

# Opiate Use Disorder in Pregnancy – A Relook at Management Options

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📁 Nursing

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## Objectives

1. Discuss the impact of opiate use disorder in the United States and in pregnancy.
2. Describe the effect that opiate use disorder has on a pregnancy regarding medical care and complications that can occur in pregnancy.
3. Explain the background behind why detoxification during pregnancy was thought to be harmful to the fetus and discuss why the option of detoxification during pregnancy is possible.
4. Describe the potential effect of chronic opiate exposure during pregnancy might have on neonatal brain size and risk for future concerns.

## Article

### Opiate Use Disorder in Pregnancy – A Relook at Management Options

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2. Describe the effect that opiate use disorder has on a pregnancy regarding medical care and complications that can occur in pregnancy.
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## Incidence and General Overview

There are numerous drugs that can be abused including tobacco, alcohol, marijuana, opiates, stimulants, sedatives, and hallucinogens. However, opiates have become a major problem in the United States in the past 10 to 15 years. To begin, it is important to discuss definitions. An addict is a person who habitually or obsessively uses a drug, whereas dependence means the drug needs to be taken to avoid withdrawal. Tolerance is a term that is used to designate the fact that higher and higher doses are ultimately needed in order to reach the same psychologic and emotional affect. Opiates or narcotics unfortunately, have all 3 of these.

The statistics regarding opiate use disorder in the United States are staggering. Eighty percent (80%) of all of the opiates used in the world are consumed in the United States; however, the U.S. only has 5% of the world's population. According to data from the Centers for Disease Control (CDC), deaths in 1999 outside of medical causes (such as cancer and heart disease) listed motor vehicle accidents as number 1 at 44,000 followed by suicide at 30,000, then firearms at 28,000, and drug overdoses were in 4th place at 19,000. Eight years later in 2007, motor vehicle accidents were still number 1 at 45,000 but drug overdose deaths had doubled and were now the 2nd most common non-medical cause for death at 38,000. The data from 2014 now show that drug overdose deaths are the leading cause of non-medical related deaths in the United States exceeding motor vehicle accidents. The number of deaths in the United States from drug overdoses reached 46,000, whereas motor vehicle accidents were stable at 45,000.

Another publication from the CDC reported that in 2010 there were 15,323 drug overdose deaths in the United States in women. This averages out to about 10 deaths per 100,000 population for women. In addition, there were close to 1 million emergency room visits that year by women that involved illicit drugs and 80% of these women were of childbearing age. Of those 15,323 deaths, 6,631 involved opiate prescription pain medications (not heroin). Comparing this to 1999, 11 years earlier, there were only 5,591 drug overdose deaths in women (showing a three-fold increase in that 11-year span) and only 1,287 of those deaths involved an opioid prescription pain medication. Therefore, from 1999 to 2010 the drug overdose deaths from prescription opiate medications increased five-fold. Another astounding statistic from 2010 is that enough opioid pain relievers were sold in the United States to medicate every adult in the United States (again every single adult in the United States) with 5 mg of hydrocodone every 4 hours for one month. Therefore, the use of opiates and their affect on the population is overwhelming in the United States.

As expected, with an increase in opiate use by adults, there has been an increase in use seen in pregnant women and this leads to an increase in neonatal abstinence syndrome (NAS). In a study by Patrick, et al, the incidence of maternal opiate use in the United States in the year 2000 was about 1 per 1000 births and this increased to more than 5 per 1000 births in 2009. Likewise in this same time period, the incidence of NAS increased from about 1 per 1000 newborns to about 3.5 per 1000 newborns in 2009. The mean hospital charge in the United States for treating one child with NAS is in the range of \$60,000. Thus, the annual healthcare costs for treating this huge increase in NAS exceeds a billion dollars.

