Episode 3: Pelvic Inflammatory Disease – Part 1

By Dr. Joe Chappelle

Hello everyone, and welcome to the OB/GYN Podcast. First off, I want to apologize. This was supposed to come out about a week ago, but as it turns out, little children are walking vats of culture medium and my child is no different. So, today is the first day I actually have enough voice to record this. The next one should come out hopefully a little bit sooner.

Today's topic is pelvic inflammatory disease. This is a rather large topic and after doing all the prep work for it, I decided that in order to do it justice, I would need to split it into two episodes. Therefore, in this episode, we'll be discussing the history, definition, causes and consequences of PID, with a detour to discuss bacteria in general. And in the second episode, we will tackle diagnosis, treatment and prevention with probably another detour into antibiotics. But for today, let's get started with Episode 3: Pelvic Inflammatory Disease – Part 1.

Pelvic inflammatory disease, or PID, has been with us for a long time. We have records of sexually transmitted diseases going back at least 500 years in western history. The first reported STD was in 1495 in Naples, Italy. Charles VIII of France had taken an army of 50,000 men to invade Naples in the First Italian War. After successfully capturing Naples, it was used as a base for a crusade to the holy land.

As men indulged themselves, in what would charitably be called celebration, but really was more like a wholescale rape of the city. Within a few days, many of the men had ulcers on their genitals, which then progressed to fever, rash, joint and muscle pain. Several months later, these men started to get painful, foul smelling abscesses all over their bodies. These turned to ulcers that in some cases, ate all the way down to the bone. When the army returned home at the end of 1495, they took the disease with them. By 1500, it had spread to every European country. And about 1520, it was in Africa, China, India and even the Pacific Islands.

It went by many names. The French called it the Neapolitan disease. The English and Italians called it the French disease. The Turks called it the Christian disease. And the Japanese called it the Chinese disease. By 1514, it was known to be transmitted sexually and in 1527, the term venereal disease was coined by Jacques de Béthencourt because he wrote "since the disease arises from illicit love it should be called the malady of Venus or venereal disease." Lastly, in 1530, a poem was published by Girolamo Fracastoro that would give it the name we know today. It was entitled "Syphilis, or the French disease," with Syphilus being a character from an ancient Roman poem, who brought a new disease down upon his people by ceasing to worship the gods.

Now, where did this new disease come from? Well, we're not really sure. Many suspect that it was brought back from the Americas by Columbus, which might be

just given all the infections that he spread. It is also possible that it is a mutated version of a preexisting disease. However, there is little evidence to support either, so I'm going to go with the Columbus one. From this time until the mid-1700s, all venereal diseases were lumped together under syphilis. Then as medical and scientific advances were made, people began to suspect that syphilis and at least gonorrhea were separate diseases. This was finally confirmed in 1838 by Dr. Philippe Ricord. During this time, in the mid-1800s, as a new wave of what we would call gynecologists emerged, doctors began to describe the condition in women, that we would later know as pelvic inflammatory disease.

The evolution of thought on PID got a firm push by French doctor Goupil Bernutz. There were several doctors before him, that had theorized on the cause of mortality in women with pelvic pain and fever. But he was the first to take a scientific approach. He performed autopsies on the women who died of PID, and he characterized his findings. In 1866, he published a case series called *Clinical Memoirs of the Disease of Women* in which he reported his findings. He championed the name pelvic peritonitis, due to the pervasive inflammation of the peritoneum most of the women he examined demonstrated.

His work was quickly seized upon and advanced by others. Unfortunately, although many cases of PID, and especially the mortal ones, end in the similar anatomic features, the root cause of PID are several, and clinical presentation is inconsistent. By 1887, this was well understood, and when Dr. Matthew Mann in Buffalo published his book, *A System of Gynecology*, he wrote the following about pelvic peritonitis: "it should, however, be borne in mind that the symptoms will differ greatly in the different diseases. This will not be a matter of surprise when we remember that a variety of pathological conditions underly pelvic peritonitis, or, in other words, that the peritoneal inflammation is in itself only a symptom of several different morbid states." He continued: "I might adduce cases of gonorrheal ovaratis, commencing in healthy girls and ending in the fusion of all parts in the pelvis into a solid, immovable mass, without the patient losing a cheerful, and even gay, visage, or making any great complaint of pain, unless interrogated closely, and then alleging the chief suffering to be from an irritable bladder." This demonstrates why it is so difficult and took so long for the diagnosis and treatment of PID to progress. And in fact, we are still working on it today.

