Neonatal Abstinence Syndrome: Presentation and Treatment Considerations

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This clinical case conference discusses the treatment of a pregnant woman with opioid use disorder in a comprehensive care program that includes buprenorphine pharmacotherapy. The presentation summarizes common experiences that pregnant women who receive buprenorphine pharmacotherapy face, and also what their prenatally opioid-exposed children confront in the immediate postpartum period. It describes the elements of a successful comprehensive care model and corollary neonatal abstinence syndrome treatment regimen. Expert commentary is included on issues that arise in the buprenorphine induction and maintenance throughout the prenatal and postpartum periods and in the treatment of co-occurring mental health problems during both the prenatal and postpartum periods, particularly the treatment of depression. There is also expert commentary on the care of opioid-exposed neonates, with attention to the treatment for neonatal abstinence syndrome.

Key Words: buprenorphine/naloxone, comprehensive care, neonatal abstinence syndrome, opioid use disorder, pregnancy

(*J Addict Med* 2016;10: 224–228)

CASE DESCRIPTION

The following case report of Jessica Johnson, although fictional, is illustrative of many substance-using women who become pregnant, and receive comprehensive treatment for opioid use disorder that includes buprenorphine pharmacotherapy. Moreover, Jessica's case is typical of a mother and child's hospital experience when the comprehensive care team is trained in neonatal abstinence syndrome (NAS) identification and treatment. However, comprehensive treatment for opioid use disorder is unusual, given both the resources and multidisciplinary expertise required. Nonetheless, research indicates that positive outcomes for mothers treated for opioid use disorders during pregnancy and their prenatally opioid-exposed children can occur when the mother engages in comprehensive care that carefully coordinates the services of multiple service providers, including obstetricians, psychiatrists, neonatologists, pediatricians, nurses, psychologists, counselors, social workers, and child care workers, who work in concert towards a unified goal of maternal and child health and wellbeing. The aims of this clinical case conference are as follows: to summarize common experiences that pregnant women who receive buprenorphine pharmacotherapy face, and also what their prenatally opioid-exposed children confront in the immediate postpartum period; and to describe the elements of a successful comprehensive care model and corollary NAS treatment regimen that has been implemented through the UNC Horizons program in the Department of Obstetrics and Gynecology at the University of North Carolina at Chapel Hill, in collaboration with the University of North Carolina (UNC) at Chapel Hill Department of Pediatrics.

Jessica Johnson, 28 years of age, was admitted to the UNC Horizons program on referral after her initial contact with a Health Department obstetrician to whom Jessica indicated she was using illicit substances. She first arrived that same week at the Horizons weekly obstetrical clinic with a singleton pregnancy of 24 weeks estimated gestation. Both arms evidenced venipuncture stigmata and her urine sample was positive for both opioids and marijuana. After her intake interview, she was diagnosed with a current substance use disorder for opioids, but not marijuana. She is HIV and HCV-C-negative, and underweight (estimated prepregnancy body mass index [BMI] of 17.9). This is her third pregnancy, with the previous 2 resulting in miscarriages at 24 and 18 weeks, respectively. She reports that her father is a ''drunk.'' Her male cousin sexually abused her from age 7 to 10. She reported the abuse to her parents, but they did not believe that sexual abuse was happening. Substance use began with cigarette smoking at age 11, followed by alcohol use at age 13; then she switched to marijuana and ''pain pills'' at age 15 after her boyfriend

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Received for publication December 7, 2015; accepted April 7, 2016.
The authors report no conflicts of interest.

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ISSN: 1932-0620/15/0901-0031
DOI: 10.1097/ADM.0000000000000222

introduced her to them. At age 20, she moved to intravenous use of heroin. She currently smokes ''a pack a day.'' She attempted suicide twice by overdose. Her substance use disorder treatment history includes 2 previous ''detoxification'' programs when she was 25 and 27 years, respectively. She reported no current thoughts of harm to herself or others; however, she does report feeling ''sad, down, and depressed'' most of the time for the past 2 months.