The exact reason behind why there has been a massive increase in opiate use disorder in the United States is not completely certain. However, in 1999/2000 the Federal Government did not believe that chronic pain issues were being adequately addressed by the healthcare system in the United States. Therefore, Congress created "The Decade of Pain Control and Research – 2001 through 2010" through a law passed in October 2000 – public law 106-386. Unfortunately, one of the outfalls of this law was the opening of more than 3000 pain clinics across the United States during this 10-year period, and with this came a massive increase in the number of prescriptions written for opiates that frequently end up being diverted to the street. The difficulty in dealing with chronic pain is "how does one truly measure pain"? There is no objective test or medical device that can be utilized to truly determine the fact that a patient has pain nor can anyone determine the true level of pain. Pain, and its severity, is based on what a patient states or describes. Therefore, changes need to be made that allow pain treatment to involve other modalities such as anesthetic blocks and physical therapy rather than prescriptions for opiate medications.

## **Prenatal Care Issues**

In evaluating the strength of opiate drugs, morphine is usually listed as the standard, and the strength of other opiates are compared to morphine equivalence. Two commonly prescribed opiate medications are hydrocodone and oxycodone. Hydrocodone is about 60% the strength of morphine, whereas oxycodone is 1 ½ times the strength of morphine. To say this another way, a 10 mg dose of oxycodone is equivalent to about 15 mg of morphine. Heroin is in the range of 4 times the strength of morphine and methadone is about 5 times the strength. Another common drug that is frequently abused on the street is oxymorphone (often called Opana) which is about 7 times the strength of morphine. Buprenorphine (which is primarily used to treat opiate use disorder along with methadone) is 40 times the strength of morphine. Therefore an 8 mg dose of buprenorphine (trade names of Subutex, Buprenex, Belbuca, and Butrans) is equal to 320 mg morphine equivalents. Buprenorphine and methadone are often used in treating opiate use disorder because of their long plasma half-life. The drug half-life for methadone is approximately 24 hours whereas the drug half-life for buprenorphine is approximately 36 hours. The primary purpose behind using these medications is to prevent a person with opiate use disorder from "craving" and obtaining another dose of opiates that is often purchased illicitly from the "street" where the purity of the drug can vary and/or may be mixed or substituted with some other drug.

In treating a patient with opiate use disorder there are many signs and symptoms of drug withdrawal. Most healthcare providers are aware of the more significant ones of abdominal pain, excessive sweating, tachycardia, hypertension, diarrhea, nausea and vomiting, and myalgias. However, more subtle signs of opiate withdrawal can involve thirst, rhinorrhea (runny nose), lacrimation (watery eyes), tremors, and frequent yawning.

Prenatal care for opiate use disorder is also very complicated. Many of these women have little or no prenatal care and oftentimes their visits are intermittent. These pregnant patients often have poor nutritional status with poor weight gain and are often unemployed. Their family histories are often complicated by physical, emotional, and/or sexual abuse; all of which leads to a low self-esteem. In addition, their habit of obtaining illicit substances off the street

produces a pattern of altering the truth and when this extends to medical care the reliability of their medical history is often low.

Likewise, these patients often have numerous obstetrical complications. In evaluating pregnant women with opiate use disorder, there is a higher rate of preterm delivery related to premature labor and premature rupture of the membranes. There is a higher rate of intrauterine growth restriction. There is an increased risk for intrauterine fetal demise or stillbirth and a higher rate of sexually transmitted diseases involving chlamydia, gonorrhea, herpes, syphilis, hepatitis B, hepatitis C, and HIV. Lastly, there is a higher cesarean section rate in this population. Regarding birth anomalies, the overwhelming majority of studies have not found a higher rate of birth defects and narcotics are usually listed as Category C drugs, which basically means that it is not fully certain as to whether or not opiates can produce birth anomalies. There was one study, however, by Broussard, et al, in 2011 that evaluated a large population of pregnancies exposed to opiates and they did find a slight increased risk for cardiac defects of atrial septal defect and ventricular septal defect, as well as, an increased risk for gastroschisis and neural tube defects. Never-the-less, these increased risks were very slight and these anomalies have not been seen in other studies evaluating opiates and the risk for fetal anomalies.

