The obstetrical and neonatal impact of maternal opioid detoxification in pregnancy

Robert D. Stewart, MD; David B. Nelson, MD; Emily H. Adhikari, MD; Donald D. McIntire, PhD; Scott W. Roberts, MD; Jodi S. Dashe, MD; Jeanne S. Sheffield, MD

OBJECTIVE: The purpose of this study was to analyze the obstetric and neonatal impact of an opioid detoxification program during pregnancy, as well as to examine variables associated with successful opioid detoxification.

STUDY DESIGN: This is a retrospective cohort study of women electing inpatient detoxification and subsequently delivering at our hospital from Jan. 1, 2006, through Dec. 31, 2011. Detoxification was considered successful if women had no illicit drug supplementation at the time of delivery. Maternal characteristics were ascertained by chart review and analyzed for variables associated with success. Obstetric and neonatal outcomes were also assessed based on maternal success at delivery.

RESULTS: Of the 95 women during the study period with complete data, 53 (56%) were successful. There were no demographic or social risk factors identified associated with success. Women with successful detoxification at delivery had longer inpatient detoxification admissions (median 25 vs 15 days, $P < .001$) and were less likely to leave prior to completion of the program than women who had relapsed at delivery (9% vs 33%, respectively, $P < .001$). Infants of mothers who were successfully detoxified had shorter hospitalizations (median 3 vs 22 days, $P < .001$), lower maximum neonatal abstinence syndrome scores (0 vs 8.3, $P < .001$), and were less likely to be treated for withdrawal (10% vs 80%, $P < .001$).

CONCLUSION: Opiate detoxification in pregnancy requires a significant time commitment and extended treatment, however, can be successfully achieved in compliant parturients. Importantly, maternal demographics and drug histories do not portend success, supporting continued opiate detoxification being offered to all women expressing intent.

Key words: drug use in pregnancy, methadone detoxification, opioid detoxification

Cite this article as: Stewart RD, Nelson DB, Adhikari EH, et al. The obstetrical and neonatal impact of maternal opioid detoxification in pregnancy. Am J Obstet Gynecol 2013;209:267.e1-5.

Maternal opioid use during pregnancy is a significant public health concern with implications for both maternal and fetal health. According to the 2010 National Survey on Drug Use and Health, approximately 4.4% of pregnant women were current illicit drug users.[1] Opioid abuse in pregnancy has been associated with a multitude of adverse outcomes for both the mother and fetus, including preterm birth, fetal demise, intrauterine growth restriction, placental abruption, and neonatal abstinence syndrome (NAS).[2] Furthermore, maternal abuse during pregnancy places the pregnant woman at an increased risk for partaking in high-risk behavior to support her drug addiction, including prostitution, theft, and violence. These behaviors place the woman at risk for acquiring sexually transmitted diseases, for becoming the victim of violence, as well as legal ramifications.[3]

Methadone has been the recommended first-line treatment for pregnant women with opioid addiction since the 1970s, with the goal of reducing adverse outcomes associated with uncontrolled narcotic withdrawal. Because of its long half-life, methadone effectively suppresses maternal cravings and can be administered in a controlled setting once daily. However, infants exposed to methadone are at significant risk for adverse outcomes including preterm birth, small for gestational age, neonatal intensive care unit admissions, as well as NAS.[4-9] NAS complicates 60-90% of infants exposed to methadone in utero and is characterized by central nervous system irritability, respiratory distress, and autonomic dysfunction, often requiring several weeks of neonatal opiate solution.[9] Opioid detoxification provides an alternative approach in well-selected patients who desire decreased opioid dosing with resultant decreases in neonatal complications.[10,11]

For many years, our group has offered pregnant opioid users inpatient hospitalization with slow taper of their methadone dosage, with the goal of reducing the likelihood of NAS.[10,11] The main argument against such a strategy has been that it might predispose to relapse, with women going back to illicit heroin use.[3,7,12] As this is a valid concern when caring for such a high-risk population, we sought to determine if certain patient characteristics could be used to better identify parturients likely to be successful with methadone detoxification, or conversely, who might be better served by a methadone maintenance program. Such information would be useful for counseling women interested in opioid detoxification or maintenance.

From the Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, TX.

Received March 8, 2013; revised April 23, 2013; accepted May 13, 2013.

