An investigation of delivery outcome in obstetric patients with pregnancies complicated by opioid agonist pharmacotherapy

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INTRODUCTION

The frequency of opioid use by the general population, as well as in pregnancy, has spiked considerably in recent years. Prescribed and illicit opioids all have the potential for misuse and abuse with the potential for respiratory depression, overdose, and death (1). Additionally, intravenous route of administration carries the additional risk of contraction of bacterial infections as well as transmission of viral infections such as hepatitis B, hepatitis C, and HIV. The true prevalence of opioid use disorder in pregnancy is difficult to define secondary to associated poor health behaviors such as inadequate prenatal care, though is estimated to have more than doubled between 1998 and 2011 to four per 1000 deliveries (2). Opioid use disorder is a pattern of opioid use characterized by tolerance, craving, inability to control use, continued use despite adverse consequences, and is considered a treatable disease (1). Acceptable treatment for opioid use disorder during pregnancy is either methadone or buprenorphine. Methadone has been used widely in pregnancy since the early 1970s, whereas buprenorphine treatment has been increasingly used in the United States starting in 2002 after its approval in France in 1996 (2).

In pregnancy, administration of opioid agonist pharmacotherapy in combination with counseling and behavioral therapy is standard of care for patients with opioid use disorder. The goal of pharmacotherapy, whether via utilizing methadone or buprenorphine, is to prevent opioid withdrawal symptoms, thereby reducing relapse risk and improving adherence to prenatal care and addiction treatment programs (1). Methadone is a synthetic opioid. By law, methadone must be distributed daily. Doses administered in pregnancy often need to be titrated up secondary to pharmacokinetic and physiologic changes in pregnancy that enhance its metabolism. Buprenorphine acts on the mu-opioid receptors as a partial agonist and may be prescribed in monthly increments by a registered DEA provider. There is less evidence for need to increase dosage of buprenorphine during pregnancy.

Since methadone and buprenorphine cross the placenta with concentrations that reflect maternal dose during pregnancy, there is a strong possibility these medications affect the fetus in utero (3). Opioid have the potential to depress fetal neurobehavioral status and may change reactivity or variability of fetal heart rate patterns. According to a study regarding fetal response to methadone administration, at peak methadone levels, fetuses displayed significantly slower fetal heart rate, reduced variability, fewer heart rate accelerations, and "looked less well" according to expert FHT clinicians (4). A paper recently published by Salisbury et al investigated the pre- and post-dosing effects of prenatal methadone compared to buprenorphine on fetal well-being, and determined that at the times estimated to be peak dosing effect, buprenorphine-exposed fetuses were more likely to have a reactive non-stress

test (NST) with more fetal heart rate accelerations and higher biophysical profile (BPP) scores than were methadone-exposed fetuses (3).

Antenatal testing of the singleton, chronic opioid exposed fetus should include third trimester serial growth ultrasounds in addition to weekly BPP or biweekly NST-AFI no later than 34-35 weeks (5,6). Depending on gestational age at time of surveillance, non-reactive NSTs and lower BPP scores could result in recommendation for delivery to avoid fetal compromise. Furthermore, it is recommended that a patient's regularly scheduled methadone and buprenorphine doses are continued during labor (1). Given that these opioid alternatives have the potential to change fetal heart tracing (FHT) reactivity, we propose an investigation of delivery outcome in obstetric patients with pregnancies complicated by opioid agonist pharmacotherapy. We hypothesize that patients receiving opioid agonist pharmacotherapy will have increased frequency of persistent Category II FHT in labor necessitating primary cesarean delivery.

