**Episode 12: Puerperal Fever – Part 2**

By Dr. Joe Chappelle

Hello everyone, and welcome back. I’m Joe Chappelle and you’re listening to Episode 12 of the OB/GYN Podcast. I want to apologize for the long gap between episodes, but as I think I’ve mentioned before on the show, I have a young child who loves to share his germs with everyone in the family. This has resulted in me having almost no voice for the last two weeks, which does make it a little bit difficult to record. But, never one to sit idly by, I have used this time to start some new projects for the podcast. This show now has listeners in almost every state in the U.S. and 39 countries around the world, including places like Myanmar, China, Ecuador, Sweden, India and Saudi Arabia. I’ve been thinking over these past couple weeks that I really want to find a way to bring us together somehow.

The problem with a podcast is that it is very one-sided. I sit here and talk on my microphone, but I never get to hear back from all of you. So, today I’m announcing two ways of allowing us all to communicate. The first is an old-fashioned message board, which you can get to at the show’s website: [www.obgyn.fm](http://www.obgyn.fm). The second is using the relatively new messaging system called Slack. Slack is a really cool messaging service which supports a wide range of messaging modalities and the ability to share files and more. It is free to join, and thankfully by default, it does not send you annoying notifications. It’s available on all the major platforms – Mac, PC, Android and iPhone – and by nature, Slack is invite-only. So, what I want to do now is invite you all to join. To do that, please send me an email at feedback@obgyn.fm and I will send you an invite. My hope is that one or more of these methods speaks to you, because I really hope that we can build something larger than just this show. Personally, and selfishly, I hope that one of these catches on, just because I want to talk to you all and hear about your experiences. I want to be able to incorporate your thoughts and knowledge back into the show and bring in some new perspectives. So, please, check out one or both of these, and I hope I’ll be talking to all of you soon.

Okay, moving on. Today we are going to continue our conversation on puerperal fever. In our last episode, we traced the history of puerperal fever form a known risk of childbirth to its rise as one of the first nosocomial infections, and then to its understanding and control with modern hygiene and antibiotic. We also discussed how we don’t have a perfect tool for its diagnosis, which leads us at times to over treatment. But also, that given the real risks of a misdiagnosis, we prefer this approach. Lastly, we covered the causes, risk factors and preventative measures for chorioamnionitis. Today, we’re going to move from intrapartum to postpartum. Postpartum fever is a more complex topic than chorioamnionitis was, simply because there are many more disease processes that can give rise to a fever. In today’s episode, we are going to cover the rather broad differential for postpartum fevers and then spend some time talking about each. So why don’t we get started with Episode 12: Puerperal Fever – Part 2.

The differential diagnosis for postpartum fever is one of the very basic things we teach medical students during their rotation in obstetrics. Maybe you remember something like wind, water, wound and walking. This is a generic list that covers postoperative fever, and to that list, we add womb and breasts for our postpartum patients. When we encounter a woman with a fever in the postpartum period, we have to suss through this differential and make a diagnosis. We’re going to dive into each one of the items on our list, but before we do, let’s lay some foundation.

How often do women have postpartum infection leading to fever? In a study performed at Brigham and Women's Hospital in Boston in 2001, they found an overall rate of 6% in the first 30 days postpartum. This rate was slightly higher at 7.4% when we looked just at caesarean deliveries, and slightly lower at 5.5% for vaginals. We need to keep in mind that this study was done before the widespread adoption of pre-caesarean prophylactic antibiotic. And as we will discuss, that change in protocol has had a profound effect. In any case, the primary driver of infectious morbidity post-caesarean was surgical site infection, which accounted for over 50% of the cases. This was followed by mastitis and UTI, with endometritis close behind those two. As you can imagine, the numbers for vaginal delivery look a lot different, because there is no abdominal incision to become infected. So, for vaginal deliveries, mastitis makes up over half of the postpartum infections, followed by UTI and endometritis and perineal lacerations, which account for just a very small percentage.