Jessica enters residential care in the UNC Horizons residential care facility, where she receives buprenorphine + naloxone that is managed by her obstetrical care provider, attends group treatment Monday through Friday, and receives individual therapy and case management. Jessica's treatment plan includes a smoking reduction and then cessation goals and strategies that are reviewed with her obstetrical provider and therapist. Based on her intake interview, she receives a referral to the Horizons psychiatric clinic. She is given the diagnosis of major depressive disorder (MDD) based on an interview and review of her symptoms. She is seen weekly in the psychiatric clinic where she receives a serotonin-specific reuptake inhibitor (SSRI). Before delivery, Jessica tours Labor and Delivery, the Neonatal Intensive Care Unit (NICU), and the Newborn nursery. She reviews her birth plan and pain management plan with her obstetrician, nurse practitioner, and pediatrician. She completes a class on childbirth and caring for prenatally drug-exposed children including neonatal opioid withdrawal education.

Jessica receives buprenorphine + naloxone for 13 weeks while in residential treatment. She delivers vaginally at $37^{1}/_{2}$ weeks gestation to a girl named Journey, weighing 2890 g, with a 5-minute Apgar score of 8. Given that Jessica has been enrolled in a comprehensive treatment program, there has been ongoing communication among the care team about her care, and the communication between the care team and Jessica has been open and consistent. Because Jessica has been engaged in treatment and all her urine screening tests for illicit substances during residential care have been negative, there was no medical reason to test her or her baby for substance use at delivery. Journey rooms-in with Jessica and is monitored by nursing staff every 3 to 4 hours after delivery for NAS (depending on how long Journey is sleeping). Jessica is educated by the nursing staff on the signs and symptoms of NAS so that she may actively participate in the NAS assessment. Jessica decides to bottle-feed Journey despite meeting with a lactation consultant regarding the possibility of breastfeeding, due to her inability to tolerate the pain felt when the baby latches. Jessica has been taught by the nursing team to keep the lights off, make visitors talk in low voices, and knows how to soothe and swaddle Journey to help minimize withdrawal. Jessica has been observed by nursing staff on each shift practicing these actions. On postdelivery day 3, Jessica has a difficult time soothing Journey. She is worried because Journey is arching her back, is difficult to hold, crying a lot, and is having loose stools. She tells the nurse what she is seeing and feeling. Journey was assessed with a neonatal opioid withdrawal scale, and morphine treatment was initiated when her scores were elevated over the threshold of 8 and were titrated daily to maintain scores in the 4 to 7 range. Journey weaned without difficulty, having required morphine treatment for 7 days. During Journey's treatment, Jessica has remained in the hospital, and Journey has remained in the room with her mother for the entire 10-day period. The maternal-child therapist visits Jessica and Journey in the hospital and begins to work on bonding and attachment during this 10-day period. On day 11, Journey is discharged to Jessica's care and they both return to the UNC residence to continue Jessica's comprehensive treatment program. At the residence, they regularly meet with the maternal-child therapist who continues to work with Jessica to establish ways to bond, and also how to best establish feeding, sleeping, and diaper changing schedules. As per the UNC Horizons postnatal protocol, at 6 weeks of age, Journey is referred for developmental assessments including speech, occupational, and physical therapy. Jessica is regularly monitored during the postpartum period, during which she is screened for depression, her craving and withdrawal symptoms are monitored, and she is asked about breastfeeding practices and problems.

DISCUSSION

Elisabeth Johnson, PhD

The case of Jessica Johnson is illustrative of the numerous issues women with opioid use disorders face. It has been estimated that as many as 80% of women with substance use disorders have a lifetime history of trauma, and 30% to 59% have posttraumatic stress disorder (Cohen and Hien, 2006). In addition, many women have faced discrimination within the healthcare system and are slow to trust individuals in authority, and as a result, are hesitant to seek routine health care. For these reasons, a multidisciplinary approach is critical to a woman's care, as frequent visits with the same healthcare providers allow the patient an opportunity to build trust and rapport with members of her comprehensive care team. As occurred for Jessica, a pregnant patient with opioid dependence at UNC Horizons will be evaluated to determine which agonist medication is best for her (methadone or buprenorphine), given that methadone may be the more efficacious choice for some pregnant women (eg, Brogly et al., 2014). Given Jessica has no opioid agonist medication history, her preference is buprenorphine, and she has no contraindications to receive it, she is treated with buprenorphine, in this case the combination of buprenorphine + naloxone. Although it is recognized that the literature regarding the treatment of opioid dependence in pregnant women has almost exclusively examined either methadone or the buprenorphine mono product (eg, Jones et al., 2010, 2012), the buprenorphine-waivered obstetrician often decides with the patient's collaboration that buprenorphine + naloxone is the best option for the patient, given concerns with diversion of the mono product and its reduced availability. Furthermore, the limited data available on its efficacy and safety during pregnancy do not suggest worse outcomes for buprenorphine + naloxone relative to either the buprenorphine mono product or methadone (eg, Debelak et al., 2013; Lund et al., 2013; Wiegand et al., 2015). Buprenorphine + naloxone is often considered to experience diversion much less frequently than the buprenorphine mono product, although this issue is not as straightforward as expected when the combination product was developed (Yokell et al., 2011).