Before we get into what PID is, we should ask, how common is it? Even though we have learned there are causes other than STDs, the prevalence is roughly correlated to that of gonorrhea and chlamydia. The first statistics that we have go back to pre-World War II. As we talked about at the top of the show, wars are breeding ground for disease and venereal diseases are no exception. In World War I, it was the second most common reason for disability in the U.S. Army. And in World War II, 43 of every 1,000 men would be diagnoses with one at some point

during the war. In the Vietnam War, that number grew to 262 per 1,000, with 90% being gonococcal.

The area we know most about in regards to PID prevalence is Sweden. Dr. Lars Weström, someone we'll be hearing a lot about, and his partners were in an ideal position to study PID. They worked in Stockholm, which is the capital, and location of the major university in that country. This attracted many young women and men to the city. Dr. Weström and his associates staffed the only gynecologic clinic in Stockholm, and therefore they saw almost every single case of STD or PID.

In their work over many decades, they found that the rate of PID doubled in the Scandinavian countries after World War II, and based on their colleagues' works, they found that it also increased by at least 50% in many other European countries. In the 1960s in Sweden, they found a rate of about 1% in women aged 20 to 24. A similar study performed in Atlanta in 1965, showed a 2% rate in the same age group. The CDC estimates that the number of sexually active women who have been treated for PID in the United States was 8.6% in 1995, 5.7% in 2002, and is now stable at 5% since 2006. And while the declining numbers are consistent across all ethnic groups, the proportion of Hispanic and Black women receiving treatment is higher, which also mimics the rates of gonorrhea and chlamydia.

Now, let's step back and try to define what exactly PID is. It has had many different definitions over the years as we have developed a better understanding of the pathophysiology. In Dr. Howard Kelly's 1891 book, *The Diagnosis of Pelvic Inflammatory Diseases*, he defined it as "including all affections of the tubes and ovaries resulting from the infection of these organs, or the pelvic peritoneum. Also, all inflammatory conditions resulting from traumatic or other causes not directly traceable to infection." He mixed many different etiologies together because the diagnostic tools, in this case physical exam, could not separate them.

The intervening 125 years have allowed us to tease things out a bit better and a modern definition by the Center for Disease Control and Prevention is "a clinical syndrome that results from the ascension of microorganisms from the cervix and vagina to the upper genital tract." You can see that we have removed the noninfectious etiologies as we understand that it is the infectious causes that are most common and treatable.

Lastly, there's a more technical definition that spun from a 2015 New England Journal of Medicine review paper that defines PID as: "PID is an infection that results in fibrinous, inflammatory damage along the epithelial and peritoneal surfaces of the fallopian tubes and ovaries, which leads to scarring, adhesions, and possibly partial or total obstruction of the fallopian tubes."

As the last two definitions illustrate, the inciting element in PID is infection. At first, we thought that most PID was caused by sexually transmitted diseases, like gonorrhea and chlamydia. There is one notable historical exception, and that is

tuberculosis, which has been known about since the 1800s to cause bad intraabdominal disease, but it's not included in this discussion.

Over the years of investigation, we have found that gonorrhea and chlamydia are only found in about one third of all PID cases with an assortment of other bacteria making up the difference. Before I get into bacteria that cause PID, I do want to take a step to the side, perhaps, and discuss bacteria. Consider this a primer or a refresher on bacterial infection.

So, bacteria. Bacteria are single cell organisms with a circular DNA and a plasma membrane. Bacteria can also have a supplemental DNA strand called the plasmid, which they can use to share with other bacteria. This is how interbacterial resistance is shared between different bacteria. Bacteria was first identified in 1676 by Antony Leeuwenhoek, but it wasn't until the mid-1800s that an attempt was made to differentiate between different types.

In 1884, Hans Christian Graham was looking for a way to stain bacteria so that he could more easily see them in tissue. He developed a technique that was named after him, called a Gram stain. It takes advantage of the fact that some bacteria have a cell membrane surrounded by a thick peptidoglycan layer while others have a thin layer of peptidoglycan sandwiched between two cell membranes. In Gram stain, crystal violet is applied to a slide containing bacteria. The peptidoglycan layer and the cell membrane layer absorb the violet. Then, iodine is added, which binds the violet. Next, ethyl alcohol or acetone is used to dehydrate the peptidoglycan layer which traps the crystal violet iodine complex. However, in Gram-negative cells, the layer's too thin to retain the complex, and the dye is washed away along with the outer cell membrane. This leaves one set of bacteria stained violet and the other, colorless.