With that, let’s dive into the differential and let’s start with mastitis. As I just told you, mastitis is a relatively common cause of postpartum infection in the first 30 days. Mastitis is an infection of the breast tissue and it’s thought to be an ascending infection passed from the neonate’s mouth. Therefore, in order to get mastitis, the baby needs to be breastfeeding regularly, and its mouth needs to be colonized with bacteria. These two requirements make mastitis relatively rare in the first 48 hours. In fact, the peak incidence is at two weeks, with a slow decline in rates up to ten weeks. Mastitis usually presents as a fever – sometimes quite high – and one-sided pain in the infected breast, with erythema and swelling. The most common bacteria responsible are Staph aureus and GBS, with enterococcus being less often seen. Treatment involves a combination of supportive measure and antibiotics. On the supportive side, it is important to effectively remove milk from the breast, either by continued breastfeeding or pumping, and to give women pain and fever control. Ice and heat to the infected breast may also help with symptoms and can be used as needed. Antibiotic treatment should be geared toward the Gram-positive bacteria that most likely caused the infection. Because Staph aureus in particular can have potent beta-lactamase enzymes, a resistant penicillin-based antibiotic or a cephalosporin are the best choices. In the U.S. at least, the most common antibiotic for postpartum mastitis is dicloxacillin, which is a beta-lactamase resistant penicillin and only treats the Gram-positive bacteria that’s likely to cause the infection. If the woman has a penicillin allergy, then cephalexin can be used. And if they have a severe allergy then clindamycin can also be used instead. Any of these antibiotics should make short work of mastitis, and we should definitely start to worry if there are no signs of improvement in 24 to 48 hours.

When we’re confronted with a treatment failure, we must consider two things: the presence of methicillin-resistant Staph aureus or the presence of an abscess or both. Abscess formation complicates about 3% of mastitis cases and can be evaluated for clinically. If present, we should consider aspiration or incisional drainage, because antibiotics have a hard time penetrating into the collection, and without drainage, it is unlikely to be any improvement. In the absence of an abscess, we should change our antibiotics to cover MRSA. These antibiotics can include TMP/SMX, clindamycin, rifampin and vancomycin. At least in my institution, 40% of all the Staph aureus cultured is resistant to clindamycin and so its use has declined. Your mileage may vary, but I tend to use TMP/SMX as my first choice because it is orally available and generally well-tolerated.

There is also a non-infectious process in the breast that can cause fever in the immediate postpartum period, and that is breast engorgement. This occurs when letdown begins, which occurs most commonly between day 3 and day 5 for first time moms. In can happen in the first 1 to 2 days for multiparous women. As opposed to mastitis, this is a bilateral process, and the fever, which is generally low grade, should dissipate when the breasts are empty. On clinical exam, the breast will be universally tender and tense to palpation throughout. Care should be made when making this diagnosis because I have found an engorgement rarely causes a clinically significant fever.

The next bullet point on our list is pneumonia, which is an extremely rare cause of postpartum fever. It occurs in roughly 1.8 per 10,000 vaginal deliveries and 4.4 per 10,000 caesarean deliveries. Most of the cases are due to community acquired infections that are preexistent on admission. Hospital-acquired pneumonias are rare but should be considered for women with prolonged antepartum stays. Treatment guidelines are the same for both pregnant and non-pregnant women and should take into consideration the prevalent bacterial causes in your community.

