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Methadone for Treatment of Pregnant Opiate Addicted Women: Is There a Safer Alternative? A Review of Literature

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ABSTRACT

Methadone is commonly used for the treatment of pregnant opiate-addicts. But, it can have severe effects on the neonate including Neonatal Abstinence Syndrome, increased length of stay in the neonatal intensive care unit, and intrauterine growth retardation. Neonatal Abstinence Syndrome includes neurological excitability, gastrointestinal dysfunction, and autonomic signs. Because of these adverse effects, studies have been conducted to determine what can help reduce the severe complications caused by methadone. Varied dosages of methadone and alternative medications, such as buprenorphine, slow-release morphine, and others have been studied. Most of the alternative medications, especially buprenorphine, are gaining popularity in Europe where there is a growing problem of opiate use during pregnancy. In the studies comparing methadone and buprenorphine, a slight decline in symptoms of Neonatal Abstinence Syndrome as well as shorter hospital stays for the neonates exposed to buprenorphine was noted. Studies of different dosages of methadone were conducted to determine the lowest methadone dose that is both effective for the mother and safe for the neonate. All of the studies have provided information that is helping in the search for the safest and most effective treatment for opiate addiction. What is known is that helping the mother overcome the addiction is very important. So far, the data collected are not strong enough to make a conclusion on the best choice for treatment. Further research is indicated for methadone itself and also for all its possible alternatives.

INTRODUCTION

Use of illicit opiates, such as cocaine and heroin, in childbearing-age women is an increasing problem in many countries.¹ In the United States, approximately 13% of pregnant women use illicit substances, and 19% of those women use opiate drugs.² Methadone has been used to treat opiate addiction during pregnancy since the 1970s.³ Methadone, which crosses the placenta, is well known to cause the fetus to become dependent on the drug. After birth, the neonate is likely to exhibit some degree of withdrawal symptoms. Even though it is an opiate, methadone use to control opiate addiction during pregnancy does have advantages over heroin, including longer gestational periods and higher birth weights as compared to untreated opiate-addicts.⁴ Methadone, however, can cause a protracted and often severe Neonatal Abstinence Syndrome (NAS) as well as a prolonged and extensive hospital stay in the special care nursery.² Fifty to ninety percent of neonates exposed to methadone and heroin will develop withdrawal symptoms or NAS and up to fifty percent will require pharmacotherapy.⁵ Methadone is important to help the opiate-dependent mother abstain from using heroin or other drugs, but its use needs to be closely monitored by practitioners to help achieve the best outcome for both mother and neonate.

Some degree of withdrawal occurs in all neonates whose mothers were treated with methadone.³ NAS usually includes neurological excitability, gastrointestinal dysfunction, and autonomic signs. Additional symptoms can include poor feeding, sleep-

wake abnormalities, vomiting, diarrhea, tachypnea, irritability, hyperphagia, dehydration, poor weight gain, and seizures. Neonatal mortality, sudden infant death syndrome, and abnormal neurodevelopmental outcomes are also possible.⁶

Methadone is a synthetic opioid with a long half-life that can provide the fetus with an environment for development that is not subject to the fluctuations associated with NAS.⁷ Buprenorphine, an alternative approved for medical withdrawal and medication-assisted therapy, may be beneficial for treating opioid-dependency because of reduced neonatal withdrawal.⁸ Buprenorphine is an opioid partial agonist and is becoming increasingly used in the United Kingdom since being licensed in 1999.⁹

There are several scoring systems used to determine NAS, including the Lipstiz, the Neonatal Abstinence Scoring, and the Neonatal Withdrawal Inventory. These scoring systems provide more objective criteria for assessing neonates and determining treatment.⁶ The onset of symptoms from heroin withdrawal tend to begin within 24 hours after birth, with clinical manifestations initially being mild. Withdrawal from methadone begins between two to seven days after birth and can be delayed up to a month.

REVIEW OF THE LITERATURE

Thirteen studies are being compared to determine the effectiveness and safety of methadone compared to alternatives such as buprenorphine.

