

## Detoxification from opiate drugs during pregnancy

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**BACKGROUND:** The current recommendation regarding the management of a pregnant patient with opioid dependence is not to perform detoxification during pregnancy because of a potential risk for preterm labor, fetal distress, or fetal demise.

**OBJECTIVE:** The objective of the study was to evaluate the safety of full opiate detoxification during pregnancy in a large number of patients through 4 different methods and analyze the rate of newborn treatment of neonatal abstinence syndrome for each method.

**STUDY DESIGN:** This was a retrospective analysis of data collected prospectively during ongoing prenatal care of opiate-addicted pregnant women. Data were analyzed for pregnancy complications including fetal demise and preterm labor of opiate-addicted pregnant women who underwent detoxification during pregnancy through 4 different methods: acute detoxification of incarcerated patients; inpatient detoxification with intense outpatient follow-up management; inpatient detoxification without intense outpatient follow-up management; and slow outpatient buprenorphine detoxification. The rates of newborns treated for neonatal abstinence syndrome were also assessed for each group.

**RESULTS:** Over 5.5 years, 301 opiate-addicted pregnant patients were fully detoxified during pregnancy with no adverse fetal outcomes related to

detoxification identified. There were 94 patients who delivered newborns treated for neonatal abstinence syndrome (31%). There was an 18.5% rate of neonatal abstinence syndrome in the 108 acutely detoxified while incarcerated, a 17.4% rate of neonatal abstinence syndrome in the 23 who had inpatient detoxification with intense outpatient follow-up management, a 17.2% rate of neonatal abstinence syndrome in the 93 who went through slow outpatient buprenorphine detoxification, but a 70.1% rate of neonatal abstinence syndrome in the 77 who had inpatient detoxification without intense outpatient follow-up management.

**CONCLUSION:** With these data and other published studies, more than 600 patients have been reported to detoxify from opiates during pregnancy with no report of fetal harm related to the process. These data highly suggest that detoxification of opiate-addicted pregnant patients is not harmful. The rate of neonatal abstinence syndrome is high but primarily when no continued long-term follow-up occurs. Once a patient is drug free, intense behavioral health follow-up is needed for continued success.

**Key words:** decreasing neonatal abstinence syndrome, opiate detoxification, substance abuse in pregnancy

The current obstetric practice is not to withdraw opiate-addicted pregnant women during pregnancy.<sup>1</sup> This recommendation states that opiate detoxification during pregnancy is associated with an increased risk for stillbirth, fetal distress, premature labor and a high rate of relapse.<sup>1</sup> The fetal concerns primarily stem from 2 1970s case reports that suggested fetal harm from detoxification.<sup>2,3</sup> Several studies since these 2 publications have reported on detoxification during pregnancy with minimal fetal harm identified.<sup>4-8</sup>

Opiate addiction in Appalachia has greatly increased over the past 5 years and is at epidemic proportions in east

Tennessee.<sup>9</sup> As expected, neonatal abstinence syndrome is also at all-time highs. In Tennessee, nearly 1000 neonates are treated for neonatal abstinence syndrome at a cost of more than \$60 million annually.<sup>10,11</sup> Because of these health care concerns, our institution has actively promoted opiate detoxification during pregnancy over the past 5–6 years.

The primary study purpose was to evaluate the safety of opiate detoxification during pregnancy because of continued concern that this process may be harmful to the fetus. A secondary study purpose was to assess the rate of delivering a neonate that was treated for neonatal abstinence syndrome.

### Materials and Methods

This study was a retrospective analysis of data collected prospectively during ongoing prenatal care of opiate addicted pregnant women managed by the Maternal-Fetal Medicine Department at the University of Tennessee Medical Center (Knoxville, TN). Data were evaluated for fetal complications of

intrauterine fetal demise, fetal distress, and preterm labor leading to delivery in pregnancies that underwent detoxification of opiate addiction during pregnancy.