Intrauterine growth restriction (IUGR) has always been listed as a complication of pregnancies complicated by opiate use disorder. Intrauterine growth restriction is classified as either symmetric or asymmetric. Symmetric usually means that it is related to the fetus and this is often constitutional (because both parents are small) or can be related to chromosome abnormalities, genetic disorders, or other fetal complications such as viral infections with cytomegalovirus virus, etc. The other form of intrauterine growth restriction is asymmetric and this is felt to be caused by the placenta. In this type of IUGR, the bones are usually spared and on ultrasound evaluation the long bone measurements as well as head measurements are closer to the actual dates, whereas the abdominal circumference can lag by several weeks. These asymmetric IUGR pregnancies are also at risk for developing a decrease in amniotic fluid (oligohydramnios) with an increased risk for fetal compromise. However, a published study in 2015 (Visconti and Towers et al.) assessed a large number of infants that were treated for NAS and the type of IUGR was somewhat different in that the long bone measurements and head measurements lagged, whereas the abdominal circumference was more consistent with dates. This leads to a question of whether longstanding opiate use can affect bone growth and/or brain growth. The issue of smaller head circumference and brain growth will be discussed later in this article.

### **Detoxification during Pregnancy**

With the rising rate of opiate use disorder and the resulting increase in newborns being treated for NAS, the question of opiate detoxification during pregnancy has been reexamined. For nearly 40 years, it has been recommended that detoxification during pregnancy NOT be performed due to a high risk for fetal distress and fetal demise. The recommendation is to place these patients in drug maintenance programs such as methadone and more recently buprenorphine, which will assure drug purity, improve contact with the medical community, and control dosages. This treatment program usually results in improved prenatal care visits. However, when examining the literature as to the origin of this longstanding recommendation, it became apparent that this was related to 2 single case reports in the literature. The first case report in 1973 came from Rementeria and Nunag. This case report describes a stillbirth that occurred in a patient at around 39 weeks gestation who shortly before her admission had undergone withdrawal symptoms and it was felt that the fetal demise was related to the withdrawal at this late gestational age. Their manuscript also reviewed the poor outcomes seen in pregnant women abusing opiates in general (primarily heroin) and the higher rate of stillbirth in this population suggesting that this occurs from pregnant women undergoing withdrawal because they are not able to obtain a consistent supply of opiates off the street. The second paper was published 2 years later in 1975 by Zuspan, et al. This paper describes a patient who was undergoing detoxification with methadone and serial amniocentesis procedures were performed to evaluate the amniotic fluid for epinephrine and norepinephrine levels. As detoxification was taking place, the levels of epinephrine and norepinephrine increased in the amniotic fluid suggesting that the fetus was under stress. Therefore the detoxification process was stopped and she was maintained on methadone and ultimately delivered at 39 weeks gestation. The conclusion from this case report as well as the one from 1973 was that detoxification during pregnancy was stressful to the fetus and could lead to stillbirth and therefore opiate detoxification should not occur during pregnancy. Therefore the standard of care since the late 1970's is to take patients with opiate use disorder and get them into a drug maintenance program for the duration of the pregnancy.

However, in 1990, Maas, et al, published an article regarding the detoxification of 57 mothers in a methadone program. This study spanned 7 years. Of those 57 mothers, 17 were successful in detoxification and only 2 newborns were treated for NAS (12%). The success rate of their detoxification program was only 30%. Of the 40 patients (70%) that were

not successful in detoxification the rate of NAS was 75%. However, there were no fetal deaths and no adverse pregnancy outcomes in this population. Eight years later in 1998, Dashe, et al, published a second study on detoxification using methadone of 34 mothers during a 7 year period. In their study, there were 20 successes (approximately 60%) and only 3 cases of NAS occurred in the delivered newborns for a rate of 15%. There were no fetal deaths and no cases of fetal distress.