METHODS AND MATERIALS

We conducted a retrospective cohort based study using data from patient charts. We obtained a list of patients who had received prenatal care at a single private practice office in Oklahoma City from 1/1/2016 through 11/30/2017. Electronic medical records were accessed. All patients were delivered at one of two hospitals in the Oklahoma City area with Level II NICU capabilities. We documented route of delivery, cesarean versus vaginal delivery, for all patients delivering in this time window. We additionally determined the number of patients whose pregnancy was complicated by opioid agonist pharmacotherapy. It was specified whether each patient on opioid agonist pharmacotherapy was taking methadone or buprenorphine. Delivery route for these patients was then assessed. There were not standardized forms or documents that contained all needed information. All of the data collection was performed by a single researcher to eliminate inconsistency in reporting.

The primary variables of interest were delivery route and opioid agonist pharmacotherapy use. If any variable could not be obtained from the documents in the chart, the patient chart was excluded from review. If there was no result when a patient's name was searched in the electronic medical record, that patient was excluded. We used contingency tables to compare the variables of interest. χ^2 analysis was then performed. Statistical significance was set at $p < 0.05$.

RESULTS

A total of 745 patient charts were obtained using the above listed criteria, 114 of which charts were excluded because no patient information could be obtained via the electronic medical record. This gave us a total of 631 charts that contained all the necessary variables. There were 412 patients who delivered via spontaneous vaginal delivery. Of these patients, 6 were receiving opioid agonist pharmacotherapy during their pregnancy. A total of 2 patients were

prescribed and taking methadone, and a total of 4 patients were prescribed and taking buprenorphine. Of the total number of patients who delivered vaginally, 1.46% of those were prescribed and taking opioid agonist pharmacotherapy. There were 219 patients who delivered via cesarean section. Of the total number of cesarean deliveries, 102 were repeat cesarean delivery and 117 were primary cesarean delivery. Of the primary cesarean deliveries, 57 were documented as being secondary to non-reassuring fetal heart tones (NRFHT). Out of the patients who underwent cesarean delivery, 4 were receiving opioid agonist pharmacotherapy during their pregnancy. Three of these cesarean deliveries were primary cesarean delivery secondary to NRFHT, two of whom were prescribed and taking methadone, and one of whom was prescribed and taking buprenorphine. The fourth patient receiving the opioid agonist pharmacotherapy methadone, who underwent cesarean delivery, was a medically-indicated repeat cesarean delivery secondary to NRFHT. Out of the total number of patients who underwent cesarean delivery, 1.83% of those were prescribed and taking opioid agonist pharmacotherapy. We additionally calculated that of the total cesarean deliveries secondary to NRFHT, 7% were on the patients prescribed and taking opioid agonist pharmacotherapy.

We used a contingency table to compare the route of delivery in patients on opioid agonist pharmacotherapy in pregnancy. There were a total of 57 patients who underwent primary cesarean delivery for NRFHT, 3 of these patients receiving opioid agonist pharmacotherapy and an additional 54 patients not taking either methadone or buprenorphine. We assumed a p value of 0.05 to reach statistical significance. There were 6 patients on opioid agonist pharmacotherapy who had a vaginal delivery and an additional 406 patients who underwent vaginal delivery. There was a statistical difference when comparing delivery route in patients receiving opioid agonist pharmacotherapy to patients not receiving opioid agonist therapy, $\chi^2 = 3.86$ with a p value of < 0.05, which supports our hypothesis that patients receiving opioid agonist pharmacotherapy will have increased frequency of persistent Category II FHT in labor necessitating primary cesarean delivery. As a secondary outcome, we hypothesized that patients maintained on methadone would have an increased frequency of cesarean delivery for NRFHT compared to patients maintained on buprenorphine. However, p value was 0.197 and was not deemed statistically significant in our group of 10 patients on opioid agonist pharmacotherapy.

