

Episode 57: Postpartum Mood Disorders – Part 1

Dr. Joe Chappelle: Hello everyone, and welcome back. I'm Joe Chappelle and you're listening to episode 57 of the OB/GYN Podcast. Today's episode is the kind that I love. One of our medical students here at Stony Brook sent me an email. Said he wanted to do an episode about postpartum depression, and in the space of a week, he researched it, wrote it, recorded it and today you're going to hear the first part of it. It's a great topic, and it deserves the treatment he gave it. He starts at the beginning of recorded time, it takes us all the way through today. In that, is the story of sexism, oppression and bad science. But it also the story of modern medicine and our expanding understanding about mental health.

This first episode is about diagnosis, and the second will be about treatment. With that, let me get out of the way and allow Gregory Kirschen to take it away. Here's Episode 57: Postpartum Mood Disorders – Part 1.

Gregory Kirschen: Hello everyone. My name is Greg Kirschen. I'm a fourth-year medical student at Stony Brook University. I first want to thank Dr. Chappelle for giving me the opportunity to come on the show and discuss a topic that I hope you will find to be interesting and important. I also want to thank Dr. Chappelle for helping with editing and putting this show together.

Today, I'm going to talk about mental illness in the peripartum setting, with an emphasis on postpartum depression. I decided to embark on this quest to find out how the concept of postpartum depression evolved from its inception to our current biopsychosocial understanding. I chose this topic because of my combined interest in obstetrics and psychiatry. I also think it is timely, since just a few months ago, the first drug to specifically treat postpartum depression was approved by the FDA, highlighting our improved understanding of this complex disorder and new strides in our ability to treat it.

Peripartum mental illness is a massive topic, and I'm certainly not going to be able to cover all of its details in this short podcast. Instead, what I'd like to do is tell you a story of some initial attempts to understand and medicalize psychiatric problems arising in the peripartum period, as well as various pathophysiological hypotheses that have circulated to try to explain these findings. I hope that by the end of the podcast, you will see how far we've come, but also how much more work is left to be done in this area.

As a disclaimer, I should mention that the views expressed on this podcast are my own, as is my interpretation of literature that I will discuss. I'm also not an expert on this topic, just an interested student. So, with that, let's get started.

Through our modern lens, in the era of the DSM-5 in 2019, we understand psychiatric illnesses as discreet definable entities with patterns of signs and symptoms that fulfill certain criteria. Interestingly, the term postpartum depression

does not appear in the DSM-5. Rather, the text describes depressive disorder with peripartum onset as five of the nine SIG E CAPS criteria, which I'll remind you of soon, lasting for at least two weeks, starting any time during pregnancy, or during the first twelve months after delivery. Criteria are the same as those for major depressive disorder: depressed mood or anhedonia plus the SIG E CAPS which are sleep changes, either increased or decreased, loss of interest in activities, feelings of guilt or worthlessness, lack of energy or fatigue, difficulty concentrating, changes in appetite, decreased or increased, psychomotor agitation or retardation and suicidality or preoccupation with death. Symptoms particular to the postpartum period can include feelings of inadequacy as a parent and ego dystonic thoughts of harming the infant, which are unlikely to be acted upon if psychosis is absent.

Why do we bother to go through this exercise of defining depressive disorder with peripartum onset? Well, we now know that this disorder is one, common, affecting between 13 and 20% of new mothers in the United States each year, and, two, in severe cases, mothers may harm themselves or their infants, making this an important diagnosis to recognize and intervene upon promptly.

Now that we understand a little about our modern concept of postpartum depression, let me ask, how did we arrive here? Well, the existence of a relationship between cognitive and mood disturbances with the childbirth experience has been documented since the time of Hippocrates, around 400 B.C.E. The supposed tie between the uterus and mental afflictions, out of which the term hysteria arose, has been written about since ancient Greece. This reflected the male physician dominated view that ailments affecting women, for which a physical cause could not be found, should be blamed on a wandering uterus.

This belief has been carried forward into the not so distant past, with the American Psychiatric Association finally dropping the term hysterical and replacing it with more modern and accurate descriptors, such as somatization or conversion disorders in the 1980s. Thus, even the medical use of the word hysteria has just recently been revised, and it still unfortunately lingers in our vernacular. How, then, did the physicians who were the first to carefully document peripartum mental illness understand these disorders? Did they simply blame it on the uterus?

The mid-1800s marked the beginning of systematic efforts to define and medicalize mental afflictions related to pregnancy and the postpartum period. Case reports and case series, which were basically considered the gold standard in terms of medical evidence in the 19th century began cropping up describing this phenomenon in great detail and attempting to explain it. What I found most surprising is that physicians in this time period lumped together many different flavors of mental illness arising in pregnancy or soon thereafter and used the umbrella term puerperal insanity.

