Sickle cell crises occur frequently during pregnancy and are difficult to treat, even with high-dose opioids. Analgesia with ketamine has been suggested as an alternative, but its use during pregnancy is underreported. Two pregnant patients with uncontrolled sickle cell pain were treated with ketamine. Patient A reported no decrease in her pain, but her opioid requirements decreased. Patient B’s pain resolved during ketamine administration. No serious maternal or neonatal adverse effects occurred. Ketamine may be considered as an adjunct analgesic in pregnant patients with sickle cell pain, although prospective clinical data are needed to fully assess its efficacy. (A&A Case Reports. 2017;XXX:00–00.)

Given her multiple admissions, a multidisciplinary care team including Acute Pain Management, Hematology, Internal Medicine, and Maternal Fetal Medicine managed patient A. The patient did not improve after 3 days of a hydromorphone patient-controlled analgesia (PCA) infusion (concentration 0.2 mg/mL), oxygen, and IV fluids. The initial PCA loading dose was 1.5 mg, with a PCA dose of 0.2 mg and a 6-minute lockout. Infectious work-up was negative. Due to concern regarding opioid tolerance, alternative pain control strategies were recommended. On hospital day 4, patient A was started on duloxetine and a 10 mg/h ketamine infusion, with a plan to titrate the ketamine as tolerated. Duloxetine was started as an adjunct to her home pain management regimen and not for acute pain. Patient A (as well as patient B) was closely monitored for side effects by in-house pain nurses visiting at approximately every 2 hours. Further, patient A had the standard monitoring that accompanies IV PCA, on medical/surgical floors; without continuous electrocardiogram or pulse oximetry. The patient did not tolerate higher doses because of dizziness and visual hallucinations; thus, the rate was kept at 10 mg/h for the duration of therapy. Patient A did not self-report a consistent decrease in her pain, which ranged from 8/10 to 10/10 throughout her admission. However, she steadily decreased the use of her PCA, hydromorphone, over the course of her ketamine therapy, from 35.2 mg in 12 hours on the day of ketamine initiation to 13 mg in 12 hours on the day the ketamine was stopped.

The patient’s daily nonstress test pattern changed after initiation of ketamine. The fetal heart tracing decreased in variability in comparison to prior tracings. Additionally, tocometry showed increased uterine irritability and multiple nonpalpable contractions. However, the patient’s cervix remained unchanged throughout the admission.

Because of continued pain and dizziness, ketamine was discontinued after 9 days. The patient agreed to intensive outpatient follow-up and was discharged on hospital day 15 with methadone, oxycodone, duloxetine, and acetaminophen for pain control.

Patient A returned 2 weeks later at 30 weeks and 3 days with preterm premature rupture of membranes and uncontrolled extremity pain. In addition to managing preterm premature rupture of membrane, the team restarted a ketamine infusion at 10 mg/h. She delivered a male infant via normal spontaneous vaginal delivery on hospital day 4 at
30 weeks and 6 days. The infant weighed 1837 g (65th percentile) with Apgar scores of 5, 7, and 10 at 1, 5, and 10 minutes, respectively. The ketamine infusion was discontinued on hospital day 5, and she was discharged home on oral pain medication.

**Case B**
A 29-year-old woman, gravida 1 para 0, at 31 weeks presented to labor and delivery with severe bilateral lower extremity pain consistent with previous sickle cell crises. She was admitted to the hospital and started on IV fluids, oxygen, home doses of oxycodone (10 mg every 6 hours), and a hydromorphone PCA infusion (concentration 0.2 mg/mL). The initial PCA loading dose was 1.5 mg, with a PCA dose of 0.2 mg and a 6-minute lockout. Infectious work-up was negative. Due to increasing PCA requirements and no improvement in pain, the Acute Pain Service started a ketamine infusion on hospital day 2. Ketamine was titrated from 10 to 25 mg/h during the first day. However, her pain did not improve throughout the day, and Hematology performed an exchange transfusion that evening. Over the next 4 days, the patient’s pain improved from 7/10 to 0/10. Because of her improved pain control, the ketamine infusion was discontinued on hospital day 5. Patient B did not complain of dizziness, sedation, or hallucinations. Nonstress tests remained appropriate for gestational age throughout ketamine administration. She was discharged on hospital day 7 on oxycodone and acetaminophen for pain control.

Patient B returned at 37 weeks and 3 days with complaints of decreased fetal movement. A bedside ultrasound revealed oligohydramnios, and the patient was admitted for induction of labor. On hospital day 2, the patient had a normal spontaneous vaginal delivery of a female infant weighing 2466 g (20th percentile) with Apgar scores 9 and 9 at 1 and 5 minutes, respectively. She was discharged home on oral pain medication on postpartum day 2.