Moving right on, let’s talk about urinary tract infections. A lot of time has been spent in recent years talking about ways to decrease the rate of catheter-associated UTIs and in the U.S., this has been labeled as a “never event.” This means that every one of these catheter-associated UTIs causes a mark against the hospital and can be tied to reimbursement. It should be no surprise that UTIs are directly related to the length of indwelling catheter, and therefore more common in women undergoing caesarean delivery. Several papers have published a 1.5% incidence in women having a caesarean delivery, with bacteria responsible being mostly E. coli, enterococcus and GBS. In order to combat these never events, providers have experimented with replacing catheters with a one-time emptying of the bladder at the start of the surgery. Surgical findings have been encouraging, and in one small-scale study they found a tenfold reduction in associated infections, which, if it holds up, is a major improvement. The two main concerns with this approach are intraoperative injuries to the bladder, because it may not be completely emptied, and postpartum urinary retention. Although these studies are small, there does not seem to be any increase in surgical complications. And although there is an uptick in retention cases, they are more easily treated than infections. This approach is attractive in resource-limited areas of the world, and as more data accumulates, maybe it will catch on in other places as well. Regardless, there is little doubt that decreasing the duration of catheterization as much as possible, will have an effect on the rate of UTIs in our postpartum women.

Another area that has been looked at is women with recurring UTIs in pregnancy, as they have a much higher rate of postpartum UTIs. The higher the number of antepartum infections, the higher the chance of postpartum infection, with the highest rate of about 45% in women with three or more UTIs in their pregnancy. One small study attempted to prevent these postpartum infections by giving oral antibiotic prophylaxis after delivery. They found a reduction from 40% to 22% in women who got the antibiotics, but because the low number of women included in the study, they failed to show significance, with a p value of 0.07. I find this result encouraging, and I do hope that they redo this study with larger numbers. Because although there are not that many women with recurring UTIs in pregnancy, addressing these cases is going to be important if we want to eliminate these postpartum UTIs. Treatment for UTIs follows the same tenets as mastitis, in which we look at the responsible bacteria, in this case, Gram-positive and Gram-negative bacteria, and then choose antibiotics that are cheap, well tolerated and cover the right organisms. For community-acquired infections, a first-generation cephalosporin, amoxicillin with sulbactam, TMP/SMX or nitrofurantoin are usually effective.

The next topic I want to spend a few minutes on is venous thromboembolism. This is not an infection per se, but since it can cause a fever, it is on our differential. VTE is also a leading cause of maternal death, in both the U.S. and around the world, and has been receiving a lot of attention worldwide over the last decade. Thankfully, the incidence is low, but unfortunately, we have very limited ability to predict who will suffer from them. In pregnancy, most VTEs occur antepartum, but about one third of DVTs and one half of pulmonary embolisms occur after delivery. Overall, just 0.05% of deliveries are complicated by VTE. And of these, only a small percentage will have an accompanying fever. The RIETE Registry, which is an international study of VTE, found that only 5% of people with VTE will have a fever, which means that only 0.0025% or 2.5 cases per 100,000 deliveries will be complicated by VTE with a fever.

Over the last 10 years, we have clearly identified many of the most important risk factors. But as I mentioned, even with this knowledge, we have not been able to prevent them consistently. Part of the struggle with proving efficacy of our interventions is that the numbers we are dealing with are so small that the study population needs to be huge, which makes the studies almost logistically impossible. With that said, low risk interventions like sequential compression devices for women on prolonged bed rest or after caesarean delivery make sense, because they have been shown to be effective in other surgeries, are low risk and are relatively cheap.

Other interventions like heparin, including the low molecular weight varieties, are more controversial. Now, why is that? Well, in a retrospective study at my institution, we found that of the six VTEs that we recorded in a six-year timespan two occurred in women with no risk factors, three occurred in women who were considered high risk but did not receive heparin and one incurred in a woman at high risk who was receiving heparin. Based on this limited data, the number needed to treat with heparin to prevent a VTE is huge. And although short courses of heparin or Lovenox are generally safe, it does raise questions about whether it’s worth it. And it is telling that all of the major colleges like the American College of Ob/Gyn, the American College of Chest Physicians and the Royal College of Ob/Gyn does not recommend the routine use of heparin, but rather recommend using it only for women at high risk for VTE. Until we have more data to work with, this is probably the best we’re going to do.