Indeed, as Dr. Loudon of the University of Oxford, reflected on 19th century psychiatry: “Puerperal insanity was one of the few clearly recognized entities in 19th century psychiatry.” As we’ll see, the word insanity, which today is no longer recognized by the DSM, although it still remains a legal term, was probably used more in the literal sense of unhealthy, rather than its modern-day connotation of psychotic. I say this because mid-19th century physicians tended to cluster psychotic disorders together with mood and anxiety disorders, which modern psychiatry no longer does.

Illustrating this point, Dr. James Reid gives us his understanding of the disorder as he saw it in his patients in his 1848 article: “The term, puerperal insanity, is not only understood to imply aberration of the mind, or derangement of the cerebral functions in the puerperal state itself, but to include those attacks which occur sometimes during the period of gestation, as well as those which we more frequently meet with some months after parturition, whilst the patient is suckling her infant. From the period of conception, during the whole term of gestation, and up to the termination of suckling, there is an amount of nervous irritability and excitement in the system, which strongly predisposes to any cerebral affection.”

Dr. Reid characterized the symptoms of puerperal insanity as including restlessness, irritability, watchfulness, inability to sleep, uncontrollable laughter at trifles or unimportant things, paroxysms of maniacal violence subsiding into a taciturn state of melancholy. He noted that it could progress to incessant talking, total negligence of and strong aversion to the patient’s child and husband, explosions of anger with “language use which astonishes her friends.”

To me, it sounds like Reid was generalizing mania, depression and psychosis into the bucket of “insanity,” though we can’t necessarily fault him for doing so. After all, the dopamine hypothesis of schizophrenia would not arise until 1956 with the discovery of reserpine. And the monoamine hypothesis of mood disorders wouldn’t be popularized until the 1960s. At the time of Reid’s writing, the focus was more on characterization of symptomatology and speculation as to possible causes.

As alluded to earlier, the timing of symptom onset and peak severity was noted to be around the time of delivery, with mental illness often thought to lie largely dormant during pregnancy. Dr. Forbes Winslow noted in the mid-1850s what he referred to as the “incubation of insanity” during pregnancy. He observed that anxiety, distrust, suspicion, melancholy and fear of the future tended to arise in much smaller numbers during pregnancy as compared to after delivery.

In any case, Reid and his contemporaries did more than just describe the condition they saw in their postpartum patients. They also postulated what might be causing this malady. As you might have guessed, the uterus was a common culprit. In his case series, Reid describes “any serious disturbance in the uterine functions speedily affects the brain; and to those conversant with the peculiar diseases of

females, numerous instances of corresponding cerebral complaints following such disturbance, will at once be in their remembrance. The uterus and ovaries seem to exert the strongest sympathetic action upon this distant organ; and should even the usual monthly functions be irregular, impeded, or altogether checked for a time, the cerebral tissue appear to share immediately in the disorder, as evidenced by headache, giddiness, depression of spirits, or sometimes by great excitability requiring judicious medical treatment.”

Clearly, Reid was still in the same camp as Hippocrates and many others. In fact, in an address at the annual meeting of the East Yorks and North Lincoln Branch of Asylums in 1886, Dr. MacLeod, superintendent of East Riding Asylum, described an update in terms of the definition and understanding of puerperal insanity, which still included mention of uterine tenderness and/or abnormal lochial discharge as part of the syndrome.

As an aside, I’m not going to delve deeply into the evolution of treatments for puerperal insanity or postpartum depression throughout the ages but suffice it to say that bloodletting was the standard therapy at the time of Reid’s publication. Although, throughout the latter half of the 19th century, physicians began to move away from bloodletting and instead recommend rest, nutrition, purging or sedation for puerperal insanity with commitment to asylums reserved for those who demonstrated severe signs, such as suicidality or homicidality.

The prognosis was generally considered favorable for those who did not demonstrate psychosis or suicidality or homicidality, with general consensus in the medical community being that puerperal insanity should last no longer than six months with full recovery to be expected. With recovery of course, being defined as willingness to perform household chores, which was typical of this misogynistic culture surrounding the psychiatry of this era.

Some physicians believed deeply in the need for treatment of mentally ill women to get at the root cause, which was of course, the pelvic organs. In a literature review published in JAMA in 1907 entitled *To what extent can the gynecologist prevent and cure insanity in women?* Dr. Henry suggested that “all insane or epileptic women should have their pelvic organs most thoroughly examined at once and all disease conditions should be relived as quickly as possible by whatever means are necessary.” He goes on to say, “not all insane women who have pelvic disease as a factor can be cured by local treatment or operations, but in the early stages, such treatment or operations in many cases would have been curative or preventative.”