DISCUSSION

The above analysis suggests a relationship between opioid agonist pharmacotherapy use in pregnancy and increased risk of cesarean delivery. While statistical significance was reached in our calculations, the population studied had a low frequency of either methadone or buprenorphine use in pregnancy, which does make it difficult to draw formal conclusions from this study. Although not reaching statistical significance due to small sample size, we noted that three of the five patients on methadone compared to one of the five patients on buprenorphine delivered via cesarean delivery secondary to NRFHT. These statistical findings are in slight contrast with a previous comparison by Wiegand et al that did not note a statistically significant difference in delivery route for patients maintained on methadone

versus buprenorphine plus naloxone (5). However, this study by Wiegand et al utilized buprenorphine plus naloxone instead of buprenorphine alone, and did not specify the medical indication for cesarean delivery. Since there were only 10 patients total in our study receiving and taking either methadone or buprenorphine, a larger sample size would be needed to truly examine statistical significance. Compared with fetal testing post-methadone dosing, post-buprenorphine dosing non-stress tests are more likely to be reactive and biophysical profile scores are likely to be higher (5). Given that previous studies demonstrate that buprenorphine exposed fetuses had higher FHT variability with more accelerations and less suppression of mean FHT than methadone exposed fetuses (3), one would postulate there could be an increased frequency of cesarean delivery for NRFHT in patients maintained on methadone compared to buprenorphine. In fact, a study published in the journal *Addiction* in 2012 found a higher incidence of cesarean delivery and medical complications at time of delivery in patients maintained on methadone compared to buprenorphine (7). However, this report was a secondary analysis from previously obtained data and was not the primary outcome of interest.

Weaknesses to our study include the small population size of patients receiving either methadone or buprenorphine, incomplete information regarding each patient's dosages of these medications, incomplete follow up of patients, and inability to review the detailed fetal heart tracings in each patient's labor. Since data was extracted by an individual instead of a computer, there is chance for error in the data collection process. We would need a much larger sample size to distinguish between type of opioid agonist therapy (methadone versus buprenorphine) and delivery outcome (cesarean versus vaginal delivery) in order to potentially determine if one opioid alternative results in better maternal outcomes in terms of delivery route.

As mentioned above, opioid misuse is increasing in frequency in the general population. Accordingly, more women are recovering from this misuse and subsequently maintained on opioid agonist pharmacotherapy during and between pregnancies, whether in the form of methadone or buprenorphine. While methadone has been in use since the 1970s, buprenorphine has a much shorter history of use since 2002 in the United States. A study by Zelder et al concluded there was moderately strong evidence indicating lower risk of preterm birth, greater birth weight, and larger head circumference when using buprenorphine compared to methadone in treatment of maternal opioid use disorder (2). In 2015, another study found a lower frequency of neonatal abstinence syndrome, lower peak of neonatal abstinence syndrome, and shorter overall hospitalization for the newborns of mothers treated with buprenorphine and naloxone (8). This study additionally found increased frequency of preterm birth in patients maintained on methadone. However, this study was comparing methadone to buprenorphine plus naloxone, so there is a possibility these findings would not be generalizable to patients on buprenorphine alone. It would be beneficial determine more definitively which opioid alternative offered the most positive outcomes for both patients and their offspring.

Plans for future research related to this paper's topic include creating a database of obstetric patients receiving opioid agonist therapy. These patients would be enrolled at their first prenatal visit and followed closely throughout their pregnancy. Details regarding their opioid alternative prescribers and related behavioral therapy would be collected. The selected opioid alternative would be specified, dosage prescribed, and any increased dosages required during pregnancy to avoid withdrawal symptoms or relapse. Patients would be drug tested throughout their pregnancy to ensure compliance with the treatment. Any comorbid medical conditions or risk behaviors would be logged. Fetal heart tracings and biophysical profiles during antenatal testing as well as FHT during labor would be analyzed. Gestational age at delivery would be documented. Delivery route would be noted as well as any FHT abnormalities that contributed to the route of delivery. This is a relevant topic for future research due to the increasing frequency of opioid agonist pharmacotherapy and its potential to affect both fetal and maternal outcomes. It is well established that treatment for these women should be individualized (1), but more years of data and research targeted to this outcome are needed to potentially definitively determine whether buprenorphine versus methadone overall offers better maternal and fetal outcomes.

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