A pregnant patient's induction onto buprenorphine + naloxone is conducted like the induction for nonpregnant patients. Jessica was encouraged to abstain from taking any substances before her UNC residential intake, including any opioid agonist medications. When she arrived, the Clinical Opioid Withdrawal Scale (COWS) was administered and she was found to be in moderate withdrawal. She was given a prescription for buprenorphine + naloxone 4/1 mg sublingual films and was instructed to take it to the pharmacy and return with the medication. Upon doing so, she was given 1 film to take. She then waited in the waiting room for an hour and the COWS was readministered. She was found to be in mild withdrawal and was given another 4/1 mg film. Jessica was then sent back to her UNC Horizons residence apartment, which is under 24-hour staffing and monitoring. The team is trained to observe for withdrawal and the patient is encouraged to report withdrawal symptoms, if they are experienced. She was given the instructions to take 2 films in the morning and to take an additional film in the afternoon if she began to experience withdrawal symptoms. On day 3, the nurse practitioner called to check on her and she reported that she was feeling much better, but had had some mild withdrawal symptoms the night before. She was instructed to take 2 films in the morning and 2 films in the evening for a final maintenance dose of 16 mg of buprenorphine daily. Jessica was seen the following week in clinic and reported that she was doing well and no longer experiencing any cravings or withdrawal symptoms. Over the course of her pregnancy, the nurse practitioner asks Jessica direct questions about her cravings and symptoms of withdrawal, and also possible feelings of overmedication. Jessica did not report any symptoms of withdrawal or overmedication. She reported an increased ability to complete her daily activities. There are few studies that have reported on buprenorphine and maternal withdrawal symptoms and if these symptoms are exacerbated during pregnancy or in the postpartum period (Jones et al., 2008). There are reports of reduced plasma levels of methadone during pregnancy, particularly during the third trimester due to increased metabolism and faster clearance. The same consequence has not been demonstrated for buprenorphine. This difference may be due to buprenorphine's slow dissociation from the mu receptor (Jones et al., 2008).

The patient is given a weekly prescription to ensure that she is frequently seen for the many aspects of care in which she is enrolled. For women enrolled in the residential program, the visits may not need be as frequent, given that she is receiving more intensive treatment. More frequent appointments for women living in the community are an effort to provide additional support. During her visits to the Obstetrics clinic, she meets with a therapist, a peer support specialist, and a nurse practitioner. During these visits, the treatment team discusses her recovery and any difficulties and challenges she may be facing. Her buprenorphine dose is reviewed at each visit and she is asked about any signs and symptoms of withdrawal. If during the pregnancy, she begins to experience withdrawal symptoms, the patient can speak to her obstetrician or nurse practitioner, and discuss an increase in dose. In Jessica's case, she did not need an increase in her dose.

When the patient is approximately 36 weeks' gestation, she is encouraged to attend a specialized tour of the hospital's labor and delivery unit. The patient is given the option of bringing family or support persons to the tour. During this tour, she is given information about neonatal abstinence syndrome. The patient is also given the time to ask questions that she may have about pain control or other concerns. If a planned cesarean section is scheduled, the patient attends an additional preoperative visit that includes a discussion with the anesthesia team that addresses postsurgical pain management. For both vaginal and cesarean deliveries, the patient taking buprenorphine is managed in a similar way to the patient who is not receiving medication-assisted treatment for opioid use disorder. However, there is the acknowledgement that women receiving medication-assisted treatment may have lower pain thresholds and their pain must be treated effectively (eg, Jones et al., 2006, 2009, 2014; Meyer et al., 2010). Additionally, if there is the need for narcotic pain medication, her buprenorphine is continued and the patient is given a scheduled dose of pain medication for a finite period of time (Alford et al., 2006). This approach is taken to support ongoing recovery and adequate pain management.