Five years after this, Luty, et al, published a 3rd study involving 101 mothers who were detoxed over a 12-year period through an inpatient methadone program. No data was supplied in this manuscript regarding the rates of NAS or relapse but there were no fetal deaths in the patients detoxed in the second or third trimester. There was one spontaneous pregnancy loss out of 5 patients detoxed in the first trimester. Again there was no way to determine if this one first trimester loss was related to the detoxification since the first trimester spontaneous pregnancy loss rate in the United States is in the 15-20 percent range. In 2008, Jones, et al, published the 4th paper that discussed 175 patients that were treated in a comprehensive care program over 7 years. Overall, 95 women went through methadone assisted withdrawal either in a 3-day or 7-day program. The relapse rate in this group was 54% and the rate of NAS overall was 28%. Of the 80 patients that were maintained on methadone, the rate of NAS was similar to those that went through detoxification. This study reported that there were no fetal losses or preterm births but because prenatal care visits were better in the maintenance group, the conclusion was that methadone maintenance was better. However, they did not identify any harm to the fetus from the detoxification process. Lastly, in 2013, Stewart, et al, reported on 95 patients that were detoxed with methadone over a 6-year period. The detoxification occurred over a 15-25 day period. They had 53 successes (56%) and the rate of NAS in this group was only 10%. In 42 patients that were not successful, the rate of NAS was 80%. The difference between these groups was highly significant at  $P < .001$ . Again no fetal deaths or fetal distress occurred during the detoxification process.

These 5 studies have largely been missed because they were published in 5 different journals over a span of 23 years. However, a large study was recently published (2106) by Bell and Towers et al, and this study evaluated 301 women who went through 3 methods of detoxification during pregnancy that produced 4 study groups. The purpose of the study was to try and fully answer the question as to whether detoxification was harmful to the fetus. The number of patients in this study that went through full detoxification was almost equal to the number detoxed in the 5 previous published studies. In this most recent study, group 1 involved patients who underwent acute detoxification because they were incarcerated. The number of patients in this group was 108. Group 2 involved patients that had detoxification as an inpatient that were allowed to enter an intense outpatient behavioral health program. Group 3 were patients who had inpatient detoxification but following their treatment were not able to get into an intense outpatient behavioral health follow-up program. Group 4 involved patients who underwent a slow outpatient buprenorphine detoxification process in conjunction with behavioral health. In this study, there were 28 patients detoxified in the first trimester and there were 2 fetal losses in this group. However, both of these were not related to detoxification. The 1st patient underwent full detoxification at 10 weeks gestation but 2 months later had a fetal demise from a placental abruption. She was still incarcerated at the time and her drug screen was negative and again this was unrelated to the detoxification process. The 2nd patient was fully detoxified at 12 weeks gestation and had an IUFD at 34 weeks gestation from a fetal anomaly; again, unrelated to the detoxification process. There were 148 patients who underwent detoxification in the second trimester with no fetal losses and 125 patients that were detoxified in the third trimester again with no fetal losses. There were no cases of preterm labor or preterm delivery or premature rupture of the membranes during the detoxification process.

When analyzing the rates of NAS in these 4 groups, those that were detoxified in jail had an 18% rate and this primarily occurred in those newborns delivered of mothers that were released from the jail who relapsed. In those newborns delivered of women that were still incarcerated, no cases of NAS occurred. Group 2 had an NAS rate of 17% and again this was a group that had inpatient detoxification followed by intense behavioral health follow-up. Likewise group 4, which was fully detoxified as an outpatient with buprenorphine in conjunction with intense behavioral health, the rate of NAS was 17%. However, group 3, which had inpatient detoxification but was unable to get into intense behavioral health, the NAS rate was 70% basically all related to maternal opiate use relapse. What this study demonstrated was that: 1) detoxification during pregnancy was not harmful to the fetus and combining these patients with the other 5 studies verifies that in over 650 patients, detoxification is not harmful to the fetus; and 2) relapse is common, however, if patients are not followed with intense behavioral health after detoxification is completed. If the 2 groups that had intense behavioral health follow-up (116 patients) are compared with those that did not have the intense behavioral health follow-up (77 patients) the rate of NAS was 17% versus 70% and this difference was highly significant at  $p < .0001$ . Therefore, detoxification during pregnancy is a possible pregnancy management option but should only be performed if intense behavioral health can occur during and after the detoxification process. If detoxification is performed and behavioral is not included, the success rate is very poor and is not recommended.

