**Episode 11: Puerperal Fever – Part 1**

By Dr. Joe Chappelle

Hello everyone, and welcome back. I’m Joe Chappelle and you’re listening to Episode 11 of the OB/GYN Podcast. Last week, we were lucky enough to have a guest speaker, and I hope that everyone enjoyed the episode as much as I did. I thought Dr. Kim just did an excellent job. So much so that we’ve already slotted her for some upcoming episodes, so stay tuned, because you’re definitely going to hear more from her in the future.

Now, after spending the last several months on Gyn topics, I’m going to switch gears and move back to some OB topics. But before we get to today’s subject, I just want to stop for a minute and thank you all for listening. The number of listeners has really been growing lately, and I’m sure that it’s due mostly to all of you telling your friends and colleagues about the show. I spend a lot of time in this little hobby of mine, and I’m just honored that so many of you find it worthy of recommending it. I’ve also had a few people reach out to me in the last few weeks with suggestions for topics, and I’m going to put them on the list. And it you have a topic you’d like to hear about, then please send it on in.

Anyway, today I’m going to start with the first of a three-part series on puerperal fever. I’m going to divide this into episodes on chorioamnionitis, endomyometritis, and group B strep in pregnancy. Today’s episode is going to cover the history of puerperal fever, its impact on peripartum mortality and the diagnosis, causes and treatment of chorioamnionitis. So, without further ado, let’s get started with Episode 11: Puerperal Fever – Part 1.

Throughout history, and in fact, still in many places today, pregnancy and birth are the most likely causes of death for women. There are many things that can happen in pregnancy and during the delivery that can ultimately be fatal to the mother, the fetus, or both. The most common causes were and are hemorrhage, infection, venous thromboembolism, preeclampsia, heart disease and stroke. All of these topics deserve their own episodes, and I’m sure at some point we’ll get to them. But today, let’s focus in on infection.

Peripartum infection, childbed fever or puerperal fever, whatever you choose to call it, has been observed and discussed throughout most of recorded human history. The history of childbirth throughout different societies in the world could probably span an entire book or two. But, for today’s purposes, let’s suffice it to say, that at least until relatively modern times, most deliveries were performed by older women who had already had children themselves. This would eventually spawn an entire line of work, called midwifery, and then later, the field of obstetrics. In the pre-modern medicine days, women would often deliver at home or in designated places for childbirth. They would be attended by one or several women to help during the labor process and were most likely the only person giving birth in that location. It is impossible to know what the rate of infection was during this time, but we do have some information on the maternal mortality in the 15’ and 1600s, at least in England. This is based on marriage and baptism records and leads to an estimate of about 2.6 mortality rate for women giving birth. Of course, this is an all-cause mortality, but we can get an idea for what the number caused by infection was. Maybe about half a percent or so.

Contrast that with some of the epidemics of puerperal fever in the 17’ and 1800s that we’re going to talk about, where in some cases the mortality rate from infection alone was 20%, and you can see that something happened at the beginning of the Industrial Age ? to make childbirth even riskier than it was before. This inflection point was actually the dawn of modern medical field and its effects on childbirth. I can’t help but think that some of the mistrust in modern obstetrics can be traced back to this early era in modern OB. A lot of this owes itself to the great population migrations that occurred during this time. As the Industrial Revolution spread throughout Europe, great masses of people moved from the countryside into the cities. This resulted in overcrowding and decreased sanitation.

This mass of people, also combined with the growing fields of medicine, and led to the creation of the first lying-ins, where women, now instead of delivering at home, would go to these facilities to give birth under the supervision of doctors and midwives. If you stop and think about it for a minute, or maybe you don’t even need that long, you can already see where this is headed. Now, instead of a birthing attendant caring for one woman during her labor, she or he was now caring for many women at the same time. Combine this with the lack of modern hygienic protocols and you can see how infections could easily be passed from one laboring woman to another.