The authors report no conflict of interest.

Presented at the 33rd annual meeting of the Society for Maternal-Fetal Medicine, San Francisco, CA, Feb. 11-16, 2013.

Reprints not available from the authors.

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2013.05.026

Materials and Methods

We conducted a retrospective cohort study of all pregnant opioid users who underwent inpatient opioid detoxification with methadone from Jan. 1, 2006, through Dec. 31, 2011, and who subsequently delivered at our institution. At our hospital, pregnant women with a history of substance use are followed up by a multidisciplinary medical and social case management team of physicians, nurse practitioners, drug counselors, and social workers. As part of this program, inpatient hospitalization and detoxification is offered to all pregnant opioid users as well as women currently enrolled in a methadone maintenance program. Contraindications to detoxification include fetal growth restriction, oligohydramnios, significant maternal psychiatric illness, or a prior unsuccessful detoxification attempt. All other pregnant opioid users are offered inpatient detoxification. Prior to making their decision, women are noncoercively counseled about potential benefits of reducing fetal opioid exposure and about the hazards of uncontrolled maternal opioid use. Regardless of their decision, women continue to receive the multidisciplinary social services offered to all pregnant women with a history of substance abuse.

Women who elect to undergo detoxification are admitted to the hospital, and detoxification with methadone is conducted according to a previously published protocol.[10] The initial dose of methadone is selected based on reported history of use and any signs or symptoms of opioid withdrawal. Methadone is distributed twice daily with tablets crushed in orange juice to blind women as to the dose they receive. Signs and symptoms of withdrawal are typically treated by increasing the methadone dose by 5-mg increments as needed. If a woman elects to undergo detoxification and has previously been on methadone maintenance, her initial dose is started at her maintenance dosage. The dose is then decreased by no more than 20% every 1-3 days as tolerated, until the woman is weaned from all methadone. Fetal surveillance is initiated in women >24 weeks' gestation. Women are observed in the hospital for several days after all medications have been discontinued. After completion of detoxification, women are offered admission to an outpatient drug rehabilitation housing facility, however rates of maternal acceptance of this program were unable to be determined. Nurse practitioners and drug counselors continue to follow up each woman in conjunction with a maternal-fetal medicine specialist. All women with a prior or current illicit drug use, regardless if they complete detoxification, elect methadone maintenance, or continue illicit substance use, are followed up in a dedicated clinic by these same specialists.

For the purposes of this study, successful detoxification was defined as no maternal illicit drug supplementation at the time of delivery. This was determined by maternal admission of relapse, maternal urine toxicology, or fetal meconium toxicology, with any one finding determining illicit supplementation. Women who were actively undergoing detoxification at the time of delivery or on methadone maintenance at the time of delivery were considered successful. Women who underwent inpatient detoxification were identified by records maintained by our program. The medical records were reviewed for maternal demographics and maternal drug history, including length of use, route of administration, and amount of use. The maternal inpatient record was reviewed for pertinent data, including infections such as hepatitis B or C, initial methadone dosage, duration of hospitalization, and success of detoxification. The delivery record was reviewed for obstetrical data as well as maternal relapse. All infants received drug testing and were followed up for evidence of withdrawal. The newborn record was also reviewed for duration of hospitalization, maximum NAS score, and need for opioid treatment for withdrawal symptoms. NAS scores were determined by physical examination by trained pediatric providers according to the Finnegan scoring system.[4]

Statistical analysis included Pearson χ^2, Student t test, Cochran-Mantel-Haenszel χ^2 for trend, and Wilcoxon rank sum. P values $< .05$ were considered significant. Analysis was performed using software (SAS 9.2; SAS Institute Inc, Cary, NC). This study was approved by the institutional review boards of the University of Texas Southwestern Medical Center and Parkland Hospital.

Results

During the study period, 95 women delivered at our hospital with maternal and neonatal outcomes available for analysis, of whom 53 (56%) were successful. Maternal characteristics were analyzed for variables that were associated with successful detoxification. Maternal demographic characteristics are presented in Table 1. There were no differences in maternal age, ethnicity, or nulliparity between those women who were drug free at the time of delivery as compared to those who tested positive for illicit drugs. When maternal drug history was analyzed, there was no difference in prior maternal substance use. Intravenous opioid use (as opposed to intranasal or oral ingestion), total amount of daily use, and years of use were not different between the 2 groups. Women with illicit substance use at delivery were more likely to have a positive hepatitis C antibody (64% vs 40%, $P = .02$) while human immunodeficiency virus, syphilis, and hepatitis B seropositivity did not differ.