After delivery, the patient continues to be seen every 2 weeks until she is 8 weeks postpartum. In the postpartum period, the patient is regularly asked about breastfeeding and screened for signs of postpartum depression, and also cravings and withdrawal symptoms. Additionally, the discussions about contraception that began in later pregnancy are continued. If a long-acting contraceptive is desired, it is initiated at the 6-week visit. At 8 weeks, the patient's buprenorphine care is transferred from Obstetrics to Psychiatry and is continued for as long as the patient continues to receive treatment services with the program. If a patient has been taking 24 mg of buprenorphine during her pregnancy, it is not uncommon for this dose to be decreased to a postpartum maintenance dose of 16 mg a day. Dose decreases would occur if signs and symptoms of overmedication are seen and/or reported.

Erin Malloy, MD

Jessica's case presents a very common occurrence when providing pharmacotherapy for pregnant women with opioid use disorder—she is experiencing mental health problems that co-occur with her substance use. Comorbidity between substance use disorders and other psychiatric disorders in pregnant women is common, with depression among the most common psychiatric comorbidities (Oei et al., 2009). An association between maternal depression and other psychiatric disorders during pregnancy and increased risk of preterm birth has been established (Männistö et al., 2016). While limited research has been published related to the relationship of comorbid prepartum depression and substance use disorders with infant development, Salisbury et al. (2016) found that the developmental trajectory of neurobehavioral, as measured by the Neonatal Intensive Care Unity Network Neurobehavioral Scale (NNNS), during the first month after birth, differed between infants whose mothers had untreated depression compared with mothers whose depression was treated with SSRIs, with infants in both groups showing

poorer performance in response to visual and auditory stimuli relative to infants whose mothers were not depressed and had not taken SSRIs during pregnancy.

The need to address depression in pregnancy and beyond is widely acknowledged in the literature, and the SSRI class of antidepressants, with the exception of paroxetine, are considered the first-line pharmacological agents (Tran and Robb, 2015). Yet, the safety and risks of fetal exposure to SSRIs are not entirely understood. The risk of NAS with SSRI exposure has been addressed, with findings of increased hospital course in infants with NAS exposed to SSRI's in utero (Wachman et al., 2011) and recent findings of increased NAS risk in neonates whose mothers filled SSRI prescriptions within 30 days of delivery (Patrick et al., 2015). However, important questions remain: are neonatal outcomes related to antidepressant treatment, neurobiological sequelae of untreated maternal depression, and/or secondary effects related to prenatal and perinatal care? Chen and Lin (2011) explored the latter hypothesis in a Taiwanese population-based study, finding that in pregnant women with depression, lower rates of prenatal medical visits were associated with higher rates of neonatal complications such as low birth weight, small for gestational age, and premature birth in neonates. Additionally, the positive impact of remission of maternal depression on child emotional and behavioral functioning has been described by the STAR*D-Child Study (Wickramaratne et al., 2011). Thus, it is critical to carefully weigh the potential risks of prenatal exposure to antidepressant treatment against the risk of untreated depression in terms of neonatal outcomes and longer-term outcomes related to maternal care of the infant and child. Importantly, despite little research to guide clinical decision-making regarding treatment of co-occurring depression and substance use, the potential effect of treatment of depression on maternal self-care and substance use on offspring is an important consideration (Tolliver and Anton, 2015). Oberlander and Wisner (2012) (also see Patel and Wisner, 2011) reviewed the importance of individualized clinical decision-making in the approach to management of depression in pregnancy, weighing risks of treatment and of untreated depression on mother, infant, and family.

In the assessment and management of prepartum comorbid substance use disorder and depression—or, really, any psychiatric disorder—emphasis on patient empowerment and shared decision-making are paramount. Patients may have had past negative experiences with clinicians and may be distrustful or without hope that they will be respected and receive help. Actively involving the patient in informed consent can be very empowering, with ongoing transparency in discussion of treatment alternatives. Inclusion of carefully reviewed data related to medication use in pregnancy and in breastfeeding is essential. The use of motivational interviewing techniques that support self-efficacy may also foster a positive sense of maternal self-care and care of the infant. A collaborative, supportive clinician–patient relationship is key to the treatment of comorbid psychiatric and substance use disorders in pregnancy to optimize the physical and psychological health of both mother and infant.

