**Episode 58: Postpartum Mood Disorders – Part 2**

Dr. Joe Chappelle: Hello everyone, and welcome back. I’m Joe Chappelle and you’re listening to episode 58 of the OB/GYN Podcast. Today, Greg Kirschen is back to discuss the treatment of postpartum depression. So, without further ado, let’s get started with Episode 58: Postpartum Mood Disorders – Part 2.

Gregory Kirschen: Hello again, everyone. My name’s Greg Kirschen. I’m a fourth-year medical student at Stony Brook University in New York. I want to thank Dr. Chappelle for inviting back for a follow-up episode on the theme of puerperal insanity.

In the previous episode, I discussed changes in the scientific understanding of the diagnosis and pathophysiology of peripartum mental illness over time, with a focus on postpartum depression. As I mentioned, it was hard for me to specifically track postpartum depression over time per se, because it was not recognized as a unique entity, and so I did my best to cobble together the first well-documented semblances of our current conception of the disorder.

In this episode, I want to continue with the theme of puerperal insanity, and this time focus on different treatments that have been tried throughout the ages, with varying degrees of success. Once again, the views expressed on this episode are my own, as is my interpretation of the literature. With that, let’s begin with an overview of the treatment of mental illness in women in general.

I think it’s appropriate to start, as we did last time, in the 1800s, when it was still freely accepted that female mental illness was an enigma, though systematic efforts were underway to figure out the root cause of these problems and develop effective treatment strategies. In his 1830 work, *A Treatise on Hysteria*, George Tate, a member of the Royal College of Surgeons of London, acknowledged the medical community’s limited understanding of the condition of hysteria at the time of his writing, although he did associate hysteria with somatic complaints. He also discusses the difficulty clinicians face in trying to manage this disorder, which may partially relate to the bias physicians at the time had that female-specific illnesses were inherently fickler to treat, due to the sensitivity and weakness of women.

He writes, “and here, I must take the liberty of saying, although pain may be considered the natural companion of disease, and that although hysteria sometimes, under the best treatment, tedious and difficult to remove, I believe its remote effects upon the delicate females who are most liable to its invasion, may, with more justice be imputed to medical mismanagement than to the unassisted agency of the disorder itself. I do believe that this class of disorders is not by any means generally understood, either by young or old practitioners. And I believe also that many of its unhappy subjects, who have had recourse to medical advice in the hope of immediate relief, have in consequence of carelessness, ignorance or rashness, been abandoned to all the horrors of a protracted sickness and of a shattered constitution.”

Basically, Tate is saying that those who endeavor to treat hysteria, usually end up doing more harm than good. Likely, because of an incomplete understanding about its root cause. But that did not stop many physicians from experimenting with various potential remedies for “hysteria of the first degree,” which involved alternating fits of laughter and weeping, starting in screaming, lying still as death and struggling with gigantic strength, along with irregular menstrual discharge.

One popular hypothesis was that the stomach, liver and/or bowels were malfunctioning. Accordingly, the treatment was to cleanse the bowels with a “brisk cathartic of calomel, which is mercury chloride, and jalop, another cathartic that comes from a tuberous root, followed by castor oil. Tate noted that “in a great majority of cases a brisk action upon the bowels will be attended with mediate relief of the fits or paroxysms.” Another recommendation was a bland diet consistent of aloe, iron and aromatic oil, which was though to regulate uterine secretions.

Parenthetically, since I’m talking about hysteria of the first degree, there is also a so-called hysteria of the second degree, of which menstruation was thought the be the principal underlying etiology. This included symptoms of pain in the loins and lumbar spine, heart palpitations, breast pain, headache, intolerance of light and a globus sensation. For this affliction, which for our modern-day lens sounds like it might have been a mixture of premenstrual dysphoric disorder and migraine headache, known to be associated with the menstrual cycle. Treatment consisted of leeching, though this was soon noted to be relatively ineffective. Heat therapy became one substitute treatment modality, and interestingly, we still see heat therapy used today for the treatment of menstrual cramps in the form of heating pads, with a slew of patented models that are commercially available.