## Potential Effects on the Neonate beyond NAS

There are still concerns and arguments against detoxification during pregnancy one of which is longterm fetal affects. This is a question that does need further analysis, but has somewhat been looked at on a small scale. In a 2014 study by Haabrekke, et al, head circumferences were assessed in newborns who were delivered of mothers with opiate use disorder and the neonate was treated for NAS. The mean head circumference in this group was 33.9 cm. There were also 22 newborns that were delivered from mothers that detoxified during pregnancy and the mean head circumference was 34.8 cm. The difference between these head circumferences was significant suggesting that the head size was larger if the mother was detoxified during pregnancy. The mean head circumference of the control population (involving newborns not exposed to opiates in utero) was slightly larger at 35.4 cm but the difference between this and the detoxified group did not reach significance. These findings are consistent with the report from Visconti and Towers, et al, published in 2015, which evaluated 322 neonates treated for NAS compared to controls. The mean head circumference < 10th percentile and < 3rd percentile was significantly smaller in the NAS group compared to the control group. Again, these two studies suggest that there could be an opiate affect on brain development and/or size.

Lastly, Walhovd, et al, has published 2 papers on this subject, analyzing brain size in children exposed to opiate drugs in utero. The first was in 2007 and this study evaluated brain sizes from imaging studies of 14 children delivered from opiate addicted women compared to 14 controls. The brain sizes at 9 years of age and greater were smaller in those children exposed to opiates in utero that underwent treatment for NAS compared to those children that were not exposed to opiates. The second study published in 2015 examined 12 children that were delivered of women that were detoxified from opiates during pregnancy comparing their brain sizes to children not exposed to opiates and the brain volumes were similar in size. These authors go on to argue that the 14 children that were delivered and were treated for NAS were actually adopted by middle class families with similar socioeconomic statuses to that of the control children; whereas, the 12 children who were delivered of women that were detoxed during pregnancy were raised by their biological mothers with a lower socioeconomic status. Despite this difference in families, the head circumference appeared to be improved if the child was not exposed to opiates throughout the pregnancy and treated for NAS postdelivery. Therefore, if any questions still exist when dealing with opiate use disorder during pregnancy, it is clear now that opiate detoxification does not produce any signs of fetal distress or increase the risk for intrauterine fetal demise. Further longterm studies need to be performed to determine the effects of continued opiate exposure during pregnancy versus detoxification. However it is very important to understand that detoxification is not recommended if good behavioral health is not also included. A concern with relapse is the risk for overdose and death and this question also needs to be further examined. Likewise, it has not been determined whether there is a lower dose of methadone or buprenorphine where the rate of NAS is minimal. It is possible that patients might be detoxed down to a very low dosage at the time of delivery, but are maintained throughout the pregnancy.

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Dr. Towers is currently Professor and Vice Chair of the Department of Obstetrics & Gynecology at University of Tennessee Medical Center Knoxville in the Division of Maternal-Fetal Medicine. He is still clinically active managing numerous high-risk pregnancies. He is also actively involved in research with over 90 publications in major medical journals. Though his research has spanned many areas in obstetrics, he has primary interests in drugs in pregnancy, infections in pregnancy, fetal heart monitoring, bleeding in pregnancy, and fetal lung maturity.

He has authored a book for consumers regarding the safety of over-the-counter medications that are used in treating the common cold entitled "I'm Pregnant & I Have a Cold – Are Over-the-Counter Drugs Safe to Use?" published by RBC

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