Carl Seashore, MD, and Emily Freeman, MSN, CPNP

Preparing mothers for the birth of their opiate-exposed newborn is an essential part of prenatal care. In this case, Jessica had the opportunity to meet with members of the newborn nursery team before delivery to discuss NAS. During her prenatal consultation, Jessica met with a nurse practitioner and a social worker, and learned about the symptoms of NAS and the possibility of an extended hospitalization, and also the critical importance of nonpharmacological interventions that she would be able to provide for her infant. Breastfeeding is an important nonpharmacological intervention, and according to the American Academy of Pediatrics, mothers on buprenorphine in a prescribed treatment program should be encouraged to breastfeed (Kocherlakota, 2014). At our institution, women who have demonstrated drug abstinence, are engaged in treatment, and have no other contraindications (eg, HIV) are encouraged to breastfeed. Lactation consultation is provided while inpatient to all breastfeeding mothers. Jessica's questions about the safety and benefits of breastfeeding were answered, including an explanation of the specific safety of breastfeeding while taking opioid agonist medication and an SSRI.

Active parental involvement should be encouraged throughout the infant's hospitalization. After delivery, the otherwise stable infant should be allowed to room in her mother. Nonpharmacological measures should be instituted immediately after delivery and include keeping the room dim and quiet, keeping the infant skin-to-skin or swaddled, and allowing pacifier use. At our institution, parents are provided with a parent-scoring tool which assesses the presence or absence of some of the subjective items found on our neonatal opioid withdrawal scale such as sneezing, yawning, sleeping, crying, stuffy nose, spitting up, tremors, and loose stools. The tool also has a list of nonpharmacological measures that reinforces their importance and how to implement them. The tool is laminated and mothers are provided with a dry erase marker to mark any symptoms they are seeing in their infant. Jessica was able to use the tool to better understand how her baby was doing, participate actively in her care, and aid in communication with her nurse about her concerns.

When pharmacologic treatment is indicated, the most commonly used agent is morphine sulfate, although there is some preliminary evidence that methadone may carry an advantage relative to morphine (Brown et al., 2015), despite the fact that its long half-life makes it potentially more difficult to titrate than morphine (Kocherlakota, 2014). Typically, the morphine dose is titrated based on neonatal opioid withdrawal scale scores. If symptoms worsen, the dose is increased; as symptoms improve, morphine is slowly weaned. Infants typically remain inpatient until weaning is complete, although some programs have robust outpatient capacity to allow weaning a stable neonatal patient at home with nurse supervision. Typically, outpatient weaning is done with methadone; however, more research is needed to fully evaluate the long-term risks and benefits of such treatment on infants and their families (Backes et al., 2012).

Mothers often feel guilt and shame when their infant develops NAS (Cleveland and Bonugli, 2014). It is important to support mothers during the transition from routine postpartum care to NAS treatment as this is a particularly a stressful time not only for infants but also for their mothers. Encouraging mothers to room-in with their infant throughout their hospitalization if possible and to actively participate in the care of their infant can be empowering for mothers. This fosters ongoing involvement in care, support for the breastfeeding mother, and improved bonding between mother and baby.

CONCLUSIONS

This fictional case was a representative presentation of a woman who had an opioid use disorder and became pregnant and then sought treatment for both her pregnancy and her opioid use disorder. She was treated in a comprehensive care program in which all aspects of care are influenced by a trauma-informed approach. The case shows how the woman was treated in an integrated manner during pregnancy, how the birth, delivery, and postpartum care were proactively discussed with her, and how the patient played a collaborative and active role in her care plan and the care of her child. Actively involving the patient in every step of the care process for her and her child is essential for optimal care. Having a unified treatment philosophy among providers that see the strengths of the woman and support her self-efficacy also serve to enhance maternal self-care and care of the infant. A collaborative and supportive clinician-patient relationship is critical to the treatment of patients to optimize the physical and psychological health of both mother and infant. Comprehensive care programs such as UNC Horizons are presently few in number. However, programs such as UNC Horizons offer the promise of the highest quality care for pregnant women with substance use disorders, and the opportunity for the decided cost savings associated with multidisciplinary care of the maternal-fetal dyad.

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