**Episode 1: Opioids and Pregnancy**

By Dr. Joe Chappelle

Hello everyone, and welcome to the first episode of the OB/GYN Podcast, a podcast about current and interesting topics in obstetrics and gynecology. As this is the first one of these, let me take a minute and tell you a little bit about myself and what I’m trying to accomplish with the show. My name is Joe Chappelle. I'm a board-certified OB/GYN who lives and works in Long Island, New York. I’ve worked for a university hospital in both clinical and administrative roles and I currently work in private practice. I'm very interested in evidence-based medicine. I am active in clinical research and I am on the editorial board for two OB/GYN journal.

Recently, I've been listening to a lot of podcasts across a variety of topics, and I have tried unsuccessfully to find interesting and accessible OB/GYN podcasts. So, after a few months of fruitless searching, I decided, hey, why not? I’ll make my own. Now, I should stop at this moment and mention doctors Fogelson and Brown who do the academic OB/GYN Podcast. If you’re interested in current topics in OB/GYN, you should definitely check them out, they do a great job.

Now, what I want to do with this show is delve deep into a single topic and give lots of background to make it accessible to everyone. I hope that other physicians will still learn interesting things that they can relate to their practice, and I can certainly tell you that preparing for this podcast I've learned a few things that I'm going to apply to mine.

I hope to put up one topic-based podcast every month, and then follow it up, one to two weeks later with a feedback, discussion and probably talk about some journal articles that relate.

Without further ado, let’s get started with the OB/GYN Podcast Episode 1: Opioids in Pregnancy.

Let's start with a story. In February 2015, 30 cases of HIV were reported in the small town of Austin, Indiana. Population, 4,000. By mid-March of that year, it had risen to 55. And by early 2016, the number had hit 190. Austin is a rural town 80 miles south of Indianapolis and like many small towns, it has fallen on tough times. 20% of the residents live below the poverty line, and the open secret is that drug use is rampant. The local hospital saw a lot of the usual side-effects of drug use: withdrawal, overdose, abscesses from infected injection sites, hepatitis and endocarditis, which is a heart infection from circulating bacteria.

The local officials knew it was bad. With the lack of resources, there was very little they could do, except treat them when they came to the hospital. Unfortunately, one of the side-effects of injecting opioids, especially if you share needles, is HIV and hepatitis C infections. The HIV epidemic in Austin brought opioid use into the light. It’s a problem that occurs in all areas of the U.S. and across all socioeconomic classes. And most of us ignore it unless it directly affects us. Only something like Austin gets into the news.

So, what are the numbers? How big a problem is it? Well, worldwide, over 33 million people used opioids illegally last year. 2.6 million of those were in the U.S. I don’t know about you, but when I think of illicit opioid use, my first thought has always been heroine. But interestingly, only 20% of the people who abuse opioids in the U.S. use heroine. The rest, over 2 million, abuse prescription painkillers.

On that note, the number of prescriptions for narcotics has risen over threefold in the last 25 years. From 76 million in 1991 to 259 million in 2015. And what I considered to perhaps be a sad statistic, the U.S., which has just over 5% of the world’s population, consumes 80% of all the world’s narcotics.

The effects of opioids abuse are many and varied. It is estimated that the cost to the U.S. was 55.7 billion dollars in 2007. This cost was divided amongst workplace productivity losses, healthcare costs and criminal justice costs. Then, there are of course the hard to measure effects, on the family and children, some of which may last a generation or more. And lastly there are the overdoses. In 2014, over 28,000 people died from overdose related events. And although men continue to make up a higher percentage of these deaths, the number of women suffering fatal overdoses is rising at twice the rate of men.

This highlights to me that women have always been the silent users, addicts, and victims of opioids. Not a lot of research was done over the years on opium or opioids until the late 1800s. During his research for an 1871 book entitled “Opium and the Opioid Appetite”, Dr. Alonzo Calkins, found that two thirds of all New York City prostitutes used opium on a regular basis. And it wasn’t just prostitutes. In 1880, Dr. Charles Earle found that 72% of all opium users in Chicago were women, and that the women came from all walks of life. About their use, he wrote: “Women often use opium for years without imparting their secret to even their nearest friends.”