The first recorded episode of an epidemic of puerperal fever was in Paris, at the Hôtel-Dieu in 1646, and many more would follow throughout Europe and America. As mentioned, some of these epidemics would lead to mortality rates of over 20%, and in some cases, there was a 100% mortality from puerperal fever. By the late 1700s, OB practitioners were starting to understand that they themselves might be part of the problem. In 1795, Alexander Gordon wrote a book entitled *Treaty on the epidemic puerperal fever*. He wrote it after an epidemic of infection in his Aberdeen, Scotland hospital that started in 1789 and didn’t end until three years later in 1792. He noted that it affected the lower classes the most, but also affected women in the higher classes if she was attended by someone who had also attended the birth of someone with an infection. In his book, he describes many cases of puerperal fever, and determines that the doctors and midwives themselves were ultimately responsible for its spread. Summing up, he wrote “it is a disagreeable declaration for me to mention that I myself was the means of carrying the infection to a great number of women.”

So, by the late 1700s we knew –although as always, many people disagreed– that birth attendants could carry infection between laboring women. But we did not yet know what was causing it or how to defend against it. The next person in our story would combine Dr. Gordon’s work with the early thoughts on germ theory to make some remarkable observations, and would ultimately prove that this horrific threat from childbirth could be mitigated with a simple technique: handwashing.

The person responsible for this early insight was Dr. Semmelweis, a Hungarian obstetrician who after his training was assigned to work at the first obstetrical clinic of the Vienna General Hospital. At this time, there were two OB clinics in Vienna. The first, where Semmelweis worked, was staffed by doctors, and the second was staffed by midwives. These clinics have been set up to give free care to women in attempt to stop infanticide, which was a relatively common occurrence in the lower classes of this era. During this time working at the first clinic, he noted that there was a significant difference in the fever rates between the two clinics. So, starting in 1841, he set about keeping strict records of all births at the two clinics so he could try to figure out what this difference was. In the first few years, he noted the first clinic had almost double the amount of puerperal fever, and by 1846, he had eliminated every difference between the two clinics that he could find, and was starting to get desperate.

This is about the time that he had a breakthrough, and unfortunately for him, it was heartbreaking. He would make that breakthrough, that he is rightly famous for, after observing the tragic death of his good friend Jakob Kolletschka. While teaching medical students during an autopsy, Kolletschka was accidentally cut by a scalpel. He quickly grew sick and died from fever within a few days. Now, Semmelweis, ever the scientist, performed the autopsy on his friend and found that he had similar findings to the women he had examined who had died of puerperal fever. The lightbulb went off. From this finding, he finally deduced what the difference between the two clinics was. The first clinic had medical students, who also performed autopsies on a regular basis. While the second clinic was staffed only by midwives, who did not.

He still did not understand about microbes, and instead called what the students carried “cadaverous particles.” But he understood enough to try to fix it. So, in the middle of 1847, he instituted handwashing with a chlorine and lime solution, and was able to decrease the number of women who died of puerperal fever at the first clinic from almost 20% to 1%. This was obviously an amazing accomplishment, but his work did little good at the time. Most practicing physicians of the era refused to believe that they were responsible for spreading disease. He was even able to repeat his efforts at the University of Pest, but again, his ideas failed to spread.

His failure to convince others seemed to combine with a mental affliction of some sort, and by 1865, his behavior was noted to become increasingly bizarre, and he frequently lashed out at his critics, even going so far as to accuse them of mass murder by not accepting his findings and washing their hands. Many theories about his mental decline have been put forward, but the one that rings truest is that he was suffering from neurosyphilis, a disease common in people who treated the lower-class women, and especially prostitutes. Whatever the cause, by 1865, he was committed against his will to a Viennese asylum. On the first day of his captivity, he tried to escape, and was beaten so severely by the guards that he died two weeks later. Ironically enough, he died due to sepsis from a gangrenous wound. It is sad to think that a person who spent so much of his life making sure that women didn’t die of infection would succumb to the very thing he fought so hard against.

Like most discoveries that were ahead of their time, his findings would resurface and act as the foundation for the work done by Pasteur and Lister. These two doctors would both advance the theory of germs and work on ways to prevent their spread. Without their ideas of aseptic technique and sterilization, none of the modern surgical or obstetric care we take for granted would exist. And they both owed a large debt to Semmelweis. Semmelweis’s ideas, and later Lister’s, would eventually permeate both medicine and society and contribute to a decrease in mortality in many settings. But nowhere else would his contributions have a greater effect than the treatment of pregnant women in labor.