Methadone detoxification data are presented in Table 2. The median gestational age upon admission for detoxification was 20 weeks, and this did not differ according to success of detoxification ($P = .80$); nor did the maximum methadone dosage required, which was 40 mg per day in each group ($P = .91$). The duration of hospitalization to complete detoxification was significantly longer in those who were successful as opposed to those who relapsed. Those women who remained free of opioid use at delivery required a median of 25 days to complete detoxification as opposed to 15 days in those women who subsequently relapsed ($P < .001$). This is

related to the number of women who left the detoxification program prior to completion, 33% vs 9% in the relapse group and the success group, respectively ($P = .004$).

Seventeen women elected to discontinue the detoxification component of the program and receive maintenance therapy. Sixteen of these women were started on methadone maintenance, and 1 chose buprenorphine. Those on methadone maintenance received doses ranging from 35−110 mg per day. Of the 17 women on maintenance therapy at delivery, 12 (71%) were supplementing with illicit drugs, including the 1 patient on buprenorphine maintenance. Two other women left the program prior to completion, refused methadone maintenance, and were subsequently supplementing with illicit drugs at delivery.

Fetal demise occurred in 3 patients. Two of these occurred in women who did not complete the detoxification program, refused methadone maintenance, did not return for prenatal care, and were found to be using illicit drugs at the time the fetal demise was diagnosed. One woman successfully completed detoxification at 15 weeks' gestation. At 20 weeks, she developed rupture of membranes and subsequently delivered a previable infant. No stillbirth or fetal demise occurred among women hospitalized for detoxification. There was no case in which an emergent delivery occurred because of nonreassuring fetal status during antepartum surveillance. One woman had a twin gestation. Therefore, 93 infants were available for analysis.

The infant outcome data are shown in Table 3. Infants born to mothers without illicit supplementation at delivery had lower maximum NAS scores (0 [0, 0] vs 8.3 [6.5, 10], $P < .001$), had shorter hospitalizations (3 [2, 6] vs 22 [15, 26] days, $P < .001$), and were less likely to be treated for withdrawal (10% vs 80%, $P < .001$). Five infants who were born to mothers without illicit drug use at delivery required treatment for neonatal withdrawal; 3 mothers were receiving methadone maintenance at doses of 35 mg, 55 mg, and 60 mg per day. The other 2 infants were born to mothers who were actively enrolled in the inpatient detoxification program. The maximum NAS scores of these 5 neonates ranged from 8−10. Those infants born to mothers who were successfully off drugs at delivery delivered at a later gestational age (39 vs 37.8 weeks, $P = .008$) and had larger birthweights (3065 vs 2788 g, $P = .01$), although preterm birth and fetal growth restriction were not different between the groups.

TABLE 1
Selected maternal demographic data and substance abuse history of women undergoing opioid detoxification

Variable	No illicit drug use at delivery n = 53	Illicit drug use at delivery n = 42	*P* value
Age, y	25.1 ± 5.3	25.9 ± 5.5	.47
Ethnicity			.52
Caucasian	24 (45)	21 (50)	
African American	4 (8)	1 (2)	
Hispanic	25 (47)	20 (48)	
Nulliparous	14 (25)	13 (31)	.63
Polysubstance use	19 (36)	19 (45)	.35
Intravenous use	35 (66)	33 (78)	.17
Reported use, $/d	50 [30, 80]	50 [30, 85]	.96
Years of use	4.6 ± 3.9	5.0 ± 5.2	.67
Incarceration	15 (28)	6 (14)	.10
Tobacco use	42 (79)	36 (86)	.41
Maternal coinfection			
HIV	0	0	NA
Hepatitis C	21 (40)	27 (64)	.02
Hepatitis B	0	1 (2)	.26
Syphilis	0	0	NA

Data reported as n (%), mean ± SD, median [First Quartile, Third Quartile].

HIV, human immunodeficiency virus; *NA*, not applicable.

Stewart. Opioid detoxification in pregnancy. Am J Obstet Gynecol 2013.