Four different methods occurred but were not specifically compared with each other because there was no randomization and the treatment methods varied because of circumstances that could not be controlled. Group 1 consisted of incarcerated patients. These pregnant women underwent acute detoxification involuntarily because the jail program in east Tennessee has no ability to provide opiates to prevent or perform an opiate-assisted medical withdrawal. The physician who oversees the incarcerated patients can treat symptoms of withdrawal with antiemetic agents, antidiarrheal drugs, and clonidine, but no opiates are provided. Furthermore, fetal monitoring is also not available and was not performed during the detoxification process, although fetal heart tones were intermittently auscultated. These patients did have excellent prenatal follow-up (while incarcerated) because

**Cite this article as:** Bell J, Towers CV, Hennessy MD, et al. Detoxification from opiate drugs during pregnancy. *Am J Obstet Gynecol* 2016;215:374.e1-6.

0002-9378/\$36.00

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<http://dx.doi.org/10.1016/j.ajog.2016.03.015>



Related editorial, page 258.

the jail system assured the scheduling of office visits and provided guaranteed transportation to and from appointments. However, if the patient was released from incarceration prior to delivery, responsibility for prenatal care visits would fall back on the patient and missed appointments would occur in some cases, but all patients were still delivered by the maternal-fetal medicine group.

The second and third groups went through an inpatient drug detoxification program that uses buprenorphine and fully detoxifies the patient in 5–8 days, treating other physical symptoms as they develop. The majority of these patients (>90%) were addicted to prescription opiates (such as oxycodone, oxymorphone, and hydrocodone) obtained through diversion. When admitted, they would be treated with buprenorphine and then rapidly tapered. Again, fetal monitoring was not performed during the process, but heart tones were intermittently auscultated. Once fully detoxified, which occurred in every case, an attempt is made to place the patient in an intense behavioral health program that involves either a home that allows for the patient to stay (with her children) that is monitored daily or a daily 8 hour program that the patient participates in Monday through Friday. These inpatient detoxified patients that have intense behavioral health follow-up make up group 2. Unfortunately, the available spaces for these intense behavioral health programs are greatly limited, and many patients cannot be accommodated. Thus, inpatient detoxification patients that are not followed with intense outpatient follow-up management make up group 3.

The fourth group involves the outpatient slow buprenorphine detoxification program, which is performed by a few clinics in the East Tennessee area that will stabilize the patient on a maintenance dose and then slowly taper them down to zero over 8 to 16 weeks depending on the motivation of the patient and the gestational age of the pregnancy. Once fully detoxified, these patients are maintained in continued behavioral health follow-up.

Because the study purpose was to evaluate the safety of opiate detoxification during pregnancy, only patients who were fully detoxified were included. All of the patients in groups 1, 2, and 3 were fully detoxified based on the process of their grouping. Some of the patients who were managed in the outpatient buprenorphine group were not successful at becoming fully detoxified, and these unsuccessful patients are part of another ongoing study.

To make the assessments equal between the groups, only those who completely detoxified in this outpatient group were included and make up group 4.

No other exclusion criteria were included. For definition purposes, the trimester for when detoxification occurred was defined based on when the process was fully completed and was easily demarcated for groups 1, 2, and 3 because of the short duration. For group 4, because the detoxification process occurred over a period of weeks, some patients may have begun detoxification in an earlier trimester.

For the secondary study objective, the incidence of delivering a neonate that was treated for neonatal abstinence syndrome was also collected for each method to determine whether there was any difference in effectiveness at minimizing this condition for the newborn. Relapse rates for all of the study patients were analyzed and relapse was defined as a positive drug screen on admission, an admission by the patient at the time of delivery that she had relapsed, or a positive neonatal meconium test.

Neonatal abstinence syndrome is a reportable condition to the State of Tennessee Health Department. Every newborn at our medical center that is delivered of a mother who is or was taking opiates during the pregnancy, either by history or by positive drug screen on admission, is followed up by the neonatal intensive care physicians for 3–5 days. Finnegan scores<sup>12</sup> are performed and if a score of  $\geq 10$  is obtained twice, 3 hours apart, or  $\geq 12$  once, then the diagnosis is made and the newborn is further treated.