Since VTE is rare in the postpartum setting, and only a handful of those who do will have a fever, it should not be at the top of anyone’s differential, but it should be there. A famous medical saying goes something like this: in order to make a diagnosis, it must first be entertained. Meaning that if we never consider the diagnosis, we’ll never make it. So, we’ll keep VTE tucked in the back of our mind when evaluating these women.

Let’s move on to wound infection. As I mentioned at the top of the show, this is one of the major causes of postpartum fever. Although perineal lacerations can also become infected, it only happens in about 0.2% of cases, and so we’re not going to talk about it today. Instead, we’re going to focus on caesarean wound infections. In the era before preoperative antibiotic prophylaxis, wound infection complicated about 16% of all deliveries. In those days, the most common bacteria cultured from wounds was overwhelmingly ureaplasma, which accounted for 62% of cases. Staph aureus was next at 32% and enterococcus last, at 28%. I would think that prophylactic antibiotics would change this list, but I was unable to find papers that addressed it. If any of you dear listeners have this information, please send it in and I’ll put it on the website.

But in any case, wound infection usually presents day 4 to day 7. It’s associated with redness around the wound, foul-smelling discharge and pain. Treatment is generally antibiotics targeted towards Gram-positive skin flora, like a first-generation cephalosporin or, if not breastfeeding, then TMP/SMX. And 90% of all women will be afebrile within 48 hours of treatment. Non-resolving or worsening infection should be evaluated for possible abscess formation, and antibiotics should be switched to more broad-spectrum to cover Gram-negative and anaerobic bacteria.

But rather than treat these infections, let’s look at ways to prevent them. The first and most successful was the introduction of preoperative antibiotics. A single dose of a first-generation cephalosporin can dramatically lower the postpartum infection rate. In several studies, they were able to reduce the rate of wound infection from 15% down to 2 to 3%. Historically, antibiotics were given after the cord was clamped so that the fetus was not exposed. This still worked somewhat, but as we have seen from the general surgical literature, it is really giving the antibiotics before the incision that gets you those big results. It seems that one single dose of a first-generation cephalosporin given within one hour before the start of surgery is the best, and most institutions in the U.S. use cephazolin. One gram is the standard dose, but several studies have demonstrated that women with larger BMIs need a higher dose to ensure adequate tissue levels, and therefore, the current recommendation is for two grams of cephazolin in women over 100 kg. or with a BMI over 35. One small study has also been done to evaluate if women with BMIs over 40 need an even higher dose, but they found that there was no additional benefit to doses over two grams.

Lastly, many people have looked at the effect of surgical technique on wound infections, and there are three things that I want to highlight: closure of the sub-q tissue, staples versus sutures and irrigation of the sub-q with iodine. There is compelling evidence that closing the subcutaneous tissue, with either continuous or interrupted sutures, decreases the formation of seromas and subsequent infection. This holds true when the tissue depth is greater than 2 cm. Closure does not seem to make a difference when the tissue depth is less than that, but it is likely that the number needed to treat is just higher in that group. And so, if you want to close it when it’s less than 2 cm., that probably makes sense too. The suture versus staples debate goes back at least 20 years, and for most outcomes there seems to be no difference. However, there was a well-designed study form the University of Alabama that found that women with staples have a higher chance of wound separation and infection. And if you dig down into that study, you will see that the average BMI for women in the analysis was greater than 35, which is much higher that other studies. And so, my takeaway from that paper is that there’s probably a benefit with women who have a higher BMI if you use sutures as opposed to staples.

The last idea is kind of a common sense one, and that is, if we irrigate the wound with iodine and reduce the bacterial load, it should reduce infection. A group from Australia evaluated this with a randomized controlled trial with over 3,000 women. And they found an overall infection rate of about 9.5%, but there was no difference between the iodine irrigation and no irrigation at all.

