**Episode 4: Pelvic Inflammatory Disease – Part 2**

By Dr. Joe Chappelle

Hello everyone, and welcome back to another episode of the OB/GYN Podcast. This is Episode 4: Pelvic Inflammatory Disease – Part 2. Now, this was originally going to be the final episode about PID, but the more I dug into today’s topic, the more I realized I was going to need an entire show to do it well. So, in this episode we’re going to focus on one thing and one thing only: how to diagnose PID.

Now, if you learned about it in school from a textbook, you might think that it’s pretty straight forward, and to be honest, that’s what I thought. However, what I learned preparing for this show is exactly the reason that I love evidence-based medicine. Because too often, what we are taught is the final product of a multidecade pursuit of information and we never question how we got there. Well, in this episode, we are going to question, and I hope that on the other side of it we’ll have a fuller understanding about the diagnosis of PID.

Before I get started with today’s episode, I want to talk about bias. My bias. I do a lot of research for these shows, and obviously not everything I read can make it into the finished product. When I’m choosing what to include, I consider many things, quality of the research being chief among them. However, I’m also trying to tell a story here, and I’m trying to make it interesting and entertaining. If I go off on a thousand tangents, the show starts to lack coherence. This makes it hard to follow.

I guess what I’m trying to say here is that when you listen to these shows, you’re getting the Joe Chappelle version of each topic. I do my best to reference the show thoroughly, so if you want to dig deeper, and you want to find the things I didn’t include, you can do so. Also, I am painfully aware that I am not an expert on most of these topics. So, if you think I missed something or if I only told one side of the story, please let me know and I will address it in future episodes. Anyway, enough preamble, let’s get started with Episode 4: PID – Part 2.

In the last episode, we established that pelvic inflammatory disease occurs in up to 5% of women at some time during their life, and can lead to infertility, pelvic pain and ectopic pregnancy. This leads to massive healthcare and personal costs. We mapped the evolution of thought on PID and the changes in definition as we learned more about the pathophysiology. We also talked about the microbiological causes of PID and how different organisms may result in different symptoms.

Because PID has many different causes with different disease patterns, the diagnosis of PID has never been easy. As new diagnostic tools have developed, they have been applied to the problem with varying levels of success. But today I want to start with the first diagnostic tool that humans ever developed: the clinical exam. To do this, I want to reintroduce Howard Atwood Kelly who was a firm proponent of clinical exam.

He was born in 1858 in Camden, New Jersey and received his schooling at the University of Pennsylvania. After obtaining his degree, he decided to pursue gynecology and spent time traveling to Europe to learn from the best surgeons of the day. When he returned to Philadelphia, he founded the Kensington Hospital for Women. After two years there, he was recruited to become the first professor of obstetrics and gynecology at the newly opened Johns Hopkins University. He spent 30 years there pushing forward the relatively new field of Ob/Gyn. He wrote several books, some which we’ll talk about today, and invented many new surgeries and tools, including the cystoscope.

In 1894, he published his experiences regarding PID in his book *The Diagnosis of Pelvic Inflammatory Diseases*, which we talked about a little bit in the first episode. In it, he established clinical criteria for PID, some of which we still use today. First, he noted that “fever is a sign of value, but it is more frequently absent than present.” And therefore, he did not consider it to be necessary for the diagnosis to be made. He very firmly recommended pelvic exam as being necessary to make the diagnosis. In fact, he stated, “an attempt to make a diagnosis without directly palpating the pelvic organs is at best but more or less clever guess-work.”

During his bimanual exam of the uterus and adnexa, he was feeling for signs of inflammation, induration and abscesses. He noted that in true cases of PID, one could feel “board-like hardness on one or both sides of the vaginal vault,” and that “if the cervix uteri cannot be easily displaced upwards, but is more or less immobile, and hard resisting surfaces are felt lateral to the uterus, the diagnosis of pelvic inflammatory disease may be made.”

As we have learned more about PID in the years after Dr. Kelly, we have learned that not all cases of PID lead to the clinical findings as he noted. He was likely detecting the most severe infections, specially those caused by gonorrhea and missing the less severe forms that mostly lead to tubal damage and infertility. In many ways, his approach made sense for the times, as there were few treatments available for these women and his criteria only included the women that he could treat surgically.

He also went to great lengths to separate what he called true pelveo-peritonitis versus pseudo-pelveo-peritonitis. He found that women with pseudo-pelveo-peritonitis had a “history of dysmenorrhea, extending over many years, intense enough in some instances to confine the patient to bed for two or three days at each period. Many of these patients are regularly addicted to opium or the bromides and the milder sedatives.” What he is describing here is most likely endometriosis or adenomyosis, diseases that had only recently been discovered in his time.