This inflection point in history has many ramifications. Before these advances, giving birth in a hospital was actually worse than delivering at home because of the increased chance of death from infection. Afterwards, with the risk of infection minimized, the benefits of hospital-based birth began to shine through. Hospitals had well-trained, experienced birth attendants, who had many more resources available to them to help achieve a good outcome for baby and mother. I do, however, believe that these early experiences and misgivings surrounding hospital-based birth remain and contribute to the growing trend of home deliveries. There are many issues here, both safety and cultural to debate regarding home vs hospital birth, and for today it’s outside the scope. But I do think that these early experiences are a part of that discussion, and I’m sure we’ll get there in a future episode when we tackle that subject.

In any case, with all that being said, why don’t we start talking about what infection during an active labor looks like? How do we diagnose it and how do we treat it? When infection occurs during labor, we call it chorioamnionitis, because we can see the inflammatory effects in both the placenta and the amniotic membranes. When the infection persists after the delivery or newly manifests after the delivery, then we call it endomyometritis. But today, we’re only going to talk about chorioamnionitis. I’m going to spend a few minutes talking about diagnosing chorio, but before I do, let’s touch briefly on what causes it.

Over the years, we have discovered and reinforced that chorio is caused by ascending bacteria from the vagina into the uterine cavity. Most commonly, this is polymicrobial, with over 65% of the amniotic fluid cultures from infected women being positive for at least two bacteria. Ureaplasma and mycoplasma are the most common types, 47% and 30% respectively. And are more common in preterm chorio. Gardnerella, which you’ll remember from the last episode, and Bacteroides, again, are next with 25% and 30%. And along with group B strep at 15% and E.coli at 8% are more common in term chorio. The wide range of bacteria responsible make it difficult to specifically target antibiotic therapy, and so, we end up using broad-spectrum combinations, which we’ll get to when we talk about treatment.

If you listened to the episode on the diagnosis of PID, you will find this next part very familiar, because there are similar themes around clinical versus histologic diagnosis. The strict definition of chorioamnionitis is “acute inflammation of the amniotic membranes and the chorion of the placenta.” Obviously, this is a histologic diagnosis, and it is made when there are increased number of leukocytes in the placenta or amniotic tissue. This definition captures both women with and without clinical symptoms, and can only be made several days after delivery, which, as you can imagine, makes it not so useful in the clinical management of women enduring labor. This has led to the development of a clinical diagnosis, which is designed to be as inclusive as possible given the risks associated with a misdiagnosis.

Because the histologic diagnosis likely captures women much earlier in the process, the two diagnostic schemas do not correlate very well. Also, the clinical diagnosis relies heavily on fever, which can be caused by multiple different factors during labor. You can see this when you compare the two. Only 62% of women with a clinical diagnosis will have signs of inflammation when the placenta is examined histologically. And conversely, many women with a histologic diagnosis do not have clinical symptoms at all. These women are often labeled as having “subclinical chorioamnionitis,” and its relevance to clinical outcomes is unclear.

Another method for examining for the presence of intraamniotic infection is to culture the amniotic fluid itself. Makes sense. This requires, unfortunately though, an amniocentesis, which is invasive, and comes with its own list of potential complications. Now, the culture, like histology, takes several days to perform. These two factors –the complications and the time– limit its utility, and it is mostly reserved for preterm women, because it aids in the decision on when to deliver them. An evaluation of the amniotic fluid can involve several different tests besides culture, and the gold standard is of course a positive growth culture, but additional tests such as Gram stain, glucose level, interlukin-6, white blood cell count, presence of leukocyte esterase or presence of matrix metalloproteinase can also be performed. These tests are alluring, because they result quickly, so let’s take a minute and look at these tests to see if they can aid in our real-time management of pregnant women, which really is our goal here.