In summary, wound infection is a common complication of caesarean delivery, and most of them can be prevented by giving a pre-incisional dose of first-generation cephalosporin or equivalent. This should be given on a weight-based basis with women with a BMI over 35 or weighing more than 100 kg. receiving more. Women with greater than 2 cm. of subcutaneous tissue should have that space closed, and consideration should be given to using sutures on women with larger BMIs as well, as it may decrease the risk of wound separation. Lastly, irrigating the wound after fascia closure seems to make no difference in infection rates.

Alright. So, now moving on to the topic that actually got me started on this in the first place, and that is endometritis. Endometritis has gone by many names over the years, including endomyometritis, and more recently, metritis with pelvic cellulitis. These all mean the same thing though, which is an infection of the endo- and myometrium. This can happen after vaginal delivery, but only occurs at about 1 to 3% of those deliveries, and it has really only become a serious clinical concern with the rise in the rate of caesarean deliveries, because they can occur in up to 27% of those deliveries. When untreated, endometritis can lead to bacteremia, sepsis and death in 10 to 20% of cases, and its early recognition and treatment is essential to halting the disease process.

Postpartum endometritis is a polymicrobial infection with both aerobic and anaerobic bacteria, and its treatment therefore ends up being broad-spectrum antibiotics. A Cochrane review from 2015 found that a combination of clindamycin and gentamycin was the most effective. In fact, when compared to ampicillin and gentamycin, women receiving clindamycin had a 35% less risk of treatment failure. At my institution we still use amp and gent, but perhaps we should switch over given this evidence. There is some concern for clindamycin and its association with C. diff., but ampicillin also carries this risk, albeit slightly less, so we should probably just concentrate on treatment failures. For those of you interested in reading further on this one, the Cochrane review is in the show notes, and well as the paper on C. diff. rates after antibiotic usage. The last thing to mention about antibiotic choice is in regard to gentamycin dosing. There has been a lot of literature regarding daily dosing of gent versus 8-hour dosing, and they all found that daily dosing is just as effective. This is because the efficacy of gentamycin is related to its peak concentration levels, not its average plasma levels. Therefore, dating back to the late ‘90s, there have been studies showing that daily dosing is effective and safe for women with endometritis. There is some concern for nephrotoxicity with gentamycin, which is also related to peak plasma levels. However, in healthy women with no preexistent renal compromise, there is little concern for kidney damage and daily dosing should be considered.

Like wound infection, women usually respond quickly to antibiotic treatment and become afebrile in 24 to 48 hours. If fever persists past the 48-hour mark, then two things should happen. One, you should reconsider your diagnosis. You should also evaluate for possible abscess formation. If you still believe the diagnosis is correct and you determine that there is no abscess, then switching to an even more broad-spectrum antibiotic is reasonable. If there is an abscess, then consider drainage, as no matter what antibiotic you choose, it is not going to get into the abscess to resolve it.

Like wound infection again, prevention is probably better than treatment. And like wound infection, preoperative antibiotics have dramatically altered the chances of developing this disease process. A retrospective observational study performed at the University of Florida from 2003 to 2014 monitored the rate of endometritis over three different preoperative antibiotic protocols. From 2003 to 2007, they gave all women one gram of cephazolin at cord clamp and recorded an endometritis rate of 16.4%. In 2008, they switched to preoperative antibiotics and over the next five years found a dramatic fall off in endometritis rates to 1.3%. Finally, in 2014 they added azithromycin to treat ureaplasma but found no difference than with cephazolin alone. This initial drop-off was huge, and it amazes me how such a small change can have such an effect. Other studies have also looked at adding azithromycin and they have been much more positive. They found a decrease in both endometritis and wound infection, and my institution is currently evaluating whether we’re going to add this to our protocol.

Another interesting approach to decreasing endometritis rates is to perform a vaginal prep with iodine before starting the caesarean delivery. This makes sense as it will decrease the bacterial load. Again, a Cochrane review has been published looking at this, and they found that there was a significant decrease in endometritis rates from 7.2% to 3.6% with the iodine prep. More importantly, they found a huge decrease for women with ruptured membranes who are undergoing caesarean delivery with a reduction from 15.4% all the way down to 1.4%. This is something that can easily be incorporated at many hospitals. And if those numbers hold up, this simple procedure would make huge difference in infection rates.