While stopping just short of recommending routine hysterectomies for all mentally ill women, Dr. Henry’s conclusions certainly speak to his belief of the intimate relationship between mental illness and imbalances in pelvic organs. Still, not all of the understanding of postpartum depression was so misguided, and some

important observations were made in the midst of this discussion. It's worth pointing out for example, that the risk of suicide for the patients who had puerperal insanity was acknowledged as early as the mid-19th century. In Bethlehem Hospital in London, it was noted that out of 111 cases of puerperal insanity, 32 women exhibiting melancholia, exhibited a "suicidal tendency." Whether that meant passive ideation, intention or action is uncertain, though.

Furthermore, the uterus was not the only hypothesized root cause of puerperal insanity, and toward the end of the 19th century, other hypotheses were gaining momentum. In 1887, Dr. Clark asked the question of whether puerperal insanity came purely from the central nervous system or rather from the periphery, for example, from some toxin in the blood. He realized that women who were medically ill in pregnancy and labor as in the case of puerperal pyrexia, often suffered emotionally as well.

Clark wasn't the first to put forth this idea, however. Through James Simpson, known best for his work in obstetric anesthesia, discovering that chloroform had anesthetic effects and implementing its use in obstetric practice, had suggested in the 1850s and 60s that a peripheral cause unrelated to the uterus was to blame for puerperal insanity. He noted that in four of his patients with puerperal insanity, all had concomitant albuminuria and thus the albuminuria hypothesis was born. Other physicians such as Dr. Arthur Dunkin endorsed this hypothesis. For instance, Dunkin published an article in 1863 entitled *The Pathological Relationship between Albuminuria and Puerperal Mania*.

The albuminuria hypothesis was soon questioned by critics, however. Disputing Simpson and Dunkin's claims, Dr. John Tuke published a case series in 1867 in which he essentially made a correlation does not equal causation argument. Comparing the albuminuria of insanity to that of Bright's disease, which was a generalized term for nephritis at the time, and implying that albuminuria was at best a marker of illness. Based on his own patients, Tuke hypothesized that an inflammatory state of some internal organ was at the core of the mental affection, which he intuited based on pulse measurements.

Although simplistic in his rationale, Tuke's hypothesis was remarkably ahead of its time. The contemporary understanding of postpartum depression does in fact invoke inflammation as playing a causative role. For instance, Miller and colleagues in 2002 showed that stress and adverse life events, such as chronic psychological stress, can increase pro-inflammatory cytokines such as interleukin-6. Subsequent work in pregnant women and pregnant experimental rodents by Cassidy-Bushrow et al. and O'Mahony et al., has shown that these women and animals exhibiting depressive or depressive-like symptoms had elevation of the pro-inflammatory biomarker IL-1 beta.

Nevertheless, the inflammatory hypothesis of depression, including postpartum depression would lay dormant for much of the ensuing century. First, the albuminuria hypothesis had to be laid to rest. And it was. In 1934 Bamford became another critic to rebuke this hypothesis, recounting based on his own experience that “insanity of pregnancy” was seldom if ever accompanied by albuminuria, and stating that in women who went on to develop puerperal insanity “the whole period of gestation has been remarkably free from any disconcerting physical symptoms. It may be that in certain predisposed individuals the toxic elements of pregnancy, instead of manifesting themselves in the usual manner on the liver or kidneys, have a special predilection for the cerebral cortex.”

Here, we see that the idea of a predisposition in susceptible individuals was raised, a concept that we invoke often in the modern medical era to explain the development of disease in certain patients based on the interaction between genetics and environment. That heredity might play a role in the pathogenesis of puerperal insanity had been postulated earlier by MacLeod in 1886.

Indeed, MacLeod was a contemporary of Charles Darwin and Gregor Mendel, well-known early thinkers in inheritance and genetics. MacLeod claimed: “among the causes which predispose a parturient woman to an attack of insanity, heredity plays an important role. It may be taken as an established rule that insanity of a parent or ancestor tends to produce in an individual a strong susceptibility to insanity, or allied nervous disorder – a pathological sensitiveness – a proneness to break down under exciting causes, which would not affect a person with a healthier pedigree.”

While today we might see this idea as a revelation and a step in the right direction, at the time it was actually twisted by some to shift blame onto mothers who gave birth to mothers with deformities or disabilities. Keep in mind the genetic basis of inheritance was still over half a century away with discovery of DNA in the early 1950s.