In modern technique, the bacteria are then stained with safranin, which stains a non-violet-stained bacteria. The ones that are stained violet are called Gram-positive, while the others are Gram-negative. This distinction will become important when we talk about antibiotics in the next episode.

Some important examples of Gram-positive bacteria are Listeria, a bacteria implicated in pregnancy loss; Staphylococcus and Streptococcus, two important skin and soft tissue bacteria; and Enterococcus and Clostridium, which are gut bacteria. Most bacteria, however, are in the Gram-negative group, and include things like E. coli, Salmonella, Shigella, Enterobacter, Pseudomonas, Legionella, Klebsiella and Proteus. Now, lastly, there is a third category of bacteria which are called Gram variable or indeterminate, like Mycobacterium and Mycoplasma, which we'll talk about in a minute as some of them are important to PID.

As we learned more about bacteria, we found that there were at least two more ways of classifying them. The first is by how they generate energy. All eukaryotes use adenosine triphosphate as an energy source. In the mitochondria, they use an

electron transfer chain to accomplish this. In aerobic organisms, the last molecule in this chain is oxygen, and so therefore oxygen is essential for them to stay alive. In anaerobic organisms, elements like sulfate, nitrate and fumarate are used. These organisms need these elements to live but do not require oxygen. To make it more complicated, some bacteria can use both. This is called obligate versus facultative. In humans, bacteria that live in our skin tend to be aerobic and bacteria that live in our gastrointestinal tract tend to be anaerobic. Again, we'll talk about this more when we talk about treatment.

Lastly, there are some small fraction of bacteria that either can or must live intracellularly. The obligate intracellular organisms lack key biosynthetic pathways and hijack their host cell to supply them with adenosine triphosphate and other essential molecules. There are only few of these and they are Mycobacterium leprae or the organism that causes leprosy, Coxiella, Rickettsia and importantly for today, Chlamydia.

Alright, so that was the micro lecture on bacteria. Let's bring it back to PID. Which of these bacteria that I mentioned cause PID? Well, like I said, the first one that was known about was Gonorrhea. It was discovered in 1879 by Albert Neisser, who lends his name to the genus Neisseria of which gonorrhea is as a member, along with Neisseria meningitidis. And gonorrhea is a Gram-negative, aerobic, facultative intracellular bacteria, with a number of nasty adaptations. It has pili that allow movement and are described as "the strongest biological motor known to date", and special proteins that allow it to bind to immune cells, which prevent immune responses. It is spread through sexual intercourse, with the pili allowing it to attach to sperm and to cellular debris in vaginal secretions. It was first treated with penicillin, but it is now almost universally resistant. Many different antibiotics have been used over the intervening decades with the most recent treatment of choice being the third generation cephalosporin ceftriaxone.

Next is Chlamydia, an obligate intracellular bacteria. It was first discovered in 1942 and finally cultured in 1957. It was discovered to be a major cause of non-gonococcal infections in the fifties and sixties. Due to the fact that it must live inside a cell, it is very difficult to culture, and polymerase chain reaction, or PCR, has become the easiest way to detect it. It can be treated with azithromycin, any of the fluoroquinolones as well as doxycycline. Azithromycin is most commonly prescribed due to the relative lack of side effects when compared to the other choices.

The last bacteria to talk about in relation to PID is Mycoplasma genitalium. It was only discovered in 1981. It is one of the smallest bacteria and lacks a proper cell wall, which makes it Gram-negative. It is very, very difficult to treat as it is resistant to most antibiotics for reasons we'll get into in the next episode. Azithromycin has been used but some studies show a 50% resistance rate. Others have tried

moxifloxacin, a fluoroquinolone, with some success, but there are very few studies to support its use.

According to the most recent statistics released by the CDC, about 35% of PID is due to gonorrhea and chlamydia. This number used to be much higher, but as we have done a better job of testing and treating for these in our outpatient clinics, the number of cases related to PID has decreased. About 40% of PID cases today are found to be polymicrobial and may be linked to bacterial vaginosis. This is thought to be due to the effect of bacterial vaginosis on cervical mucus. Now, cervical mucus acts as a physical and chemical barrier to the upper migration of bacteria into the uterus and pelvis. In 1994, a study in the American Journal of Obstetrics and Gynecology, found that two proteases that degrade cervical mucus were found in higher concentrations in the vaginas of women who were clinically diagnosed with BV. In a second study from the same journal in 2000, another group reported that white blood cell produce protease inhibitors that prevents this from happening were also decreased in women had BV. This combination may allow for the destruction of this barrier and the free flow of bacteria up into the uterus and fallopian tubes.