So, how did all these women get their hands on opium? Sadly, it was from their doctors. Opium was used by doctors to treat a variety of female ailments. In his 1876 review on the use of opium in Michigan, Dr. Orville Marshall (?) wrote: “The most frequent cause of the opium habit in females is the taking opiates to relieve painful menstruation and disease of the female organs.” And then, in 1896, wrote that he found women who have been prescribed opium for reasons such as falling of the womb, female weakness, vaginitis, depressed menstruation and dysmenorrhea.

Some of this was that there wasn’t a lot of good medication to prescribe for many of these women. But also, there was a gender stereotype that was being reinforced. For example, going back to Dr. Earle’s work, he wrote: “This is undoubtably due to the fact that women more often than men are afflicted with disease of the nervous character, in which narcotic remedies are used sometimes for a long period.” All of this meant that a lot of women were prescribed opium and for long periods of time. In fact, in 1911, it was found that two thirds of all opium users were women, and that most of them started out by using opium prescribed by their physicians.

Before I get into opioid addiction and its medical consequences, let's take a step back and talk about what an opioid actually is. Opioids are molecules that are opium-like. Simple enough. They can be derivatives of opium or they can be synthetic, but it all started with opium.

Opium has been with us for a long time. In fact, the oldest opium seeds have been found in human settlements going back over 5,000 years. Opium has been used for a variety of issues throughout human history and its use has been well documented in both eastern and western civilization. Opium usually takes about 9 to 12 weeks to grow, although some varieties now currently grown in Afghanistan, take only 55 days to mature. After the plant ripens, the opium pod is cut, and the milk is allowed to leak out and collected. The opium milk is often converted to morphine base, right there in labs near the field. They do this because morphine base is one tenth the weight of the raw opium and makes it easier to transport.

Opium itself contains three different opioids: morphine, codeine and thebaine. The oldest opium plants contained about 12% of these molecules by weight, while modern opium plants that are currently used in cultivation are over 92%. A hundred acres of poppy plants is required to make 13 kg. of opium, which converts into 1.3 kg. of morphine base. This is then converted to heroine to produce about 1 kg. Now, although I find this topic interesting, I do want to remind us that, at least in the U.S., 80% of the opioid users are using prescription painkillers, not heroine.

Alright. So, that’s how heroine and opioids are made. But what do they do to the human body? Well, like most things, it’s complicated. There are at least five opioid receptors in the human body and activating them has different effects.

The first is delta receptors. They’re found in the brain and peripheral sensory neurons, and they’re responsible for some of the pain control effects, but also have an antidepressant and proconvulsant effects.

Kappa receptors are similar to the delta, but they're also found in the spinal column. These are responsible for the hallucinogenic, sedative and euphoric values of the opioids.

Next up is the mu receptor. This is the big one. They're found in the same areas as the kappa, but also in the GI tract. There are three subtypes: mu-1, mu-2 and mu-3. Mu-1 gives pain relief and is implicated in dependence. Mu-2 is the one of the most important ones, as it is the receptor responsible for respiratory depression. This is the major cause of all overdose related deaths. Mu-3 is less important, as its only function is to mediate dilatation of veins. The next is nociception, which gives us anxiety and appetite suppression. And lastly there is zeta, which interferes with tissue growth in many areas of the body.

Now, let’s talk about potency. When we use opioids in medicine, we often talk about morphine equivalents. For example, codeine is one tenth as potent as morphine. This means that if we wanted to give someone a dose of codeine that was equal to one milligram of morphine, we would need to give 10 milligrams of codeine. Some other commonly prescribed opioids are oxycodone, which is 1.5 times as strong as morphine; hydromorphone or Dilaudid, which is five times as strong; fentanyl, which is mostly used in anesthesia and is currently in the news due to the Prince overdose, is 100 times as potent as morphine; and the strongest human-grade opioid is sufentanil, which is 1,000 times as strong as morphine. To say that another way, 0.001 milligrams or 1 microgram of sufentanil is the same as 1 milligram of morphine.