Demographics of age, ethnicity, gravidity and parity, gestational age at the time of full detoxification, gestational age at delivery, and newborn outcome with Apgar scores were collected. Admission to the neonatal intensive care unit and development of neonatal abstinence syndrome were also collected.

This study was reviewed and approved by the Institutional Review Board of the University of Tennessee Medical Center (Knoxville). Study patients were obtained during a 5.5 year period from 2010 to 2015. Comparisons were conducted by  $\chi^2$ , Fisher exact, and Student *t* test where applicable, and  $P < .05$  was considered significant.

## Results

A total of 301 opiate-addicted pregnant patients were fully detoxified during pregnancy with no adverse fetal outcomes related to detoxification identified. Demographics are seen in [Table 1](#). There were no differences in mean maternal age, maternal age range, or the number of patients under the age of 30 years. However, as depicted, 3 of 4 patients were younger than 30 years of age, consistent with what has previously been reported.<sup>9</sup>

The majority of patients in each group were multiparous, with a 78% rate for the entire study population. Group 1 had a statistically higher number of multiparous patients when compared with groups 2 and 3 at  $P = .008$ . Additionally, 88% of the entire study population was white. There were a statistically higher number of African-Americans in group 1 compared with the other groups ( $P < .01$ ).

[Table 1](#) also depicts the gestational age at the time of detoxification and the admission rate to the neonatal intensive care unit. Of the 301 patients, there were 28 detoxified in the first trimester from 5 through 13 weeks' gestation. Two intra-uterine fetal demises occurred in this group and both were patients acutely detoxified. One involved a patient who was acutely detoxified at 10 weeks' gestation but had an intrauterine fetal demise at 18 weeks' gestation with a placental abruption. She was still incarcerated and her drug screen at the time of

TABLE 1

**Demographics, gestational age at the time of detoxification, neonatal intensive care unit admission, and pregnancy outcome of the opiate detox study population**

Demographics	Group 1	Group 2	Group 3	Group 4	Total
Number	108	23	77	93	301
Mean maternal age, y	26.9 ± 3.7	26.4 ± 3.5	26.6 ± 3.6	27.2 ± 3.9	26.8 ± 3.7
Maternal age range, y	18–43	17–38	18–39	17–39	17–43
Maternal age <30 y	82 (76%)	18 (78%)	55 (71%)	67 (72%)	222 (74%)
Multiparity	94 (87%)	14 (61%)	54 (70%)	73 (78%)	235 (78%)
White	85 (79%) <sup>a</sup>	22 (96%)	74 (96%)	84 (90%) <sup>a</sup>	265 (88%)
African-American	22 (20%)	1 (4%)	3 (4%)	8 (9%)	34 (11%)
Gestational age at detoxification and NICU admission					
Detoxification first trimester, 5–13 wks gestation	10 (9%)	4 (17%)	12 (15%)	2 (2%)	28 (9%)
Detoxification second trimester, 14–27 wks gestation	65 (60%)	10 (43%)	36 (47%)	37 (40%)	148 (49%)
Detoxification third trimester, ≥28 wks gestation	33 (31%)	9 (39%)	29 (38%)	54 (58%)	125 (42%)
Preterm deliveries prior to 37 wks gestation	21 (19%)	3 (13%)	13 (17%)	16 (17%)	53 (17.6%)
Neonatal intensive care unit admission	32 (30%)	5 (22%)	60 (78%)	22 (24%)	119 (40%)
Pregnancy outcome					
Rate of NAS	20 (18.5%)	4 (17.4%)	54 (70.1%)	16 (17.2%)	94 (31%)
Rate of relapse <sup>b</sup>	25 (23.1%)	4 (17.4%)	57 (74.0%)	21 (22.5%)	107 (36%)

Group 1 consisted of acute detoxification (incarcerated patient). Group 2 consisted of inpatient detoxification with intense behavioral health follow-up. Group 3 consisted of inpatient detoxification without intense behavioral health follow-up. Group 4 consisted of slow outpatient buprenorphine detoxification.