The last 15% of PID cases are found to have either respiratory or GI bacteria, like Strep, Staph and E. coli. How and why these bacteria get into the upper genital tract is unknown, but it may have something to do with BV as well.

Now, lastly, like I mentioned, there is Mycoplasma genitalium. It has not been studied much, but there has been found to be an association between PID and Mycoplasma, especially when either coinfected with chlamydia or in women with HIV. It is therefore possible that this is more of an opportunistic infection rather than the inciting agent.

As you can see, there are many different pathways, and they all lead to what we call PID. These different pathways lead to much different consequences. For example, gonorrhea-related PID tends to lead to more abscesses. While chlamydia tends to be more of a subacute infection resulting in fallopian tube damage.

As the prevalence of each of these inciting factors has waxed and waned, so have the long-term effects. Going back to Lars Weström, he detailed the effects of PID in his home country of Sweden in his 1965 paper *Effect of Acute Pelvic Inflammatory Disease on Fertility*, published in the American Journal of Obstetrics and Gynecology. He followed 414 women who were treated for laparoscopically confirmed PID, which was a standard at the time in Sweden, for up to 10 years. He found that 21.2% of the women in his study were infertile. Most of these were due to tubal occlusion. He found that the rate was directly correlated to the number of episodes of PID each woman had suffered. There was a 12% rate after one episode, 33% after two and a 75% rate of infertility after three. He also found that

tubal occlusion was more common after what at the time was called non-gonorrheal PID, or chlamydial. He also reported in that study that 18% of the women with a history of PID would go on to develop chronic pelvic pain, and that 0.4% had an ectopic pregnancy compared to 0.06% in women without PID. These are sobering statistics. A 12% infertility rate, or 18% chronic pelvic pain rate after one episode of PID has large and varied downstream effects that can ripple throughout a woman's life and through the healthcare system.

That was the 1960s and 1970s. Okay, maybe as we developed new antibiotics and diagnostic tools, we reduce the severity of PID. Well, a subgroup analysis of the Design of the PID Evaluation and Clinical Health trial or PEACH study published by Ness et al. in 2005 in the Obstetrics and Gynecology Journal, followed 831 women with a clinical diagnosis of PID between 1996 and 1999. Note there's a slight difference in these two studies. Weström's study used only women who had confirmed PID on laparoscopy, and we're going to talk about diagnosis in the next episode, in this study, it's all about clinical diagnosis.

All women were randomized between inpatient treatment with IV cefoxitin and doxycycline, versus outpatient treatment with intramuscular cefoxitin and oral doxycycline. The women were then followed for an average of 84 months or seven years. 75% of the women were Black, 65% percent were less than 25, and a third of the women reported having gonorrhea or chlamydia prior to enrollment in this study. There ended up being no difference between treatments for any of the major outcomes. They did find that 18% of the total group had infertility during the seven year follow up period. 29%, which is close to double the rate that we found in Weström's study, had chronic pelvic pain. And 0.6 had an ectopic, which is comparable to what Weström described. One thing that Weström did not report in his paper was the rate of recurring PID. In the PEACH study, they found that 15% of the women were treated for at least one additional episode of PID during the follow up period.

So, it would seem that the 30 years of medical advancements in the diagnosis and treatment PID did not have any effect on the outcomes. The knowledge about the causes of PID has undergone significant evolution in the last 150 years, from a disease of unknown etiology but recognizable clinical outcome, to one in which we know almost exactly what microorganisms are responsible. What has not changed in the intervening years is that it has serious long-lasting, and if untreated, mortal consequences.

In this episode, we highlighted that PID affects up to 5% of U.S. women at some time in their life, and with a large percentage subsequently being affected by infertility or chronic pelvic pain. The cost to society of these consequences in 1998 was estimated by Drs. Rein, Kassler and Irwin and published in 2000 in the Journal of Obstetrics and Gynecology. They estimated that we spent one billion dollars on acute treatment, 166 million dollars on chronic pelvic pain, and 295 million on

ectopic pregnancy, with the last been 360 million on infertility. The cost to care for each woman diagnosed with PID was estimated at $1,167 with most of that being for the initial management. One thing they did not try to estimate, because it's really hard to measure, is the effects that PID and its aftermath have in the lives of these women.

In summary, we have known about, and been studying PID in some form or another for 500 years, and we are still learning new things about it. What we do know is that it is relatively common, there are multiple causative agents, maybe some yet to be discovered, and that the consequences can be long lasting and severe, and the personal and societal costs are huge. I hope you will join me in the next episode, where we'll be discussing the diagnosis, treatment and prevention of PID.

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