On the street, heroine is usually cut with a variety of products to help stretch the supply. Sometimes they use oxycodone, or they use Dilaudid or even fentanyl. When they use fentanyl, you can imagine, since it’s so strong, that a little bit of it can go a long way. This often leads to overdoses.

There was a story recently of a rash of overdoses in Ohio that was related to heroine that was cut with carfentanil, which is a synthetic opioid used in elephants. It’s 10,000 times stronger than morphine. Speaking of heroine, how strong is heroine? Well, in its pure form it’s about 4 to 5 times as potent as morphine, but like I said, it’s rarely sold that way.

The last thing I want to mention about opioids is their half-life. Half-life is how long it takes for half of the drug to be metabolised by the body. The half-life of almost all opioids is three to six hours, which is part of the reason they can be so addictive. The effect wears off quickly, and you need another hit to feel good again. There are two long-lasting opioids, and not surprisingly, they’re the two that are used in treating people with addiction. Those are methadone, which is about five times as potent and buprenorphine, or Subutex, which is 40 times as strong.

I did mention addiction earlier, and dependence. So maybe it’s time to define these things. There are three things that happen with chronic drug use. The first thing that happens when you take a medication chronically is you develop a tolerance to it. This means that you will need more of the medicine to achieve the same effect. For opioids, unfortunately, this occurs quickly for the pain-relieving effects and slower for the mood, itching and respiratory effects. Which means, if you’re a chronic opioid user, you have to take more and more and more to feel the same high, but unfortunately, you’re building up on the respiratory effects, and this can lead to overdose as well.

Next is dependence. This is a physiologic adaptation to prolonged exposure. The primary manifestation of this is withdrawal. Withdrawal symptoms from opioids include dysphoria, irritability, sweating, nausea, vomiting, runny nose, terror and muscle pains. Again, this is a physiologic certainty when taking narcotics for a long period of time and is not necessarily addiction.

Lastly, we have addiction. Addiction is a chronic brain disease that is characterized by compulsive drug-seeking and use despite harmful consequences. So, importantly, as you can see, although tolerance and dependence are necessary for addiction, being dependent or tolerant does not necessarily mean that you are addicted.

Alright. We’ve come a long way. Maybe we should start talking about opioids’ effective in pregnancy. This may probably come as no surprise, but I like to get started with some stats. 14.4% of women are prescribed narcotics at some point during their pregnancy, and in a study by Assadi *et al*. published in 2008, 1% of pregnant women reported non-medical use of opioids during their pregnancy and 0.1% of pregnant women are estimated to use heroine at some point during their pregnancy. An urban hospital that recently implemented universal drug screening found that 2.6% of women screened positive for opioid use and over 5% for any drugs.

Chronic opioid use has many effects on the fetus. Several case-control studies have found that an association between early-trimester opioid use and congenital heart disease exists. Chronic use is also associated with poor fetal growth, stillbirth, and preterm labor. Thankfully, these are all bad things, but they occur relatively infrequently, even in women who use opioids regularly or even large doses. The most common outcome in these pregnancies is withdrawal of the baby after it is born. This is called neonatal abstinence syndrome, or NAS. Every year, approximately 0.6% or about 24,000 babies suffer from neonatal abstinence. This number has tripled since 2012.

NAS babies suffer from a variety of symptoms, the largest one being uncoordinated sucking reflexes, which unfortunately makes it difficult for them to feed, extreme irritability and a high-pitched piercing cry, which once you hear it, you can’t forget. The symptoms usually start within 48 to 72 hours after birth, and the symptoms can last one to two weeks. Taking care of these babies is expensive. In 2012, it was estimated to cost 1.5 billion dollars to care for these babies. And like I said, the number of these babies has tripled since then, which means that, every year, we are spending over 4 billion dollars treating these babies.