TABLE 2
Variables of inpatient detoxification admission compared by illicit maternal drug use at delivery

Variable	No illicit drug use at delivery n = 53	Illicit drug use at delivery n = 42	*P* value
Gestational age at program entry, wk	19.9 ± 8.6	20.4 ± 9.8	.80
Maximum methadone dosage, mg/d	40 [30, 40]	40 [30, 40]	.91
Duration of detoxification, d	25 [17, 38]	15 [5, 21]	< .001
Left program prior to completion	5 (9)	14 (33)	.004

Data reported as n (%), mean ± SD, median [First Quartile, Third Quartile].

Stewart. Opioid detoxification in pregnancy. Am J Obstet Gynecol 2013.

TABLE 3
Infant outcomes of women electing inpatient opioid detoxification compared by illicit maternal drug use at delivery

Variable	No illicit drug use at delivery, n = 53	Illicit drug use at delivery, n = 40	*P* value
Max NAS score	0 [0, 0]	8.3 [6.5, 10]	< .001
Infant treated for withdrawal	5 (10)	33 (80)	< .001
Infant hospital duration, d	3 [2, 6]	22 [15, 26]	< .001
Gestational age at delivery	39 ± 1.9	37.8 ± 2.4	.008
≤34 wk	4 (8)	4 (10)	.69
≤36 wk	5 (10)	7 (18)	.27
Birthweight percentile	3065 ± 487	2788 ± 516	.01
<10th	7 (13)	12 (30)	.05
<3rd	1 (2)	2 (5)	.40
5-min Apgar <4	0	1 (3)	.26
pH <7	0	0	NA
Neonatal death	0	0	NA

Data reported as n (%), mean ± SD, median [First Quartile, Third Quartile].

NA, not applicable; *NAS*, neonatal abstinence syndrome.

Stewart. Opioid detoxification in pregnancy. Am J Obstet Gynecol 2013.

We further subdivided our cohorts into 3 groups: women who completed detoxification and had no illicit drug use; women on methadone at delivery—either maintenance or undergoing detoxification (no illicit drug use); and women with illicit drug use at delivery. In doing so, there was no longer a significant difference in maternal hepatitis C antibody status between those who did not resume illicit drug use as compared to those who resumed illicit drug use (data not shown). All other results remained the same.

Comment

This study was undertaken to determine maternal factors associated with methadone detoxification success to better define admission criteria for this component of our drug use in pregnancy program as well as to improve our counseling. We found that women who were not using illicit drugs at delivery had been hospitalized approximately 10 days longer than those who relapsed; however, their infants were hospitalized nearly 20 days less. Women who left the program prior to completion had higher rates of illicit substance use at delivery, likely resulting in the higher maximum NAS scores and the markedly increased percentage of infants requiring treatment for withdrawal.

Prolonged maternal hospitalization is costly, both monetarily and emotionally, however the benefit of incurring these costs is the significant reduction in infant hospitalization and withdrawal. Previous reports of patient detoxification used regimens that were more accelerated than the program used at our institution.[12] These programs consisted of structured methadone tapers of either 3 or 7 days. Such rapid tapers would be expected to have decreased success rates and more maternal relapse rates, and when compared to methadone maintenance, they did. However, our program slowly tapers women off of opioids based on maternal symptoms. The benefit of extended detoxification is not only that the patient is able to gradually wean from opioids with minimal withdrawal symptoms, but they are also able to have intense daily counseling and resources provided to them. Establishing relationships with drug intervention programs during the antepartum period also allows for the mother-infant pair to continue this rehabilitation program into the postpartum period, providing continued support during this time. A caveat to these benefits of extended detoxification is that the patient must be motivated and willing to undergo such an intense therapy and prolonged hospitalization.