But, getting back to the main discussion, it’s unclear exactly how the link between the gastrointestinal system and uterus was established. From my search, it seems to have started with the perceived association between hysteria and bouts of constipation. Dr. Smith published his observations of hysteria in 1830 in the Boston Medical and Surgical Journal, describing his understanding of the connection between the uterus and GI system, invoking the spinal cord. As he puts it, “the constipation so often observed in hysteria, and by some regarded as an excitant of those diseases, I think may be looked on more in light of an effect than a cause, depending on spinal irritation.”

Similarly, Drs. Griffen and Griffen published a case series in 1829 in the London Medical and Physical Journal, in which they posited that hysterical and other nervous disorders may be traced to dysfunctions of the spinal cord. Around the same time, Tate made the bold claim that “hysteria appears to be caused immediately by the spinal affection, which is, in its turn, the result of some hidden association or sympathy between the contents of the upper portion of the vertebral canal and due to the performance of menstruation.”

Dr. John Rein would later pick up this tread in the 1840s. As I discussed in the previous episode, Reid felt that the uterus was intimately connected to the nervous system, and in the pregnant state, would cause nervous irritability and excitement, leading to insanity. It’s worth mentioning that, anatomically speaking, the physicians at the time were not wrong in their suspicion that the nervous system provides a tie between the uterus and the bowels in one real sense. Indeed, the spinal cord does innervate the uterus via parasympathetic fibers of the pelvic splanchnic nerves S2 through S4, the same nerves that innervate the descending colon and rectum.

The gap in logic seems to lie in the belief that the connection between the uterus and the spinal cord led to issues with the bowels, and thus, that irrigation of the bowels should relieve hysteria or insanity. And it seems by all accounts at the time, that it was an effective treatment at relieving hysteria. Maybe because the patients were so dehydrated and their electrolytes so deranged from all the diarrhea that the hysteria was replaced by lethargy and hemodynamic collapse, but that’s just my speculation.

Anyway, now that we understand a little bit more about how hysteria outside of pregnancy was handled medically, how did practitioners attempt to address mental illness when the uterus was gravid? Well, it should be unsurprising by now that various bowel regimens were trialed. In his 1886 medical pieces on puerperal insanity, Dr. Clark lays out the treatment for this set of mental illnesses, carefully describing nutrition and laxative plans for his contemporaries who would be treating these women.

In his section on digestive, hepatic and intestinal causes of puerperal insanity, he recommends, based on the standard practices of the time, a diet consisting of custards, eggs, beef tea, milk and whiskey. As I read that, I thought to myself, I hope these women weren’t breastfeeding with all that whiskey, but I’m sure they were. And this was to be supplemented with calomel and castor oil for laxative effect. Likewise, treatment of mania required “suppositories every eight hours, thrice daily for 18 days to reduce muscular excitement and moderate the amount of mental *furore*.”

The deep seeded belief that bowel imbalances strongly affected the course of puerperal insanity extended far past the 19th century, seeping into standards of practice well into the 20th century. As late as 1929, Vivian Barkin, the assistant medical officer at Napsbury Mental Hospital in St. Albans, and by the way the first female author I’m citing thus far, published her observations on the efficacy of a bowel regimen in tandem with a typhoid vaccine to treat puerperal insanity. She describes a patient who presented six weeks postpartum with hallucinations, restlessness and confusion, who was put on a light diet so as to clear the intestinal tract, supplemented with “unlimited lemon juice and bland fluids,” as the patient was treated with gradually increasing doses of the vaccine, with good resolution of her mental status.

Although the focus of this case report was on a possible therapeutic role of vaccinations for puerperal insanity, it also shows us that GI health was a strong consideration in the overall treatment package of these patients. To be fair, treatment of puerperal insanity certainly did not focus solely on the bowels. In fact, as mentioned briefly on the previous episode, the standard treatment in the 19th century for many medical and psychiatric disorders was bloodletting, and puerperal insanity was no exception. After all, the blood of those suffering from insanity was thought to contain some toxin or poison, which would be released from the body if the subject were allowed to bleed. Thus, the logic for the use of bloodletting.