There is some good news. It seems that, at least in the long-term, there may be no lasting damage. There isn’t very good data here, but there’s one paper, from Kaltenbach that showed no long term effects up to age 5 when compared to healthy control children.

The last piece here, in relation to pregnancy, is the association between drug use and HIV and hepatitis C infection. As I mentioned at the beginning of this episode, HIV and Hep C commonly follow in areas where narcotics are injected. HIV and hepatitis C are serious concerns in pregnancy, with a whole host of bad outcomes, and importantly, including transmission to the fetus.

So, I think we’ve established that chronic opioid use and abuse in pregnancy is bad. Now, what do we do about it? The treatment options all revolve around decreasing the withdrawal symptoms and gradually decreasing the dose. This treats the dependence that we talked about earlier, but I should note that treating dependence and treating addiction are not always the same thing. One is a physiologic process and the other is psychological.

The first drug that has been used to treat addiction is methadone. Methadone was created in pre-World War II Germany as an analgesic. In 1949 it was first used to treat heroine addiction in the U.S. The early studies weaned people down in one to two weeks, and not surprisingly, the relapse rate was over 90%. In New York City, in the late sixties and into the early seventies, there was a heroine epidemic, and trials with shorter acting opioids had failed.

And so, in 1964, Rockefeller University opened a trial to see if methadone could be used not as a way to wean people off but as a maintenance to get people back on their feet. They found that within several days to weeks, the sedative properties of methadone wore off, and that patients were able to find employment. They also found that methadone doses in the 80 to 120 milligram range blocks the effect of injected heroine. This made it very useful to help these people stay clean. This research led to the first full-time methadone clinic in 1965 at the Beth Israel medical center. Now, New York was the pioneer in methadone clinics, and continues to have the majority of methadone clinics in the country. This model though, was exported to the rest of the country and is currently in use nation-wide.

Methadone clinics must be licensed either by the state or the federal government, and patients must come daily for evaluation and for their methadone doses. Most states and the federal government also require that these clinics provide social services and the NIH, or the National Institute of Health, found that: “Methadone maintenance, coupled with relevant social, medical and psychologic services, has the highest probability of being the most effective of all treatments for opioid addiction.”

Methadone treatment had a profound effect on 1970s New York, where for each 1,000 admissions to a treatment program, there were almost 4,000 fewer thefts, 1,200 fewer arrests for drugs, 75 fewer cases of hepatitis, and 16 fewer deaths. These are remarkable numbers, and when you calculate the reduction in police costs alone, it probably paid for the treatments.

The effects of methadone in pregnancy are similar, with a couple of small caveats. Pregnant women’s levels are much more variable, and their dosing requirements usually increase throughout pregnancy. This is due to a few factors. First, pregnant women increase their plasma level by up to 50%, which means that the concentration of methadone in the blood will decrease. These effects level off by about 28 weeks of gestation. Next, the placenta and the fetus are also metabolizing the methadone, and this can lead to the regular dose wearing off within 24 hours. So, pregnant women on methadone need to be screened regularly for withdrawal symptoms to determine if a higher dose is needed. And, I should say, why do we worry so much about this? Well, adult withdrawal can be managed, while clinicians have no access to an unborn child, and if mom withdraws, baby can withdraw, which can lead to seizures and possibly stillbirth.

The second medication used in the treatment of opioid addiction is buprenorphine or Subutex. Buprenorphine is a synthetic analogue of thebaine, which is one of the three primary compounds in opium, along with codeine and morphine. It is a partial agonist at the mu and nociceptor receptors, and an antagonist of the kappa and delta receptors. The antagonist effects mean that this drug has very little constipation or, importantly, respiratory depression, which is often seen in other opioids. Lastly, it binds the other receptors tightly, which does not allow other opioids to bind. This means, like methadone, that if you inject heroine while you’re taking buprenorphine, you’ll have very little effect.

