated, they still found a decrease, but it was much less dramatic. Only from 9.5% to 2%. The consequences of postoperative cuff cellulitis are unclear and therefore, the cost-effectiveness of routine screening is up for debate. No clear guidelines exist, and we’ll have to wait for more data before we can decide to implement routine preoperative screening for women undergoing hysterectomy.

The last consequence of BV that I’d like to address is its association with HIV. BV has been associated with increased risk of HIV acquisition and transmission through its alteration of the immune health, specifically in the vagina. An in vitro study by Patterson et al. show that presence of Gardnerella actually weakened the vaginal epithelial layer, compromising its barrier functionality and leaving the tissue more vulnerable to HIV acquisition. On a more molecular level, Petrova et al. demonstrate how the presence of Gardnerella increased the production of RANTES, which has been shown in regions plagued by HIV epidemic in the Sub-Sahara, to be the single most predictive marker for increasing risk of HIV acquisition. To put it simply, the balance in vaginal microflora is so integral, that its disruption alters the vaginal immune health, affecting the type of inflammatory markers present and subsequently, its protective ability.

After going through all the bad effects of BV, I am happy to report, thankfully, treatment exists. Treatment is actually quite simple, although with a bit of a caveat to be explained in a bit. The goal of treatment is to essentially decrease the relative abundance of the pathogenic bacteria giving the good lactobacillus a chance to one again dominate, and thereby restore the normal microflora. Because most of the bad bacteria in this case are anaerobic, the ideal treatment will target those classes of bacteria while leaving the rest alone. If you remember back to the episode where we discussed antibiotics, you’ll remember that there are a few antibiotics that’d be ideal for this targeted therapy. The best choice is metronidazole, because the drug is only activated by metabolic pathways located in anaerobic bacteria. This makes it active against only the particular bacteria we are trying to eliminate here. Metronidazole can be given either orally or vaginally, which gives us flexibility in how we administer it. Alternatively, we can use slightly less good options, like clindamycin and tinidazole.

So, that sounds simple enough, right? This is where that caveat comes in. Unfortunately, about 30% of the women who are successfully treated will experience a recurrence within the next 3 months, and often, repeatedly. In these cases, the women can be placed on suppressive therapy of 0.75% metronidazole gel twice weekly for 4 to 6 months. These women could also be offered intravaginal boric acid 600 mg. daily for 21 days and then suppressive therapy with metronidazole. Unfortunately, there is not much data on the efficacy of suppressive therapy, but for women who suffer from recurrent infection, it is at least something to offer. And unlike other sexually transmitted infections, treatment of sexual partners has not been shown to decrease recurrence.

We talked a lot about how BV develops, its consequences and its treatment, so let’s step back and focus on who is at risk and whether there are ways to prevent BV. Multiple epidemiologic studies have shown that multiple sex partners, low socioeconomic class, smoking, presence of sexually transmitted infections, ethnicity and immunocompromised state are associated with increased risk of BV. Ethnicity in particular is interesting, and in fact, African Americans are more than twice likely to have BV than women of European ancestry. That race should affect something like BV is, on the face of it, a little weird. To look into this, Fettweis et al. performed a study in 2014 in which they sequenced the vaginal microbiome of different ethnic groups noted to have higher prevalence of BV. Interestingly, they found that the vaginal microbiome in these groups differed significantly. Women in the high-risk ethnic groups had greater microbial diversity and lower rates of lactobacillus. These differences persisted even after controlling for other risk factors like smoking and number of sexual partners. Which suggests that depending on the microbes present, slight perturbations may shift the flora to the direction of BV more easily in some groups.

Knowing that there may be inherent differences in the vaginal microbiome between people and the possible consequences that we talked about earlier, it makes us ask, is there a way to somehow promote a healthier, more stable microbiome? Many people have been focused recently on probiotics and there are currently several ongoing studies that are looking for new therapies in not only treating but also preventing bacterial vaginosis. Since BV is not necessarily an infection, these studies aim at restoring the balance and possibly introducing healthy microbes to the vagina, especially in high-risks populations, since like we just discussed, high-risk groups harbor a different microbial diversity.

Going beyond prevention, Ling et al. in 2013 compared the efficacy of vaginal metronidazole with vaginal probiotics, which contain lactobacillus. They demonstrated that symptomatic BV improves in 85% of those who received probiotic therapy versus 45% in the metronidazole group. Although, this study did not look at quantitative measurements, and only reported patient symptoms. But still, it’s impressive. Looking at recurrence, Menard, in 2011 looked at using probiotics as suppression compared to metronidazole. They found that probiotic-suppressive therapy led to greater stabilization of the vaginal microflora, preventing a shift toward BV-associated microbes.

While these are promising, they are small studies, using non-standardized probiotic therapies and different measures of success. Until more work is done to study the complex nature of the human vaginal microflora, and subsequently its role in promoting vaginal health that are unlikely to be any guidelines regarding the use of vaginal probiotics. We are over 100 years into our quest for knowledge about BV. We have learned a significant amount about the vaginal microbiome and its effects on many far-flung health issues, including preterm delivery and overall immune health. We have learned to recognize shifts in flora before a woman even has symptoms and we have just started to recognize that each woman with BV is different, and that treatments may need to be tailored based on new molecular techniques.

Bacterial vaginosis, something that on the surface sounds so simple, has turned out to have many intricate layers. What started out with Döderlein’s discovery in 1894 of lactobacillus, has progressed to today’s sequencing of individual women’s microbiome. While we have a better understanding of what defines BV, the players involved and the consequences, there is still much to be learned.

Dr. Joe Chappelle: Thank you, everyone, for listening. And thank you, Dr. Kim, for that excellent review of bacterial vaginosis. I look forward to many more episodes from her in the future. And remember, if you have a topic that you want to hear about, or by chance, you want to get involved and do an episode yourself, please contact me at feedback@obgyn.fm. We’ll be back next week with the first episode on puerperal fever, so until next time, thanks for listening.