For the Gram stain, greater than six bacteria per high-power field is considered positive, and this is very specific. But it only has a sensitivity of 24%. Low glucose, which is low because bacteria is using it as a food source, and white blood cell count are relatively useless, because they have a sensitivity of only 57% and a specificity of only 74%. Interlukin-6 and metalloproteinase are slightly better, with sensitivities about 85%, which is not bad, and a specificity of about 80%. And lastly, the presence of leukocyte esterase seems to be the best of the group with a sensitivity of 85%, and even better, a specificity of 95%. All of these additional tests were designed to give a faster result, but as you can see, none of them, except maybe the leukocyte esterase, performs well enough to take the place of an old-fashion culture. So, given that two to three day wait period and the risk of rupture after amniocentesis, none of these methods are employed very commonly, even in preterm patients.

This leads us all the way back to clinical diagnosis, which, again, should sound familiar to those who listened to the PID episode. The clinical criteria used to make a diagnosis of chorio are two temperatures of greater than 100.4 at least one hour apart, with the addition of at least two other signs, such as uterine tenderness, maternal tachycardia, fetal tachycardia and the presence of foul-smelling amniotic fluid. Additionally, many institutions also use one temperature greater than 101 without any other findings to be sufficient to make the diagnosis. Each of these factors by themselves perform poorly, but the more you have, the better the correlation to histologic chorio.

As I just mentioned, fever is essential to the diagnosis, and is required in most schemas. However, epidural has also been associated with fever, which obviously lowers the specificity of fever alone to make the diagnosis, especially when it’s less than 101. Maternal tachycardia, meaning greater than 100 beats per minute, or fetal tachycardia, meaning greater than 160 beats per minute, can obviously be caused by infection, but also can be caused by pain, anxiety, medications like ephedrine and beta agonists. However, the combination of fever and maternal and/or fetal tachycardia correlates strongly with histologically confirmed chorio. Other often cited signs of chorio are uterine tenderness on palpation and foul-smelling amniotic fluid. Both of these are very subjective, and in the case of uterine tenderness, may be masked by epidural use. Therefore, neither of these signs are used routinely in the diagnosis of chorioamnionitis.

Overall, the sensitivity of clinical diagnosis nears 100%, especially with two or more factors. The specificity, however, is generally poor. How specific it is depends on what you compare it against, whether it’s histologic chorio or positive amniotic fluid culture. In any case, as we add more factors to our criteria, we do increase the specificity, because it is unlikely that all of them will be caused by any other process.

I have been thinking a lot about what makes a perfect diagnostic model. In an ideal world, our tests would be able to differentiate between women who need treatment, either for themselves or their babies, and women who won’t have any downstream consequences like endometritis or neonatal sepsis. It also should be fast, cheap and reliable. To take this thought experiment further, if we wanted to find this ideal test, we would need to design a study where we don’t treat women with fever and we see who gets sick, and then we go back and we find the clinical or laboratory data that correlate with these bad outcomes. Then we would need to test our test with a randomized controlled study to makes sure that it performs how we think it will. Only then can we truly have a good test. Of course, we can’t ethically do that study, and so we’re going to be stuck with less robust tests, and therefore, in order to make sure we don’t let any mothers or babies get sick, we will always err on the side of overtreating,

I spent the last few minutes talking about if we don’t treat, we’ll have bad outcomes. But let’s get a little more granular on that. What are those bad outcomes? On the maternal side, women with chorio have an increase in caesarean delivery rate, increased risk of endomyometritis, wound infection, intraperitoneal abscesses, bacteremia and postpartum hemorrhage. As a side note here, the most common organism found in women who have bacteremia are GBS and E. coli. On the fetal side, the risk is correlated to gestational age at delivery. When compared against non-infected controls, there is a higher rate or pneumonia, sepsis, respiratory distress, neurodevelopmental delay and death in preterm deliveries complicated by chorio. In specific, preterm neonates affected by chorio have a 20% rate of pneumonia versus 3% without chorio. For sepsis, it’s 28% versus 6%. For neonatal death it’s 25% versus 6% and for respiratory distress it’s 62% versus 35%.