Unfortunately, one of the side effects of this is that if someone taking buprenorphine needs pain relief for surgery or other issues, they require a very high dose of usual fentanyl or sufentanil. Now buprenorphine, like other opioids, can give a higher high when it’s injected. And this has historically been one of the issues with buprenorphine treatment. To combat this, buprenorphine has been combined with naloxone, which is an opioid antagonist that blocks and can reverse the effects of all other opioids. The combination is given either sublingually or orally, because naloxone is not absorbed that way, and therefore it will not block the effects of buprenorphine. However, if the combination is injected, it completely blocks the effects of buprenorphine and will cause immediate withdrawal.

Buprenorphine treatment is regulated differently than methadone. It can be prescribed by any licensed practitioner who has completed an eight-hour course. At first, they only allowed a practico-inert to care for 10 patients, then that number was up to 100 and then finally, a few years ago, to 275. This has made buprenorphine treatment much more available. However, I should note, that unlike methadone, there are no mandated social services with buprenorphine treatment. The looser regulations around buprenorphine leads to greater accessibility, but like I said, without the same level of support in recovering from the non-medical aspects of addiction. That being said, when France initiated a primary care setting for buprenorphine, about a decade ago, it found a decline in heroine use among opium addicts from 75% to 25%, which is a great reduction and shows the power of accessibility to treatment for addiction.

Let’s bring it back to pregnancy for a minute. Both methadone and buprenorphine are acceptable methods of treatment in pregnant women. When using buprenorphine in pregnancy, it is used without naloxone for fear that a pregnant woman may inject it, which would lead to a fast and dangerous withdrawal, which as I said, can lead to stillbirth or other fetal effects.

There is very little evidence looking at the effects of buprenorphine or methadone on neonatal abstinence syndrome. However, there was one paper by Jones *et al*. that was published in the New England Journal of Medicine in 2010. They found that babies that were born to women using buprenorphine needed 89% less morphine, stayed in the hospital 45% shorter time and had an overall treatment time of 60% less than babies that were born to women using methadone. Perhaps buprenorphine may be superior to methadone in pregnant women, but more data needs to be collected.

Lastly, I would like to spend a short amount of time discussing screening in pregnancy. One of the difficult things with screening for opioid use is that there is no typical person who is an opioid addict. The disease is spread across all socioeconomic layers. Therefore, one of two approaches needs to be undertaken.

The first is universal screening. There were 3.9 million births in 2014, and at the cost of $100 per urine toxicology, it would mean that it would cost 390 million dollars to test every pregnant woman on admission to the hospital for delivery. This seems like a lot of money, but when you consider that the U.S. spent over 3 trillion dollars in healthcare last year, 390 million seems like a very reasonable price. The problem here is that it’s the individual hospitals that bear the cost, and not the system, which can make it difficult to implement.

However, universal screening does have the ability to detect all women who are chronic opioid users and/or abusers. This allows us to identify and treat babies at risk for neonatal abstinence syndrome. Under federal law, each woman must give consent to drug screening, and if they do not, then it is equivalent to performing an illegal search and seizure. In hospitals that use universal screening, if the woman does not consent, then they test the baby after birth. This can be done without consent, and it still gives providers a way to ensure the safety of the neonates.

One of the thorny issues that arises with this approach is who gets the information regarding the drug screen. In 1989, South Carolina implemented universal screening, There was no consent process, and there was mandatory reporting to the police. The goal was to help the children of these mothers, but the consequences were severe. Hundreds of women were arrested in their hospital beds immediately after giving birth. So, not surprisingly, some of these women sued, which lead to a 1993 Supreme Court decision that gives us the mandatory consent process that we have today.