There are a couple of other surgical technique factors that can lower the risk for endometritis. First, in caesarean deliveries, there is now plenty of evidence to recommend allowing spontaneous delivery or to apply cord traction and uterine massage to deliver the placenta. When compared to manual removal, both of the former is associated with less endometritis and less blood loss. Also for caesarean deliveries, is the act of irrigating the pelvis before closing the fascia. In deliveries complicated by chorioamnionitis, irrigation lowers the risk of postpartum infection, while in non-infected labors there seems to be no benefit. Of note, irrigation is associated with an increase in intraoperative nausea, so it should really only be performed when there is proven benefit.

For vaginal deliveries, there is really only one modifiable factor, and that incurs in cases where a manual removal of placenta is needed. For these women, providers often give prophylactic antibiotics to prevent endometritis. There have been now several meta-analyses looking at this, and they have all determined that giving a single dose of antibiotics after delivery does not reduce the risk of developing endometritis and should not be given.

Alright, I just threw a ton of information out there, so let’s take a minute to summarize it all. Postpartum endometritis is more common after caesarean delivery. Many cases can be prevented by given pre-incisional antibiotic prophylaxis with a first-generation cephalosporin, and we should all consider adding azithromycin to cover ureaplasma. Women with a BMI over 35 or a weight over 100 kg. should get an increased dose to ensure proper tissue levels. We should all consider adding an iodine vaginal prep for women undergoing caesarean delivery, especially for those with ruptured membranes. We should avoid manual removal of the placenta during caesarean deliveries if possible. And we should irrigate the pelvis with saline in cases complicated by chorioamnionitis. And lastly, we do not need to give a dose of antibiotics after manual removal of the placenta. For treatment, we should give gentamycin, perhaps in daily dosing, and clindamycin. And we should reconsider our diagnosis if there is no improvement in 24 to 48 hours.

Overall, the differential diagnosis of postpartum fever is an interesting one. When evaluating women with a fever, we need to integrate our clinical findings with our knowledge of the most common culprits. The most likely diagnosis will change as we get further out from delivery. In the first few days, endometritis is the most common cause of fever, and then by days 4 to 7 it’s wound infection, UTI and mastitis, which rise quickly in incidence. As we get further from delivery, mastitis becomes the main cause of fever, but we can also never forget about VTE, lest we miss the rare but potentially fatal event. Of all the things that we talked about, I think the one that sticks with me the most is how such a simple intervention, like preoperative antibiotics, makes such a profound difference. Having policies and protocols to ensure that all women receive the appropriate antibiotic is one of the most important things that we can do to prevent postpartum infections.

I published a paper a few years ago in which we used our newly implemented electronic medical record to prompt practitioners to use the correct antibiotics for caesarean deliveries. And just by putting in some extra text into the order set that included the current recommendations, we were able to increase the number of women receiving the correct preoperative antibiotics from 85.7% to 92.6%. We are still trying to get that number to 100%, but it demonstrates how we can use our systems to increase patient safety. I apologize for tooting my own horn there, but I want to show what a small change can do and challenge everyone to think about ways they can help do the same at their hospitals.

Well, that was a little bit of a tour de force about postpartum fever, and I hope I didn’t bore anyone too much. I know we covered a lot of material, and I have a link to a lot of sources in the show notes for those that want to explore further. As always, you can find the show notes on the website, at [www.obgyn.fm](http://www.obgyn.fm) and as of today, you can also find the message board if you want to strike up a conversation or ask a question. Also, please remember to email me at feedback@obgyn.fm if you want to be a part of that Slack community. I set this up for all of you, and I hope that you will take advantage of it to interact with people who share your interest from all over the world.

I think the next episode is going to be a guest speaker, and I’ll be back the episode after that to talk about group B Strep in pregnancy. But until then, thank you all so much for listening.