It’s a reasonable idea, given the toxins believed to be generated during pregnancy would lead to all sorts of abnormalities in the internal organs, causing such findings as albuminuria and inflammation. Indeed, Dr. James Bates in 1846 argued in favor of small volume bloodletting in cases of insanity, which he felt to be both safe and effective. I still cringe though, at the thought of intentionally bleeding pregnant women and depriving their developing fetuses of the much-needed oxygen and nutrients, all with no chance of any real benefit to the mother.

Thankfully, there were several competing forces, which probably explain the shifting tides and how bloodletting eventually fell out of favor, at least with prospective a treatment of puerperal insanity. First, it was generally known by the mid-1800s that women had a predisposition to become anemic, due to the monthly menstrual blood loss. And by the way, for reference, the oxygen-carrying capacity of hemoglobin was discovered in 1840 by Dr. Hünefeld.

Knowing this and pointing out that women did not tend to tolerate anemia, developing many secondary diseased in its presence, Dr. Mackenzie in 1851, argued that blood loss should be strictly avoided to prevent nervous irritability and susceptibility to puerperal insanity. Making this point, Mackenzie quotes Dr. Williams, who describes in morbid detail the natural history of untreated, severe anemia: “I have met with several cases more or less corresponding with the following description. A young female becomes anemic and after exhibiting various symptoms of feeble general circulation, with headache, drowsiness and impaired sensorial functions, suddenly becomes worse, passes into a state of stupor, with dilated pupils, sometimes buried by slight manifestations of delirium, throbbing of the carotids, and partial heat of the head, and dies comatose.”

Mackenzie goes on to describe several cases of laboring women with anemia and how this was a dangerous combination. The fact is that parturition itself is a very bloody situation, and back in the 1850s, there was no Pitocin or Hemabate to control postpartum hemorrhage, so women were effectively bloodletting themselves at the end of pregnancy, often with fatal consequences. There was no need to further empty the tank iatrogenically, especially in a woman prone to puerperal insanity. For Mackenzie, at best, she would survive but with more severe insanity and, at worst, she would exsanguinate. And it’s very hard to follow long-term psychiatric outcomes in patients who bleed to death in childbirth.

So, by now we’ve talked about cleansing the bowels, we’ve talked about bloodletting, but how did we transition into 20th century treatment of peripartum mental illness? A revolution in the treatment of peripartum mental illness was a shift in paradigm from focusing on the uterus to a greater emphasis on maternal sedation and anesthesia.

So, James Simpson, who many regard as the father of obstetric anesthesia, was the first to use ether during labor to successfully perform version or breech extraction in the late 1840s. He subsequently introduced chloroform gas into obstetric practice, which offered the advantage of a longer duration of action than ether, up to two hours versus up to about an hour respectively. Although chloroform would subsequently be abandoned due to hepatotoxicity and risk of cardiac arrythmia. However, in the midst of this experimentation with chloroform in the obstetric setting, it was discovered that the drug might actually relieve symptoms of puerperal insanity.

Writing in 1857, Dr. Waters describes the use of chloroform in the treatment of puerperal insanity. He explains, “I drew the attention of the members of the medical society of Liverpool to the great benefit to be derived from the use of anesthetics in the treatment of certain forms of puerperal mania. The administration of chloroform in the case of mania is a subject that has already been under inquiry by those engaged in the treatment of insanity. But whether from too much having been anticipated from it, from its having been indiscriminately used or from some other cause, it seems to have fallen into disuse.”

He goes on to discuss how, despite the controversial role of anesthetics for treatment of puerperal insanity, those with the most experience know that remedies addressing the nervous system are most likely to be effective. “Sedatives and narcotics are the sheet anchor. Before, however, these are administered, cathartics, more or less powerful, should be used, for almost invariably in these cases the bowels are much loaded, and much relief is obtained by evacuating their contents.” Whether Waters believed that evacuating the bowels was a good idea because of the constipating effects of opioids or because it was another standard treatment for puerperal insanity is uncertain, however.