This was almost 25 years ago, but it’s recently come full circle. Three states, Tennessee, Alabama and again South Caroline have made it a crime to use drugs illicitly during pregnancy, and women can be prosecuted if they or their baby screen positive. The American College of Obstetricians and Gynecologists or ACOG does not recommend this approach, because they believe that it destroys the trust between a doctor and a patient.

Cincinnati took a different, and in my personal opinion, a much wiser approach, when they started their own universal screening in their city hospitals. What they do is they ask each woman to consent to screening and inform them that the results will only be used in the treatment of themselves and their baby and will not be shared with anyone else. This has led to far greater acceptance by these women, which has led to much better care for their babies.

So universal screening, although probably superior, may not be feasible except in certain endemic areas, so we need other ways to screen. The American College of Obstetricians and Gynecologists recommends using one or more of three risk-scoring systems. The first is to ask a woman if her parents or her partner use drugs, if they have used drugs in the past or are they currently using drugs. Any yes to these questions should initiate a urine drug screen.

The next tool that they recommend is called CRAFFT. In it you ask the following questions: have you ever driven or ridden in a car while someone was high? Do you ever use drugs to relax? Do you ever use drugs while you were alone? Have you ever forgotten anything while you were using drugs? Does your family ever suggest you cut back? And, have you ever gotten into trouble while using drugs? Again, any yes should lead to further screening.

Lastly, they recommend that any risk factors or warning signs should prompt screening. These include late or inconsistent prenatal care, signs of sedation or intoxication, erratic behavior or symptoms of withdrawal at visits. They also suggest that you look for absences or track marks from injection, and that any new diagnosis of hepatitis B, C or HIV prompts further screening.

There are no studies that look at how many women you miss with this approach, versus universal screening. So, there is no right answer. The approach taken at each hospital or prenatal center must take into consideration the prevalence of opioid abuse in the area and the amount of resources available for drug screens. My only caution, and this is something I think I can’t stress enough: there is almost always more opioid abuse going on than we think there is, and there is not a single type of person who is an opioid user.

Opioid abuse and addiction permeate our society and have real and lasting effects on every facet of it. So far, I have tried to keep my own biases out of this, but I would like to, if you’ll allow me, editorialize for a second. As a society, we have two ways of dealing with drug abuse. We can criminalize it and do our best to put away people for their addictions, or we can treat it as the chronic medical condition that it is.

Our 20 plus year war on drugs has failed. We have the highest *per capita* rate of incarceration in the world and we have very little to show for it. Thankfully, these policies are starting to change. I think that as a society we have realized that we need a different approach. In general, end of care will always be better and cheaper than the alternative. In addiction, it means identifying and treating individuals to prevent the negative health and socioeconomic effects. It means more available treatment centers and social services. It means making buprenorphine more available. But it also means adding the social services that are so important in treating the non-medical problems that go along with it.

During pregnancy, it means screening and treatment. It means not condemning or criminalizing these women, because we know that this prevents them from getting the help that they need. It means identifying babies at risk for neonatal abstinence syndrome and knowing that their treatment shouldn’t end when they leave the hospital. If we don’t treat moms’ addiction, then all we’re doing is sending these babies home to begin another round in the negative feedback cycle that is addiction.

I hope that everyone who listened to this learned some new things about opioids, how they work and why we become dependent and addicted. And more importantly, I hope, how we treat it and what the consequences are to healthcare and society. More importantly. I hope that you all fully understand, if you didn’t before, what a massive and pervasive issue opioid use and drug use in general is, and that we need to spend our time and our money on prevention and treatment, and not on making more criminals.

Okay, well thank you. That’s all I have today. Thank you for listening and please look through the show notes for the references and links. If you have any feedback, questions or suggestions, please shoot me an email at feedback@obgyn.fm, that’s feedback@obgyn.fm. That’ll be in the show notes as well. I would love to hear from anyone who has stories to tell, if you think I got something wrong or if you think I missed something important. I’ll be back in a couple of weeks to discuss any feedback and to talk about some related journal articles. So, until then, thank you.