Our results also again highlight the benefits of successful detoxification, namely fewer infants requiring treatment for withdrawal or NAS, and shorter infant hospitalizations. The consequences of NAS include central nervous system irritability, tachypnea, apnea, poor feeding, and failure to thrive. While indices such as preterm birth and low birthweight did not differ within our study, we believe that the benefits of successful detoxification are evident. Recent studies have focused on the severity of NAS in mothers who are receiving methadone maintenance for opioid addiction. These studies have noted that there is no association between increasing methadone doses and severity of neonatal withdrawal.[5,7,8] Of note, within these studies the average doses used in methadone maintenance ranged 60—100 mg per day, with comparisons made between methadone dose thresholds of 80—100 mg per day. In our experience, methadone doses are associated with less neonatal withdrawal, lower NAS scores, and shorter infant hospitalizations, especially in doses of <20 mg per day.[11] The discrepancy in methadone dosage makes comparisons between these studies difficult. It may be however, that in an attempt to fully suppress maternal symptoms, increasingly higher doses of methadone maintenance are well above the dosage threshold that is necessary to decrease the rate of neonatal withdrawal.

Our program of methadone detoxification had a success rate of 56%, which is stable from what we previously have reported.[10] By comparison, recent reports of methadone maintenance during pregnancy have demonstrated comparable success rates of 63-82%.[5,7,8,12,13] Success within these previous studies was variably defined. Similarly, high

relapse rates have consistently been documented within the nonpregnant literature, highlighting the fact that the treatment for addiction is not an acute process.[14] Detoxification, therefore, should be viewed as merely a step in the process of treating this disease. Detoxification must also transition to a long-term management plan to provide meaningful maternal and neonatal benefit. The hazards of simply providing detoxification or maintenance without the proper support, follow-up, and long-term management cannot be overemphasized.

Given that maternal demographic characteristic and drug history do not portend success, and that infant benefits are significant, inpatient opioid detoxification may continue to be offered to all women who express intent. Importantly, women and providers must both be aware of the significant commitment of time and resources that is required to make a program like this successful. Intense support and resources should be provided to these women, both during the detoxification process and after discharge. Based on our results, we continue to offer detoxification and methadone tapering to appropriately counseled and motivated women. ■

REFERENCES

1. Substance Abuse and Mental Health Services Administration. Results from the 2010 national survey on drug use and health: summary of national findings, NSDUH series H-41, HHS publication no. (SMA) 11-4658. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2011.

2. Kaltenbach K, Berghella V, Finnegan L. Opioid dependence during pregnancy. Obstet Gynecol Clin North Am 1998;25:139-51.

3. American College of Obstetricians and Gynecologists. Opioid abuse, dependence, and addiction in pregnancy: committee opinion no. 524. Obstet Gynecol 2012;119:1070-6.

4. Finnegan LP, Kron RE, Connaughton JF, Emich JP. Assessment and treatment of abstinence in the infant of the drug-dependent mother. Int J Clin Pharmacol Biopharm 1975;12:19-32.

5. McCarthy JJ, Leamon MH, Parr MS, Anania B. High-dose methadone maintenance in pregnancy: maternal and neonatal outcomes. Am J Obstet Gynecol 2005;193:606-10.

6. Luty J, Nikolaou V, Bearn J. Is opiate detoxification unsafe in pregnancy? J Subst Abuse Treat 2003;24:363-7.

7. Berghella V, Lim PJ, Hill MK, et al. Maternal methadone dose and neonatal withdrawal. Am J Obstet Gynecol 2003;189:312-7.

8. Cleary BJ, Eogan M, O'Connell MP, et al. Methadone and perinatal outcomes: a prospective cohort study. Addiction 2012;107:1482-92.

9. Cleary BJ, Donnelly J, Strawbridge J, et al. Methadone dose and neonatal abstinence syndrome—systematic review and meta-analysis. Addiction 2010;105:2071-84.

10. Dashe JS, Jackson GL, Olscher DA, Zane EH, Wendel GD. Opioid detoxification in pregnancy. Obstet Gynecol 1998;92:854-8.

11. Dashe JS, Sheffield JS, Olscher DA, Todd SJ, Jackson GL, Wendel GD. Relationship between maternal methadone dosage and neonatal withdrawal. Obstet Gynecol 2002;100:1244-9.

12. Jones HE, O'Grady KE, Malfi D, Tuten M. Methadone maintenance vs methadone taper during pregnancy: maternal and neonatal outcomes. Am J Addict 2008;17:372-86.

13. Jones HE, Johnson RE, Jasinski DR, et al. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. Drug Alcohol Depend 2004;75:253-60.

14. Amato L, Davoli M, Ferri M, Ali R. Methadone at tapered doses for the management of opioid withdrawal. Cochrane Database Syst Rev 2013;2:CD003409.