NAS, neonatal abstinence syndrome; NICU, neonatal intensive care unit.

<sup>a</sup> One Hispanic in group 1 and one Asian in group 4; <sup>b</sup> Relapse rate is defined as a positive drug screen on admission, an admission by the patient at the time of delivery that she had relapsed, or a positive neonatal meconium test (and includes all of the patients who had neonates treated for neonatal abstinence syndrome).

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the loss was negative. The second was also acutely detoxified at 12 weeks' gestation and was found to have an intrauterine fetal demise at 34 weeks' gestation of a fetus with hydropic changes. Autopsy was declined and her drug screen and testing were all negative at the time of diagnosis as well.

There were 148 detoxified in the second trimester from 14 weeks through 27 weeks, and 125 detoxified in the third trimester from 28 weeks' gestation and greater with no episodes of intrauterine fetal demise. There were no cases of preterm premature rupture of membranes or preterm delivery that occurred during the process of detoxification.

Regarding the rate of treatment for neonatal abstinence syndrome (seen at the bottom of the Table 1), 94 patients (31%) overall delivered a neonate that was treated for neonatal abstinence syndrome. Of the 301 patients, 108 were acutely detoxified while incarcerated

(group 1 patients), and 20 cases of neonatal abstinence syndrome occurred following delivery, for a rate of 18.5%.

There were 100 patients who were detoxified as an inpatient with 23 who were placed in long-term follow-up behavioral health programs following the detoxification (group 2 patients), and 4 newborns had neonatal abstinence syndrome after delivery for a rate of 17.4%. The remaining 77, who were without intense outpatient follow-up management (group 3 patients), delivered 54 neonates that were treated for neonatal abstinence syndrome for a rate of 70.1%. Finally, there were 93 who were fully detoxified with buprenorphine as an outpatient (group 4 patients) and 16 newborns were diagnosed with neonatal abstinence syndrome for a rate of 17.2%.

A positive drug screen on admission, an admission by the patient at the time of delivery that she had relapsed, or a

positive neonatal meconium test was found in all of the neonates treated for neonatal abstinence syndrome. Table 1 depicts the numbers of women in each group who relapsed back to taking opiates as defined. As shown, relapse is higher than the rate of treatment for neonatal abstinence syndrome for each group because there were some that relapsed as defined, but the neonates did not experience neonatal abstinence syndrome.

Excluding group 1 patients who were acutely detoxified following incarceration, group 2 and group 4 patients combined represent those who were fully detoxified and remained in long-term behavioral health settings. The rate of neonatal abstinence syndrome in this combination was 20 in 116, or 17.2%. If this is compared with group 3 (those detoxified and managed without intense outpatient follow-up management) with a rate of 54 in 77, or 70.1%,

the difference is highly significant at  $P < .0001$ .

The overall delivery rate prior to 37 weeks' gestation (53 patients) is somewhat high at 17.6%, but 28 of these (53%) were inductions of labor for a diagnosis of severe intrauterine growth restriction. Interestingly, at the time of delivery, the fetal weight was  $<5\%$  in only 16 of the 28 (57%). The preterm delivery rates were no different based on when detoxification occurred. Likewise, 40% of the newborns were admitted to the neonatal intensive care unit, but this includes the 31% treated for neonatal abstinence syndrome. The remaining 9% primarily included admissions for prematurity or for extended observation for signs of neonatal abstinence syndrome.

## Comment

### Principal findings

These data highly suggest that detoxification from opiates during pregnancy is not harmful. Additionally, the rate of treatment for neonatal abstinence syndrome is less if long-term behavioral health management occurs in this patient population once the patient is fully off opiates. Whether this treatment management should become common practice in obstetrics will take further study as to whether detoxification/long-term behavioral health programs can be universally developed, implemented, and funded.