One theory that arose from the concept of heritability in the context of puerperal mental illness was known as maternal impressions. The basic idea, articulated by Ballantyne in 1892, was that emotions experienced by pregnant women could cause birth defects in the fetus. The question of whether maternal mental illness could produce birth defects raged from the 1870s well into the 20th century. For instance, Fisher published an article in the *American Journal of Insanity* in 1870 entitled *Does Maternal Mental Influence Have any Constructive or Destructive Power in the Production of Malformations or Monstrosities at any Stage of Embryonic Development?*

Parenthetically, it's amazing that he was able to get away with the term monstrosities in the title of his paper. Likewise, in 1911, as a cautionary tale, Pohlman described an anecdote in which a pregnant woman who saw a child with

a “double thumb” became so preoccupied with the thought of this malformation that it was actually reproduced in her own child. It seems that the onus was on pregnant women to control their emotions during gestation so as not to harm their developing fetuses.

Fortunately, the theory of maternal impressions was largely abandoned with the rise of modern genetic theory in the 20th century. With it came the rise of teratology, the scientific study of congenital abnormalities. While maternal stress does not lead to malformations as originally believed, the idea of maternal impressions may still have laid the groundwork for our modern understanding of the interplay between the maternal environment and fetal and infant development.

For instance, it's now understood that maternal stress can affect prenatal epigenetic programming via methylation of genes for key neurotrophic factors, potentially affecting subsequent brain development. Beyond pregnancy, mothers with postpartum depression are also less likely to breastfeed or produce breast milk, less likely to bring their infants to routine well-child visits, less likely to immunize their infants and less likely to use infant safety precautions, including placing infants on their backs to sleep.

Likely as a consequence of some of these biological as well as social factors, children of mothers with postpartum depression are at increased risk of respiratory or gastrointestinal infections and poor growth. A meta-analysis of the effects of postpartum depression on child development conducted by Beck in 1998 found a small but significant negative effect of postpartum depression on children's cognitive and emotional development. Moreover, recent work by Tuovinen and colleagues has shown that children of mothers with chronic and severe postpartum depression are more likely to exhibit delayed developmental milestones compared to their peers. Perhaps these factors in concert with genetics contribute to the recurrence of postpartum depression across generations that MacLeod and others observed at the turn of the 19th century.

Finally, let's ask how it is that we moved away from the term puerperal insanity and parsed this large class into more discreet entities such as postpartum blues, postpartum depression, postpartum mania and postpartum psychosis. The fact that puerperal insanity fell out of favor can be seen as part of a broader movement within the field of psychiatry to classify disorders of the mind in terms of common features, and eventually, common underlying neurobiology.

A landmark paper published by Foundeur et al. in JAMA in 1957 entitled *Postpartum Mental Illness: A Controlled Study* addressed this issue head on. In the article, they state: “because of diverging criteria and definitions, few studies of mental illness associated with pregnancy and childbirth have been comparable. Major sources of confusion have been the lack of a proper definition of postpartum

mental illness, whether there's a specific psychosis occurring in the postpartum state and to what extent the common factor, childbearing, influences the course."

In their Table 1, they neatly lay out four categories of postpartum psychiatric illnesses. One, psychoneurosis, which includes anxiety, reactive depression and mixed states. Two, dementia praecox which is subdivided into catatonic, paranoid, simple, hebephrenic, which basically is what we'd call disorganized schizophrenia and other subtypes. Three, manic-depressive illness, which is subdivided into depressive, manic, mixed, circular and perplexed subtypes. And four, other, which includes various personality disorders, substance use disorders and miscellaneous psychoses.

Here, we see the first attempts at systematically parsing peripartum psychiatric illness into discreet entities that could be then studied scientifically and managed differently based on the underlying ideology, whether through psychotherapy, medication, electroconvulsive therapy or a combination of these things. We can start to recognize these 1957 definitions as the rough sketches of the diagnoses we are more familiar with today.

It's worth mentioning, however, that even in 2019, we still do not have a complete understanding of the genetic, neurochemical, psychological and social factors that contribute in various ways to the development of peripartum mental illness. But at least now we have better tools at our disposal, both diagnostically and therapeutically to help improve the lives of women suffering these afflictions.

So, with that, I hope I've been able to give you all a glimpse into how our modern understanding of postpartum depression developed. It was clearly not recognized as a distinct entity until relatively recently. And even today, there are still likely subcategories based on symptomatology and genetic factors that we have yet to work out.

This problem is so pervasive and potentially devastating, that I hope it'll continue to receive the media attention and research funding that it deserves. I'm also excited to follow the development of novel therapeutics, such as the recently approved brexanolone and IV formulation of allopregnanolone that has been shown to reduce depression scores among women with severe postpartum depression, likely through allosteric modulation of GABA-A receptors in the brain. This is just one example of how our improved understanding of psychiatric illness can aid in rational drug design. I look forward to seeing other such developments in the future and hopefully being able to contribute to their discovery and use in clinical practice myself.

And with that, I'd like to thank you all for your time in listening to this podcast, and I hope you've enjoyed listening to it as much as I have enjoyed putting it together. Again, a big thank you to Dr. Chappelle and the OB/GYN Podcast for making this happen.