This is an important part of the differential diagnosis of pelvic pain and it emphasizes how many diagnoses can be made through a proper history and physical. Lastly, I find it amazing that he could so accurately describe a condition that he didn’t even really know existed. Dr. Kelly’s definition of PID was widely read and adopted. Over the subsequent decades unfortunately, the diagnosis of PID did not evolve until the next major breakthrough in our story. And that was laparoscopy.

Laparoscopy was invented in 1902 by George Kelling in Germany using dogs. In 1910, Hans Christian Jacobaeus from Sweden used it for the first time in humans. Steady progression of laparoscopic technique resulted in broad adoption in the 1950s and 1960s. Given the optical limitation at the time, namely the lack of cameras, the surgeon would have to look directly down the scope, which limited the procedure to diagnostic indications.

Laparoscopy comes into our story by the way of Lars Weström. You might remember him from the first episode. He and his group in Sweden published their first paper on the subject in 1969. It was titled *Objectivized diagnosis of acute pelvic inflammatory disease* and was published in the American Journal of Obstetrics and Gynecology. They evaluated 814 women who were clinically suspected of having PID. To be included, the women had to have acute pelvic pain plus two or more of the following signs and symptoms: abnormal vaginal discharge, fever, vomiting, menstrual irregularities, urinary symptoms, symptoms of proctitis, marked tenderness of the pelvic structures or an erythrocyte sedimentation rate of greater than or equal to 15 mm. per hour.

All women were then taken for laparoscopy to evaluate the pelvis. Their criteria for PID based on laparoscopy were hyperemia of the fallopian tube surface, edema of the tube or sticky exudate on the tubal surface or from the fimbriated end. Upon evaluating the data, they found that 65% of women with clinical signs or symptoms suggestive of PID also had laparoscopic signs corroborating the disease. Of those, they found that 41% also had a fever, 33% had irregular menses and that few had any rectal symptoms. And most women had two or more of these symptoms.

The women with laparoscopic confirmed disease were also found to be very likely to have tenderness on exam, 92%, a palpable mass, 50%, an elevated ESR, 75%, or vaginal discharge, 63%. Of their many women in this study, 12% had a different diagnosis on laparoscopy, such as appendicitis, endometriosis, ovarian cyst or tumor, and 23% had no identified pathology. Lastly, they found that 91 who had had laparoscopy for other reasons were also found to have salpingitis, about half of whom had no complain of pain.

Now, what should we take away from this study? Well, like most disease processes, PID has a spectrum of severity, which makes a crude visual examination of the pelvic structures problematic. The fact that 23% of women had no pathology noted on laparoscopic evaluation makes me wonder if those women were just caught earlier in the disease process. It also makes sense that women with more signs and symptoms were more likely to have laparoscopic findings. On the flip side, the number of women with signs of salpingitis without pain is striking, and highlights that clinical exam alone is probably insufficient.

I’m dwelling on this study because laparoscopy is going to become the gold standard for many of the other studies that we will discuss, and so it is important to understand its limitations. This issue regarding the accuracy of laparoscopy in making the diagnosis of PID was studied further by Sellors et al. in their 1991 paper published in AJOG, *The accuracy of clinical findings and laparoscopy in pelvic inflammatory disease*.

They studied 95 women with a clinical diagnosis of PID who underwent laparoscopy to confirm diagnosis. In addition to the visual inspection as described by Weström, they also took micro-biopsies of the fallopian tubes, to allow for histologic evaluation. 67 of the 95 women had visually normal tubes, which, as a side note, is much smaller than in the Weström study and may speak to the clinical criteria used for enrollment. Of the 67 women with normal-appearing tubes, 16 had histologic signs of infection, which I think highlights that laparoscopy is not a great tool in the early stages of PID.

They then used their small dataset to determine the accuracy of clinical criteria in the diagnosis of PID when using laparoscopy or histology as the gold standard. In both cases it was not very good. They found a positive predictive value of 74% when using laparoscopy as a gold standard, which means that 26% of the time, someone will be diagnosed with PID clinically and no evidence will be found on laparoscopy. With histology as the gold standard, it was even worse. Sellors concluded in his paper that “although laparoscopy has been considered the standard for the diagnosis of pelvic inflammatory disease, it has a high intra-observer variability and might not detect endometritis or early tubal inflammation.”

He was not the first person to be critical of laparoscopy and so many other tools would be applied to the diagnosis of PID. Today, we’re going to talk about two different categories. One is an attempt to find a histologic diagnosis and the other will attempt using imaging.