### Meaning of our observations as it relates to other studies

The standard of care for more than 35 years in obstetrics has been to take opiate-addicted pregnant patients and place them in a methadone maintenance program. More recently, buprenorphine maintenance has also been recommended as another treatment option for this population.<sup>1</sup> The concern for opiate detoxification during pregnancy has largely been a safety issue for the fetus. Other reported concerns involve a high rate of relapse following detoxification and better prenatal care follow-up for the patients in the maintenance programs.<sup>1,7</sup>

The fetal concerns are primarily based on 2 cases reports from the

1970s. Rementeria and Nunag<sup>2</sup> in 1973 reported a stillbirth that occurred in a patient who had withdrawal symptoms shortly before delivery at 39 weeks' gestation. This publication also discussed the varying data in the literature from the preceding 10 years regarding stillbirth and meconium stained amniotic fluid in drug-addicted pregnancies. The author's conclusion was that many of these detoxified women relapse, and because of a greater risk of withdrawal, methadone maintenance programs should be encouraged.

The second case report was from Zuspan et al in 1975.<sup>3</sup> This study reported on elevated levels of epinephrine and norepinephrine (suggesting fetal stress) obtained during serial amniotic fluid assessments over a 10 week period from a patient being detoxified from methadone during the pregnancy. Thus, opiate detoxification during pregnancy was not recommended.

There have been 5 studies that have reported on opiate detoxification during pregnancy since the 2 case reports. Maas et al<sup>4</sup> in 1990 reported on 57 patients who joined an outpatient methadone detoxification program during a 7 year period, and 17 (30%) became drug free. Only 2 cases of neonatal abstinence syndrome (12%) occurred in these 17 patients vs a 75% rate in the ones not successful. No adverse outcomes because of detoxification were reported.

Dashe et al<sup>5</sup> in 1998 reported on 34 pregnant patients who elected to undergo inpatient methadone detoxification during a 7 year period, and 20 (59%) were successful. Three of these (15%) were treated for neonatal abstinence syndrome. There were no cases of fetal demise, and no cases had fetal distress during detoxification. Luty et al<sup>6</sup> in 2003 reported on 101 patients who underwent an inpatient methadone detoxification program spanning 12 years. One spontaneous abortion occurred in 5 patients detoxified in the first trimester, but no other losses occurred in those detoxified in the second and third trimesters. Neonatal abstinence syndrome rates were not reported.

Jones et al<sup>7</sup> in 2008 reported on 175 pregnant patients treated at a

comprehensive care center devoted to addiction in pregnancy. Of these, 95 went through methadone-assisted withdrawal during either a 3 day or 7 day program vs 80 who ultimately were maintained on methadone. The overall relapse rate of the 95 detoxified patients was 54%. No increased risk of fetal loss or preterm birth was reported with detoxification, but the patients maintained on methadone attended more obstetrical visits.

Lastly, Stewart et al<sup>8</sup> in 2013 reported on 95 pregnant patients that elected to undergo inpatient methadone detoxification during a 6 year period, and 53 (56%) were successful. The rate of neonatal abstinence syndrome in the detoxification group was 10% compared with 80% in the patients who were not successful, and this difference was significant at  $P < .001$ . There were no cases of fetal demise, and no cases had fetal distress during the detoxification process.

Our primary study purpose was to determine whether full detoxification from opiates during pregnancy was harmful to the fetus. With our 301 study patients and the patients reported in these 5 follow-up studies, more than 600 patients have undergone detoxification during pregnancy, with no report of intrauterine fetal demise or preterm delivery related to the process.

The secondary study question involved the rates of neonatal abstinence syndrome treatment in each of the groups. No study including this report has found an absence of neonatal abstinence syndrome in the delivered newborns of mothers who were fully detoxified. All of the newborns treated for neonatal abstinence syndrome in our study came from mothers who had relapsed. This included the 4 patients in group 2 who were living in a behavioral health home or seen on a daily basis. This confirms that treating addiction is difficult and failures will occur, whether it is alcohol, tobacco, or opiates. Furthermore, relapse rates are high in nearly all of the studies to date. However, our data demonstrate that relapse can be substantially reduced if detoxified pregnant women are followed up in intense



behavioral health programs once they become drug free.

