Drug and Alcohol Dependence 180 (2017) 200–203

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Short communication

Maternal and infant outcomes following third trimester exposure to marijuana in opioid dependent pregnant women maintained on buprenorphine

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ARTICLE INFO

Keywords:
Buprenorphine
Pregnancy
Marijuana
Opioid use disorders

ABSTRACT

Background: To determine whether maternal and infant outcomes are associated with exposure to marijuana during the third trimester in a population of opioid dependent pregnant women maintained on buprenorphine.
Methods: This retrospective cohort study of 191 maternal-infant dyads exposed to buprenorphine during pregnancy examines a variety of variables including gestational age, birthweight, method of delivery, Apgar scores at one and five minutes, duration of infant hospital stay, peak neonatal abstinence syndrome (NAS) score, duration of NAS and incidence of pharmacologic treatment of NAS in infants exposed to marijuana during the third trimester as compared to infants not exposed to marijuana during the third trimester.
Results: Analyses failed to support any significant relationship between marijuana use in the third trimester and a variety of maternal and infant outcomes. Two important variables – the likelihood of requiring pharmacologic treatment for NAS (27.6% in marijuana exposed infants vs. 15.7% in non-marijuana exposed infants, $p = 0.066$) and the duration of infant hospital stay (7.7 days in marijuana exposed infants vs. 6.6 days in non-exposed infants, $p = 0.053$) trended toward significance.
Conclusions: Preliminary results indicate that marijuana exposure in the third trimester does not complicate the pregnancy or the delivery process. However, the severity of the infant withdrawal syndrome in the immediate postnatal period may be impacted by marijuana exposure. Because previous study of prenatal marijuana exposure has yielded mixed results, further analysis is needed to determine whether these findings are indeed significant.

1. Introduction

The opioid epidemic is a national crisis in the United States. With more than 59,000 drug overdose deaths in 2016, it is now the leading cause of death among Americans under 50 (Rudd et al., 2016). Maine has been particularly hard hit with 376 persons dying from drug overdose in 2016, a nearly 40 percent increase over 2015 (Office of the Maine AG, 2017). Maine also has the second highest rate of infants born drug affected at nearly 1 of every 12 births in 2015. On a national level, the mean length of hospital stay for drug affected infants is 16.9 days with a mean cost of $66,700 per infant (Patrick et al., 2015).

A growing body of evidence suggests that buprenorphine is a safe and effective alternative to methadone in the treatment of pregnant women with opioid use disorders. Buprenorphine appears to be linked with a shorter duration and less severe neonatal abstinence syndrome (NAS) (Jones et al., 2010). Variables that predict the likely severity of NAS in infants exposed to buprenorphine during pregnancy have not been studied extensively. Later gestational age, higher birthweight and nicotine use have been correlated with a more severe NAS within populations of infants exposed to either methadone or buprenorphine (Kaltenbach et al., 2012). Male gender and concurrent exposure to antidepressants have been associated with a more severe or longer course of NAS in infants exposed to buprenorphine alone (O'Connor et al., 2013; O'Connor et al., 2016). When compared to women maintained on methadone during pregnancy, women on buprenorphine had significantly longer gestations, fewer instances of preterm birth, and, on average, had infants with greater birth weight and head circumference (Meyer et al., 2015). While nicotine use has been relatively well studied in pregnant women with opioid use disorders, little is known about the impact of concurrent in utero exposure to marijuana.

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http://dx.doi.org/10.1016/j.drugalcdep.2017.08.012
Received 12 March 2017; Received in revised form 5 August 2017; Accepted 14 August 2017
Available online 07 September 2017
0376-8716/

Marijuana is the most commonly used illicit drug in pregnancy. The self-reported prevalence of marijuana use during pregnancy ranges from 2% to 5% (American College of Obstetricians and Gynecologists, 2015). Women who use marijuana during pregnancy tend to have a lower education level, have a household income below $20,000, and be unemployed (Van Gelder et al., 2010), although the strongest indicator appears to be marijuana use by the biological father of the child (Marroun et al., 2008). Marijuana and its metabolites cross into maternal circulation, the placenta, and to the fetus. After delivery, the active metabolites of marijuana can be found in umbilical cord blood, neonatal urine, and meconium. Cannabinoid receptors are naturally found in the central nervous system of the developing fetus at around the fourteenth week of gestation (Day et al., 2015). Exposure to exogenous cannabinoids is thought to alter the development and ultimately the function of the pre-frontal cortex, which is responsible for behavior, mood, working memory, and executive function (Warner et al., 2014). The endocannabinoid system also exists in maternal uterine tissues and may be associated with pregnancy complications, such as pre-term labor, miscarriage, and intrauterine growth restriction (IUGR) (Warner et al., 2014).