In the first of the histologic techniques, researches performed endometrial biopsies on women with a clinical diagnosis of PID prior to them undergoing laparoscopy. The paper I’m going to discuss was performed in Seattle in the mid-eighties and published in 1990 in the American Journal of Surgical Pathology by Nancy Kiviat el al. They had a lower threshold for the clinical diagnosis of PID in that they only required women to have abdominal pain for less than three weeks and tenderness on bimanual exam.

Their laparoscopic criteria were similar to Weström and their histologic criteria were the presence of neutrophils in the endometrium, the presence of stromal plasma cells or germinal centers containing transformed lymphocytes. They included 69 women in their study and found that 54% had both laparoscopic and histologic diagnosis, while 16% were found to have salpingitis without histologic evidence of infection and 29% had neither. This transferred to a 92% sensitivity and an 87% specificity for endometrial biopsy predicting laparoscopic-confirmed salpingitis. These sound like great numbers, but keep in mind that 16% of the women in this small study would not have been treated for PID if they were using endometrial biopsy alone to make the diagnosis. Also, again, they were using laparoscopy as their gold standard, which as we discussed, may not be the best.

The next histologic technique involved examining pelvic fluid obtained either at the time of laparoscopy or by culdocentesis. This study was published in 1985 by Jorma Paavonen in AJOG and was titled *Comparison of endometrial biopsy and peritoneal fluid cytologic testing with laparoscopy in the diagnosis of acute pelvic inflammatory disease*. This was an extremely small study, with only 27 women. All women had laparoscopy, endometrial biopsy and pelvic fluid collection. 67% had laparoscopic-confirmed salpingitis, 70% had endometrial biopsy diagnosis and 67% had signs of inflammatory pattern in the pelvic fluid.

They used laparoscopy as the gold standard and found that endometrial biopsy and pelvic fluid analysis were equivalent. Importantly, both had a negative predictive value of roughly 25%, meaning that 75% of the women with laparoscopic-confirmed salpingitis would not have been diagnosed using histologic criteria alone. Both of these studies illustrate that histologic tools are not sufficient and do not add much to the initial clinical or laparoscopic approaches to the diagnosis.

Next, we will discuss transvaginal ultrasound and MRI. Both modalities made great strides in the late seventies and eighties and became more and more available to clinicians. Transvaginal ultrasound in particular transformed gynecology and remains one of our most valuable tools. In 1986, Bruno Cracciatore et al. published their experience with the technique in the Green Journal. They included 51 non-pregnant women with lower abdominal pain and no history of recent GYN procedures. All women had a transvaginal ultrasound and an endometrial biopsy performed by different blinded providers. They then treated all women with a histologic diagnosis and reimaged them four weeks later.

They found that 25% of women had endometritis, of which 11 of the 13, or 85%, had thickened or fluid-filled tubes. They also found that women with endometritis were likely to have polycystic-appearing ovaries or free pelvic fluid. When using these three criteria, they found that ultrasound had a sensitivity of 85% and a specificity of 100%. And importantly, and this will come up again in the next paper, no women with a normal ultrasound had endometritis. When they reexamined these women four weeks later, they found that 60% had complete resolution of the ultrasound findings. This just highlights that even with treatment, the damage to the pelvic structures can remain and lead to infertility and chronic pelvic pain, because 40% of those women still had ultrasound findings consistent with tubal damage.

The last imaging study compares laparoscopy with ultrasound and MRI. It was published in the Journal of Radiology in 1999 by Tukeva et al. They had 32 women in their study who had clinical symptoms of PID, 21 of which had the diagnosis confirmed by laparoscopy. Using MRI and ultrasound criteria that I’m going to omit for brevity’s sake, they found that MRI was 95% sensitive and 89% specific, while ultrasound was 81% sensitive and 78% specific. Again, however, they noted that ultrasound and MRI were good at ruling out pain that was resulting from other pelvic ideologies, like ovarian cysts or ectopic pregnancy.

The last study I want to talk about in detail, involves the use of CA-125. This is a tumor marker that is expressed by the epithelia of the female reproductive tract. CA-125 along with CA-15.3, 19.9, CEA and IGF1 were studied for their presence in PID. Moss et al. published their work in the International Journal of Gyn & Obstetrics in 1994. They found that of the five markers, only CA-125 was elevated consistently. Unfortunately, CA-125 is a very non-specific marker, as it can be elevated in a range of pelvic pathologies, including ectopic pregnancy and ovarian cancer. There are many other papers looking at various cytokines and interferons that I will not get into today but suffice it to say that there is not enough evidence to start including them in any diagnostic schema.