### Clinical and research implications

An important question involves long-term outcomes for neonates born of drug-addicted mothers. Currently there are no long-term follow-up studies on newborns delivered of mothers who were detoxified during pregnancy, and this warrants further evaluation. There are studies that have evaluated long-term outcome in infants born of drug-addicted mothers including those on methadone, but it is always difficult to know how much effect is related to the in utero drug exposure vs the lifestyle in which these children grow up.<sup>13,14</sup>

At the present time, if a pregnant patient is found to be addicted to opiates, she is most likely to be referred to a methadone maintenance program, a process whereby the opiate intake is managed by the maintenance program while prenatal care is performed by the obstetrical provider. For detoxification during pregnancy, if the process is to remain similar, systems would need to be developed, such that the opiate-addicted pregnant woman is referred to the drug detoxification/long-term behavioral health program for drug management, and the prenatal care would occur with the obstetrical provider.

These drug detoxification/long-term behavioral health programs currently do not exist nationwide and therefore would need to be created and funded if any success is expected. Nevertheless, the cost of treating 1 neonate for neonatal abstinence syndrome in the state of Tennessee is about \$63,000 as of 2011.<sup>10</sup> In Tennessee, nearly 1000 newborns are treated for neonatal abstinence syndrome, leading to a health care cost of more than \$60 million annually for the state.<sup>11</sup> Therefore, developing and providing long-term behavioral health for pregnant women once they are successfully detoxified will require funding, but the cost savings on decreasing the number of newborns treated for neonatal abstinence syndrome would easily overshadow these expenses.

### Strengths and limitations

The strength of this study is the large number of patients fully detoxified during pregnancy through different processes that could also assess the rate of neonatal abstinence syndrome based on the method of detoxification. This study, however, has several limitations. Because of the sensitive nature of drug addiction during pregnancy, to obtain approval from the jail system, the inpatient detoxification program, and the institutional review board, once the collected data were analyzed, all patient identification had to be removed from the database. Thus, no further information or further follow-up of patients can take place.

Second, this process cannot be instantly incorporated into routine prenatal care because it has taken an extensive period of time to develop outpatient detoxification and long-term behavioral health programs in east Tennessee, and this will likely take time in other areas of the country if the decision is made to begin a similar program.

Third, the incarcerated patients are unique in this study, and this process will not likely be extrapolated to routine prenatal care. These patients, however, can be used to show that acute detoxification during pregnancy does not result in a large number of poor outcomes, which was the primary goal of this study. Unfortunately, the timing of when patients were released from jail could not be accurately obtained to make any conclusion on the rate of relapse once these patients were no longer incarcerated.

Fourth, our buprenorphine population is also different in that some who attempt complete detoxification do not fully succeed. However, because those in the jail and those detoxified as an inpatient were all drug free at a given point in time during the pregnancy, we included only buprenorphine patients who were completely drug free at a given point in time during the pregnancy. Those who were maintained on some amount of buprenorphine are being evaluated separately to see whether there is a

dosage level whereby the risk of neonatal abstinence syndrome is minimal.

A fifth limitation is that complete safety of detoxification in the first trimester cannot be addressed with our data because of small numbers. Intrauterine fetal demise occurs in all groups of pregnant patients, including the low-risk population,<sup>15</sup> and an intrauterine fetal demise will eventually occur in an opiate-addicted pregnant patient who undergoes detoxification, but these data do not suggest that the process of detoxification would be the cause.

### Conclusion

In conclusion, detoxification of opiate-addicted pregnant women does not appear to be harmful. In addition, the rate of neonatal abstinence syndrome can also be reduced if continued long-term behavioral health follow-up occurs once a patient is drug free. ■

### Acknowledgment

We thank Beth Weitz, WHNP, and Stephanie Porter, WHNP, for their meticulous research coordination throughout this project.

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Received Jan. 30, 2016; revised March 9, 2016; accepted March 10, 2016.

This study was supported by the Blue Cross Blue Shield Research Foundation.

The authors report no conflict of interest.

Presented orally (number 96) at the 2016 annual meeting of the Society for Maternal-Fetal Medicine, Atlanta, GA Feb 1-6, 2016.

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