These are pretty profound, and these differences do remain in term pregnancies as well, but they’re much less pronounced. In term babies, it’s 4% versus 0% for pneumonia. 8% versus 0% for sepsis. 20% versus 2% for respiratory distress, which is a pretty big difference. And 2% versus 0% for neonatal death. Interestingly, there’s also a sharp increase in cerebral palsy, over fourfold, even in term neonates when the delivery is complicated by chorio. Which we don’t really understand, but it may have something to do with inflammation and decreased oxygenation. All of these outcomes reinforce our decision to be inclusive in our diagnostic schema. And because as you can see, the consequences of a misdiagnosis can be severe.

On the flip side, I think it is worth mentioning the consequences of a wrong diagnosis. In most hospitals, diagnosing a woman with chorio sets in motion a chain of events that significantly affects the first few days of a neonate’s life. They’re often separated from their mother, which can affect bonding and breastfeeding. Additionally, they are likely given antibiotics for 24 to 48 hours. This is great if they’re at risk for developing sepsis. But it they are not they’re getting a substantial number of medications with only the side effects and none of the benefits. This is not to say that we shouldn’t treat these women and babies, because the consequences, like I said, of a misdiagnosis seem more severe than overcalling it. But rather, we should not be happy with our current diagnostic schema. We should continue to try to find better methods for accurately determining who needs treatment.

Thankfully, treatment does substantially decrease the likelihood of all these bad outcomes, with one study demonstrating an 80% reduction in neonatal sepsis in women who were given timely intrapartum antibiotics. So, what do we treat these women with? Well, as I mentioned earlier, we need to choose something that’s broad-spectrum given the multitude of bacteria involved. The time-honored regimen is ampicillin every 6 hours and gentamicin in either a q.8h or a q.24h dosing schedule. Clindamycin is then added to this regimen if a caesarean is needed, for its anaerobic coverage. Obviously, this is more for maternal rather than fetal benefit. This regimen has been compared against ampicillin and sulbactam or cefotetan which both should to deliver the same antimicrobial activity. These studies are very small, they’re not that great, but in a Cochrane review of 11 of these studies, they found that there was no difference in neonatal or maternal outcomes between the different regimens. The review did reinforce that starting antibiotics as soon as the diagnosis was made resulted in much better outcomes than waiting until after delivery to start them.

So, although the type of antibiotics are relatively agreed upon, with most protocols still favoring the amp and gent route due to its cost and availability, how long the antibiotic should be continued after delivery is a little more debatable. Some people recommend continuing it for 24 hours while others recommend only one additional dose. There is, however, a growing body of literature to support giving only one dose after delivery. In one randomized controlled trial from Edwards et al. in 2003, they found that when compared against an additional 24 hours of antibiotics, the one single dose after delivery was no different when they looked at treatment failure. Multiple other studies have been done since then which also support this finding, so it makes me think that we might want to move towards this one additional dose due to the decreased medication, patient convenience an also cost. In either case, though, studies have been done that show that there is absolutely no benefit to giving a prolonged oral course of antibiotics after delivery, whether you do 24 hours IV or orally one dose.

Another aspect I want to touch on today is the treatment of ureaplasma. If you’re following along, you will note that neither ampicillin nor gentamycin cover ureaplasma despite it being present in 47% of amniotic fluid cultures. Although there have been no trials that show that there’s a benefit to adding something like azithromycin to cover ureaplasma, there has been recent evidence that it might decrease the risk of endomyometritis after caesarean delivery. Therefore, it is not unreasonable to suspect that perhaps the treatment failures noted in other studies are really due to untreated ureaplasma. This is pure conjecture, but I think it’s interesting to think about. For homework, you can all think about how you might design a study to determine what percentage of treatment failures, if any, are due to ureaplasma in this population.

To sum up the treatment of chorio, you should begin broad-spectrum antibiotics as soon as the diagnosis is made. It should be continued throughout the labor and at least one dose should be given after delivery. The time-honored choice of antibiotics is ampicillin and gentamycin with clindamycin added for caesareans. There is no reason to think that other broad-spectrum combinations won’t be effective, but amp and gent are cheap and do have relatively low side effect profiles. Gentamycin however does have a risk of nephrotoxicity and alternatives for Gram-negative coverage should be entertained in women with preexisting renal disease.