Now, I know that was a lot of papers, and I hope I didn’t lose anybody there. I know you’re all thinking, “okay so maybe each one of those tools is not so good by itself, but what if we combine them all together? Maybe that will be useful.” Well, I’m glad you asked that question, because it allows me to bring the discussion back again to Lars Weström. In 2003, he published his last paper on the subject of PID entitled *Diagnosis of pelvic inflammatory disease: time for a rethink*.

This was a meta-analysis of the different approaches taken over the almost 40 years since his first paper on PID. He found that only three variables, fever, ESR and tenderness on exam, were useful, and that they only correctly classified PID 65% of the time. That’s not so good. But his real finding is that the only study they could find that had enough women to make real conclusions was his own. And that was published in 1969. His study had 814 women included in it, while all the other papers I just talked about had less than 100.

He noted that almost all clinical and laparoscopic criteria that every other subsequent paper used were based on his one study from 1969, and he had several issues with this. The first was that during the time of his study gonorrhea was the most common cause of PID, while in most industrialized nations today, that is no longer the case. Second, he felt that all women in his study were examined by gynecologists, while today, most women who are diagnosed with PID are seen by primary care providers who are not as trained, at least in the gynecologic section. Lastly, he noted what we already saw, and that is that laparoscopy may lack sensitivity and specificity when compared to histologic techniques.

He concluded with the following statement: “A new evidence base is urgently needed but this will require either a new investigation of the association between clinical presentation and PID based on a laparoscopic gold standard or the development of new a diagnostic technique.” Well, what are we supposed to do now? The most knowledgeable person in the field of PID just told us all that our diagnostic tools suck. What do we do now? Well, we come full circle, that’s what.

If none of these newer, expensive tools work, then I guess we should do what Howard Kelly says and trust our clinical exam. And that’s exactly what the CDC tells us to do. When comparing clinical exam to laparoscopy, the CDC finds that clinical exam has a 65 to 90% positive predictive value and that the clinical exam is much cheaper and has much less risk. Because the downside to overtreating is low compared to the downside of undertreating, they recommend a lower threshold for treatment.

The CDC recommends the following criteria: abdominal pain that cannot be attributed to other processes with one of the following: cervical motion tenderness, uterine tenderness or adnexal tenderness. They found that this approach had terrible specificity but that it only missed 5% of women with PID. They also state that we can use many of the other criteria that we discussed previously, such as fever, discharge, ESR, C-reactive protein, a positive gonorrhea/chlamydia, or others to increase specificity of the clinical diagnosis. But they caution against the use of endometrial biopsy given the need for a skilled pathologist and the invasive nature of the tests.

Now, you will note that nowhere, have I mentioned laparoscopy as part of the workup. The CDC does not recommend the routine use of laparoscopy. However, the one tool that they do recommend that we use is ultrasound, because as we talked about earlier, it can help to rule out other pelvic pathology.

I know that we just covered a ton of information in this episode, but I thought it was important to trace where we came from and how we came all the way back around to using the clinical criteria for out diagnosis of PID. I always tell the residents that I work with to question everything. Why do we do the things we do? In this case it is because a doctor published a paper in 1969 that is probably not even relevant anymore, by his own admission, and we continue to use it as the foundation for our entire diagnostic approach to an infectious process that can leave women disabled by pain, infertile, or both. Given all of this, I think the CDC has the right approach. Until we can find another method, we might as well cast the widest net at the lowest cost. And in this case, that means using the clinical approach first championed by Howard Kelly in 1894.

Thank you for taking this journey with me. I hope I have illustrated how important it is to know how we got where we are today. There is nothing wrong with the CDC guidelines. In fact, they’re the best we have. And it is important to know that they’re based on potentially flawed data. Unfortunately, this is not limited to the diagnosis of PID. If you look closely at most of the things we do on a daily basis and really examine what the data supports, you will be surprised to learn how little we actually know.

I don’t mean to depress or scare anyone with that statement. In fact, I mean to do quite the opposite. I want to inspire each of us to use that knowledge to question and probe. And when we find areas like this, to design research to better answer them. This is what I teach my residents, and when it comes to research, start by asking simple questions, and eventually you can find one that can be answered. Design your study understanding the limitations of the ones before you, and you can contribute on how we care for people. And yes, sometimes a question can’t be answered, and that’s okay. But if we never ask, we never grow. And each major breakthrough starts with someone asking “why?”

This is going to conclude Episode 4 of the OB/GYN Podcast. Thank you all for listening and I hope you will join me for the conclusion of PID in the next episode. As always, please send your comments to feedback@obgyn.fm and consider leaving your review in iTunes if you enjoy the show. So, until next time, thank you.