In any event, Waters discusses several cases of women suffering from puerperal insanity in the Liverpool Royal Asylum, all of whom benefited from chloroform administration. For example, he cites one case of a postpartum woman who had confined herself to her house, had refused food, had become restless, violent, paranoid and sleepless and vigilant. What we would likely refer to today as a manic episode, which is exactly what Waters called it. Good for him. Remarkably, upon administration of a cocktail of morphine and chloroform, her state was “greatly improved. She eats and sleeps well, answers questions for the first time.” It’s worth noting that many of the mood stabilizers and antipsychotics we use in the treatment of bipolar disorder today have sedative properties not unlike the first crude anesthetic treatments, which may have explained their effectiveness at the time.

It wasn’t long before we transitioned from sedatives and anesthetic agents to other central nervous system-acting compounds that would be discovered or synthesized across the 20th century. As psychiatric illness of the peripartum period became better delineated in the 1950s, and a separate postpartum depressive syndrome was described, the first drugs to actually target depression, the monoamine oxidase inhibitors, or MAOIs for short, were employed in this setting.

As a brief introduction to MAOIs, the first to be used in the 1950s was actually an anti-tuberculosis agent, iproniazid, a cousin of the isoniazid we use today. By coincidence, Drs. Smith, Kamman and del Pino, found that some of their depressed patients treated with iproniazid experienced elevated mood, increased appetite, engagement with the world, weight gain and improved sleep and sociability. Dr. Lurie, a psychiatrist, coined the term antidepressant for this drug and started using it to treat his depressed patients with impressive effects. Subsequent MAOIs were developed, all equally hard to pronounce, including isocarboxazid, tranylcypramine, phenelzine and mebanazine.

How did this new class of medications work in depressed women who had recently given birth? One of the first reports of MAOI use in patients with postpartum depression came from Dr. Agin in 1963. He studied a cohort of 300 women with either of two subtypes of depression, psychoneurotic depression or psychotic depression outside of pregnancy and one woman with postpartum depression and found that phenelzine resulted in a 70% response rate in women with depression independent of pregnancy, and a good response in the one woman with postpartum depression.

I think the reason for including just one woman with postpartum depression in this study probably relates to the increased understanding of the risks associated with potentially harmful effects of drugs in pregnant or breastfeeding women, and hence the need to limit the scope of experimental research studies in these women. After this and other landmark papers demonstrating the efficacy of MAOIs in postpartum depression, and with the rise of other classes of antidepressants, including the tricyclic antidepressants and selective serotonin re-uptake inhibitors, pharmaceutical options for women suffering from postpartum depression continued to rise.

It’s worth mentioning that the SSRIs are considered the safest antidepressants for breastfeeding women, in particular sertraline and paroxetine. When these drugs are ineffective or contraindicated, tricyclics can also be tried, in particular nortriptyline and imipramine are the most evidence-based TCA studied for postpartum depression in this setting. All the other classes of medications were at some point or another also trialed for patients with bipolar disorder who exhibited depressive symptoms in the postpartum period. However, they were swiftly avoided for this indication due to the possibility of precipitating postpartum mania.

Since it was reported as early as 1962 by Blacker et al. that the antipsychotic chlorpromazine could be detected in significant quantities in breastmilk, scientists and physicians began seriously considering alternative approaches to treating peripartum psychiatric illness. In tandem with developments in psychotherapy, electroconvulsive therapy, or ECT, also gained popularity for patients with peripartum mood or psychotic disorders.

The principle behind ECT, although the exact mechanism of action is still poorly understood, is that seizure or seizure-like activity can actually regulate neurotransmitter and neurohormone levels in the brain, potentially counteracting imbalances occurring in mental illness. The first observations of this phenomenon were documented in depressed and suicidal patients who intentionally overdosed on insulin and exhibited hypoglycemic seizures and coma. Among those who survived the attempt, some exhibited remarkable resolution in their depression, or even remission. The so-called insulin coma became a clinically accepted therapy for a factory depression with suicidality for a short time before the advent of ECT, the latter being much safer and not requiring patients to achieve life-threatening hypoglycemia.

Experimental studies of ECT in pregnant or recently postpartum women with severe depression, suicidality, mania or psychosis, began in the 1940s with surprisingly promising results and few adverse effects. A landmark literature review of 1,400 patients treated with ECT by Williams and Barrera in 1950, published in the Psychiatric Quarterly concluded that pregnancy or postpartum status should not be considered a contraindication to ECT.