**DISCUSSION**
Acute pain crises occur more frequently during pregnancy with over 50% of pregnant sickle cell patients suffering at least 1 crisis. The increased incidence of pain may be due to the physiologic stress of carrying a pregnancy, dehydration, or infection. The American College of Obstetricians and Gynecologists suggests opioids for pain management; however, a Cochrane review highlights the absence of randomized trials supporting their efficacy in this population. Thus, additional analgesics must be considered.

Nonopioids are important alternatives for several reasons. Prolonged opioid use can lead to tolerance, hyperalgesia, dependence, and addiction. Additionally, in opioid-tolerant patients, escalating doses often fail to reduce pain. Finally, opioids are far from benign agents because opioid-related adverse events lead to significant morbidity and mortality. In neonates, adverse pregnancy outcomes that have been described in association with opioid use include preterm birth, low birth weight, sudden infant death syndrome, small head circumference, neonatal abstinence syndrome, and congenital malformations. As for long-term opioid use during pregnancy, a meta-analysis of studies on neurodevelopmental outcomes in children of opioid-dependent mothers did not show adverse effects of prenatal exposure. Patients on opioid therapy are also at risk of respiratory depression, overdose, tolerance, dependence, and addiction.

Ketamine has been proposed as an alternative or adjunctive agent based on its classification as an N-methyl-D-aspartate (NMDA) receptor antagonist. Ketamine receptor upregulation has been hypothesized as a mechanism of opioid tolerance and hyperalgesia. One review of ketamine use to control sickle cell pain showed a reduction in daily morphine requirement and numeric pain rating in 14 out of 17 cases. One patient experienced nystagmus, hypertension, and unresponsiveness, and ketamine was discontinued. However, this patient received an unintended extra bolus of ketamine. No other serious side effects were reported. In a large systematic review of ketamine for pain control, where dose administration (bolus versus infusion versus PCA) was heterogeneous among 37 trials, 20 trials reported pain improvements, and 17 did not find benefit to be clinically significant. Doses ranged from infusion rates of 5 to 20 mg/h, weight-based infusion rates of 0.12 to 0.6 mg/kg/h, weight-based boluses of 0.15 to 0.75 mg/kg of PCA basal rate of 1 to 2.5 mL/h, and intramuscular doses were also used in pediatric populations. Concomitant narcotic use was also diverse among the included studies, with the most common medication being morphine. Adverse effects included psychomimetic effects, vivid dreams, central nervous system side effects, and dysphoria. No serious adverse effects were noted. These studies suggest that in the nonobstetric population, ketamine may be a safe and effective adjunct to opioid therapy, although studies on dosing, infusion rates, and other medication use are inconsistent.

In studies of analgesics, measuring pain improvement and determining the significance of side effects often proves difficult. In assessing pain improvement, increasing patient functionality is as important as a reduction in opioid use. Thus, identifying side effects that limit functionality is imperative. Major side effects that limit ketamine use are psychomimetic, such as hallucinations; cardiovascular, mainly hypertension and tachycardia; and dizziness. These cardiovascular side effects are unlikely at low doses used for pain control; however, hallucinations and dizziness may limit ketamine’s use as an analgesic, as seen in patient A. Dizziness is a common side effect of many medications, including opioids; thus, it is often difficult to attribute to ketamine administration alone. However, side effects are usually dose dependent and may abate with dose reduction.

Additionally, ketamine crosses the placenta, and it is equally important to consider potential fetal side effects. To date, no human data are available regarding its teratogenicity. In pregnant rodents, ketamine did not increase the incidence of malformations; however, there were histologic changes of unknown significance in the fetal heart, liver, and kidney. Ketamine has been used for decades for pain relief during labor or cesarean delivery. Ketamine may not change Apgar scores or umbilical pH, although concerns remain regarding the effect of ketamine on neurodevelopment. Additionally, ketamine is reported to increase uterine tone. With widespread prospective trials, the frequency and significance of these concerns may be addressed.
Although there are no randomized trials demonstrating the efficacy of opioid medications in pregnant patients with sickle cell pain, they remain the standard of care. Furthermore, many patients with sickle cell disease are treated with prolonged opioid therapy for their chronic pain, and as a result, become opioid tolerant. Consideration of different classes of medications is needed. We report the use of an NMDA antagonist, ketamine, in 2 pregnant patients with varied success, but with no serious adverse maternal or neonatal effects. Case A had limited success, and case B was confounded by an exchange transfusion, which likely contributed to lessening the patient’s pain. Well-designed prospective clinical trials are necessary to better evaluate the efficacy of ketamine in pregnant patients in sickle cell crisis.

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