Birth outcomes following exposure to marijuana during pregnancy have been variable, however. After controlling for a variety of confounders, marijuana use during pregnancy was associated with low birth weight, preterm labor, small for gestational age and admission to the neonatal intensive care unit (Hayatbakhsh et al., 2012). Fried et al. (1987) determined that prenatal marijuana exposure was associated with "symptoms similar to mild narcotic withdrawal;" however, this is in contrast to Hudak and Tan (2012) who determined that prenatal exposure to marijuana "does not cause clinically important neonatal withdrawal signs," and to Warner et al. (2014) who found no evidence of neonatal withdrawal from marijuana exposure in any prospective, longitudinal studies. Several studies have reported no association between prenatal marijuana exposure and mean birth weight, low birth weight, gestational age at delivery, preterm delivery, intrauterine growth restriction and placental abruption (Bada et al., 2005; Shiono et al., 1995; Van Gelder et al., 2010). Data about the long-term effect of prenatal marijuana exposure suggest subtle but measureable effects on attention, executive functions and behavior, particularly as marijuana-exposed youth develop from adolescence into early adulthood as well as higher rates and earlier onset of marijuana use in adolescence and a higher incidence of psychotic symptoms (Day et al., 2015; Warner et al., 2014). The purpose of this study is to determine whether maternal and infant outcomes are associated with exposure to marijuana during the third trimester in a population of opioid dependent pregnant women maintained on buprenorphine.

2. Materials and methods

The institutional review board of MaineGeneral Medical Center granted approval to conduct a retrospective chart review of all maternal and infant records for pregnancies maintained on buprenorphine at a family medicine residency program from December 2007 to December 2015. The clinic cares for a socioeconomically disadvantaged patient population in rural Maine that has limited access to health care. The women received all of their prenatal and substance abuse treatment in an integrated medical and behavioral health program. Women were seen at least twice per month, and urine toxicology testing was completed at every visit. Infants were observed for NAS in the hospital setting for at least five days after birth. A modified Finnegan scoring system was used to measure symptoms of opioid withdrawal (Finnegan et al., 1975). Peak NAS score is defined as the highest score on the NAS scale during infant hospitalization. Time to onset of NAS resolution is defined as the number of hours from birth until the last time the peak NAS score is reached.

Pharmacologic intervention for NAS was indicated after three consecutive scores of eight or higher (or the average of three consecutive scores was eight or higher) or after two consecutive scores of 12 or higher (or the average of two consecutive scores was 12 or higher). First-line therapy was either an opioid medication (morphine sulfate or methadone) or phenobarbital when there was concern of polysubstance exposure during pregnancy. While the American Academy of Pediatrics (AAP) recommends the use of an opioid medication when the pharmacologic treatment of NAS is required, AAP also indicates that there is "insufficient evidence to state whether an infant born to a mother with multiple drug abuse who meets criteria for pharmacologic therapy of withdrawal signs is best treated with an opioid, barbiturate, a medication from another drug class, or a combination of drugs from different classes." (Hudak and Tan, 2012).

Descriptive statistics were used to define the maternal and infant populations. Differences between categorical data were tested using Fisher's exact tests while differences between continuous data were tested using *t*-tests as distributional assumptions were met. Statistical analyses were performed with Stata software version 14 (Stata-Corp, LP, College Station, TX, USA).

3. Results

A total of 191 maternal-infant dyads in which the pregnant women were maintained on buprenorphine were identified. Opioid abuse varied across the maternal population and included the abuse of both prescribed and illicit narcotics as well as heroin. Similarly, routes of administration varied and included oral, intranasal, intravenous and inhaled use of opioids. Of the 191 women, 76 had urine drug screens that were positive for marijuana during the third trimester of pregnancy. The remaining 115 women did not screen positive for marijuana use during the third trimester. The total number of urine drug screens collected during the third trimester was not significantly different across the two populations.

Women that tested positive were not routinely asked why they were using marijuana. Those who disclosed the use of marijuana often cited nausea, anxiety, insomnia and pain as the symptoms they were trying to control with their marijuana use. Women were discouraged from using marijuana and encouraged to use safer, more studied alternatives for the treatment of their pregnancy symptoms. Table 1 provides a comparison of a variety of variables in the population of women that used marijuana during the third trimester as compared to the women who did not. There were no differences in socioeconomic status (as measured by insurance type) across the two populations and no differences in race as both were more than 95% Caucasian.

4. Conclusions

There were no significant differences in maternal characteristics when comparing third trimester marijuana users versus non-marijuana users. Rates of delayed entry into treatment, psychiatric diagnoses, tobacco use, and the use of other illicit drugs (including illicit opioids, stimulants, cocaine and benzodiazepines) were similar across the two populations. Similar rates of hepatitis C infection were observed across the two populations; none of the women tested positive for HIV.

From an infant perspective, the analyses failed to support any evidence of a relationship between marijuana exposure in the third trimester and gestational age at delivery, method of delivery, birthweight or how well the infant tolerated the birthing process as measured by Apgar scores. These findings support Van Gelder et al. (2010) who found no relationship between marijuana use and mean birth weight or gestational age at delivery but conflict with those of Hayatbakhsh et al. (2012) who found that marijuana use was associated with an increased risk of having a low birth weight infant in a largely Caucasian population of women in Australia. However, their analysis was based on self-reported data and only 2.6 percent admitted to having used marijuana during pregnancy.

While not statistically significant, two important variables trended