There were of course concerns about the safety of ECT. In 1964 Drs. Matthew and Constan published a case series of adverse effects they observed after three years of ECT use at their institution. Amongst the most serious complications, there was one case of cerebral hemorrhage, one case of coronary artery occlusion, one case of aspiration pneumonia, one pulmonary embolism and two cases of acute abdomen. Whether all these adverse effects could really be attributed directly to ECT itself is uncertain. However, we do know that aspiration is a concern, which is why patients undergoing ECT do require preprocedural dental clearance and should be NPO for at least eight hours.

With reference to ECT during pregnancy in particular, there was a theoretical concern for fetal damage that had been inferred from adverse neonatal outcomes observed in patients treated with insulin coma, noted by Dr. Sobel in 1960. But, in retrospect, these were likely the result of maternal hypoglycemia rather than any untoward effect from the locally applied electricity. Especially with the increased use of muscle relaxing agents that created a more controlled nonconvulsive seizure in patients, the risk of lactic acidosis in the mother of fetus were minimized. And even today, ECT remains a powerful tool in the modern psychiatrist’s armamentarium for refractory cases of psychosis, severe depression and catatonia in or outside of pregnancy.

Speaking of today, I’d like to spend a minute talking about current guidelines and recommendations for the treatment of peripartum or postpartum depression. According to the American Academy of Family Physicians, psychotherapy is recommended as first-line monotherapy for patients with mild or moderate depression, with cognitive behavioral therapy having the greatest evidence base for its efficacy behind it. For patients with severe postpartum depression who are breastfeeding, there is a grade 2B recommendation for the treatment with an antidepressant medication, with SSRIs being a cornerstone of treatment. Psychotherapy along with pharmacotherapy is recommended.

There is no strong evidence to suggest that one SSRI should be chosen over another, although sertraline is considered to have the most evidence in favor of its use in breastfeeding women. Slow titration of the SSRI, starting at half the regular dose and up-titrating as tolerated is recommended by some experts. For patients in whom SSRI treatment fails, the TCAs fluvoxamine or triptorelin have been studied in breastfeeding women and are considered safe.

For a helpful chart showing the levels of safety of various commonly prescribed antidepressants as per the American College of Obstetricians and Gynecologist, feel free to check out Langan and Goodbred’s 2016 article in the journal American Family Physician entitled *Identification and Management of Peripartum Depression*.

Finally, I’d like to end the show with a brief discussion of an exciting new treatment for postpartum depression. Just a couple of months ago, from when this podcast was recorded, the first FDA approved drug specifically targeting postpartum depression hit the market. The drug, generic name brexanolone, is an intravenous formulation of allopregnanolone, chemically identical to the endogenous ligand, a metabolite of progesterone, which is produced in the corpus luteum as well as the brain. The drug is an allosteric modulator of GABA-a receptors, which is a notably novel mechanism of action for any treatment of depression.

Preclinical trials in animal models of postpartum depression were the first to demonstrate anxiolytic, anticonvulsive and sedative-hypnotic effects of brexanolone. Over the past several years, human trials have since shown decreased depression scores in women with severe postpartum depression treated with a continuous 60-hour IV infusion of the drug, with rare adverse effects including suicidal ideation, intentional overdose attempt, altered level of consciousness and fainting.

Although the cost of the drug is still prohibitive for most patients and its root and timing of administration remain inconvenient, the ongoing success of this new therapy makes me optimistic. I think we’ll likely see expanded indications for this drug in the near future, as well as an array of structural analogues that may provide greater specificity and efficacy. More importantly, this new development holds a lot of promise for unlocking a more complete understanding of the unique pathophysiology of postpartum depression. We’ve come a long way from mercury, castor oil and bloodletting.

And with that, I’d like to thank you all for listening to the podcast, and to Dr. Chappelle for his help in putting this show together. I hope you found this journey through postpartum mental illness as fascinating and humbling as I have. The main message I’d like to get across is that, despite all the efforts and the tremendous progress that have been made in this area, we as healthcare providers need to continue to advocate for our pregnant, soon to be pregnant or postpartum patients suffering from mental illness, and continue to push the envelope for better treatments and fewer barriers to care, which remains a challenge, especially in this patient population.

Thank you all for listening.