Now that we have covered treatment, let’s talk about who is at risk and whether chorio can be prevented in the first place. Some of the risk factors are pretty obvious. These include length of time of labor with ruptured membranes, length of time pushing, number of vaginal exams and use of internal monitoring, with length of rupture being the highest conferrer of risk. These make clinical sense because they involve giving more time to bacteria to ascend into the uterine cavity or giving these bacteria help in getting there. Other risk factors include GBS colonization and a diagnosis of bacterial vaginosis. Again, these make sense because GBS is a major cause of chorio, and the polymicrobial overgrowth of deleterious bacteria associated with BV would make infection more likely. These risk factors give us a jumping-off place for looking at preventive measures.

We need to divide this next section into preterm and term. For preterm rupture of membranes, which is a whole other topic, it is recommended to give ampicillin and azithromycin to help prevent neonatal sepsis and to delay the onset of labor. We’re going to cover this in a future episode, so I’m not going to go into it too much but the evidence for that is pretty strong. For term women, prevention really comes down to limiting cervical exams and internal monitoring. This is not to say that these should not be done if clinically warranted, just that we should think about whether we actually need the intrauterine pressure catheter before we place it and only examine the cervix when we plan to use that data for management decisions. When looking at the length of rupture, we need to weigh the risk of regressive augmentation of labor versus the risk of developing chorioamnionitis. Most women with premature rupture of membranes will go into active labor within 12 to 24 hours, while augmentation can lead to an increased number of caesarean deliveries. In healthy pregnancies without sign of infections, we should really consider limiting exams and allowing women time to enter women naturally, especially in GBS negative women. In GBS positive women, we should start penicillin immediately or the appropriate antibiotic for pen allergic women as this has been shown to dramatically decrease the rates of GBS sepsis in neonates. For women who are GBS unknown, we should start considering penicillin after 18 hours of rupture of membranes due to the increased risk of neonatal sepsis with prolonged rupture. We’re going to talk about GBS screening and treatment in part three so I’m going to leave that there for now and move on. As for BV, there is only a little data, but it all suggests that even though BV is correlated with chorio, that treating the BV does not reduce the risk of preterm delivery or infection. This is a little confusing and the data here is severely limited, so I will consider the jury’s still out on this, but it is something to think about and to look for more information in the future. All told, the prevention of chorioamnionitis in term deliveries boils down to using appropriate treatment for group B strep, limiting exams and the judicious use of internal monitors.

Chorioamnionitis has been with us since the dawn of the human race and continues to be a major factor in maternal and neonatal morbidity and mortality. In the developed world, it can be and is controlled with antibiotics. But in less resource-rich areas, it remains a common threat. There is still a lot to learn here about the disease process and which mothers and babies may benefit from treatment. I touched on it briefly, but again, I want to go back, because maybe there’s a downside to treatment. Dr. Kim spent some time in the last episode on BV talking about the microbiome. As she told us, the research into microbiome continues to show us how important it is to overall health. Giving women and their fetuses large doses of antibiotics most certainly alters their microbiomes. How important this is and what effects this may have are completely unknown, but I think it’s worth thinking about as we continue to tease out the best diagnostic criteria, and hopefully, we’ll get closer to our ideal test.

Until then, we must continue using the methods available to us, but never forgetting their limitations. We must also remember that just like the obstetricians that Semmelweis was trying to educate, that we, the OB providers, whether it be doctors or midwives or other, by our actions contribute to the problem. Just like those doctors, we do what we do because we think we are doing best for the women under our care, but we must remember to periodically challenge our firmly-held beliefs and not be afraid to change out management when the new data is presented to us. Just think of how many women and babies would still be alive if people had listened to and believed Semmelweis in the mid-19th century.

So, for now, I implore you all to evaluate the need for each exam or monitor and to carefully consider when antibiotics are needed. Our interventions, and sometimes our non-interventions can substantially affect the life and health of mothers and babies. And as new techniques become available, we should be ready to consider and implement them if we feel that they will help us achieve our goal of ensuring the safety of pregnant women.

And with that, I’m going to bring this episode to a close. I hope that you enjoyed this discussion about this small portion of puerperal fever, and I hope that you’ll join me in a couple weeks when we come back to discuss the second part: endomyometritis. But until then, as always, thanks for listening.