Table 1. Comparison of Studies

Author	Purpose	# of Subjects	Inclusion/Exclusion Criteria	Study Design	Conclusions
Fischer G, Ortner R, Rohrmeister K, Jagsch R, Baewert A, Langer M, et al ¹	Comparing the effects of methadone directly to buprenorphine in both the mothers and their neonates.	14 neonates and mothers	Inclusion: patient must be opiate-dependent as described by the DSM-IV, older than 18 years, provide an informed consent, be HIV-negative, and be between weeks 24 to 29 of pregnancy. Exclusion: if they had either severe somatic or other severe psychiatric diseases or a high-risk pregnancy.	Double-blind, double-dummy, randomized control study Inferential statistics, χ^2 , Fisher's exact tests, τ -tests, and the Mann-Whitney test data.	There was earlier onset of NAS in neonates born to the methadone (mean 60 hours) than to the buprenorphine groups (mean 72 hours after last medication)
Dashe J, Sheffield J, Olscher D, Todd S, Jackson G, Wendel G. ³	Methadone doses were reviewed to determine if higher doses caused an increased risk of NAS.	70 pregnant women	Inclusion: pregnant women with opioid addiction who delivered live-born singletons of at least 25 weeks' gestation between April 1, 1990 and April 30, 2001. Exclusion: if there was evidence of fetal growth restriction or oligohydramnios.	Retrospective cohort study Chi-square, analysis of variance, Mantel-Haenszel chi-square for trend, Spearman correlation coefficient and Kruskal-Wallis. ⁸	Maternal methadone dosage was associated with duration of neonatal hospitalization, neonatal abstinence score, and treatment for withdrawal. Heroin supplementation did not alter this dose-response relationship
Lainwala S, Brown E, Weinschenk N, Blackwell M, Hagadorn J. ⁵	Compare LOS of infants treated for NAS with methadone, compared to other oral preparations.	46 infants	Gestation \geq 36 weeks, presence of NAS requiring pharmacologic treatment, in utero exposure to methadone and/or opiates.	Retrospective Study Chi-square and Mann-Whitney tests.	Similar LOS in all groups, but LOS increased with higher maternal methadone or other opioid doses.
Jones H, Johnson R, Jasinski D, Milio L. ⁸	Comparing the transition from short-acting morphine to buprenorphine or methadone.	18 pregnant women	Inclusion: patient must be opiate-dependent as described by the DSM-IV, between 21 and 40 years and between 16 and 30 weeks pregnant, provide an informed consent, and be HIV-negative. Exclusion: if there was polysubstance abuse as well as either severe somatic or other severe psychiatric diseases or a	Randomized controlled study Chi-square, \log_{10} transformation to stabilize variances, univariate analysis of variance, and Mann-Whitney test.	Significantly decreased neonatal LOS for buprenorphine exposed neonates

			high-risk pregnancy.		
Lejeune C, Simmat-Durand L, Gourarier L, Aubisson S. ¹⁰	Compared the effects of methadone directly to buprenorphine in both the mothers and their neonates	260 neonates and 259 pregnant women	35 centers followed opioid exposed neonates Inclusion: opiate dependent mothers on high dose methadone or buprenorphine	Prospective observational Study Chi-square or Fisher's exact test, or multivariate analysis	Comparing methadone with high dose buprenorphine, respectively, mean age at the maximum Lipsitz score was 81 h versus 66 h (P = 0.066).
McCarthy J, Leamon M, Parr M, Anania B. ¹¹	Methadone doses were reviewed to determine if higher doses caused an increased risk of NAS.	81 pregnant women and 81 neonates	Women were included if they received the treatment offered: trained counseling, obstetric care, written consent for providers to share information, psychiatric assessment, supportive psychotherapy, and participate in a weekly support group for both pregnant and early postpartum patients, and random weekly urine drug screens Exclusion: 2 women left treatment; 2 patients requested to taper off methadone, and 2 patients had unavailable outcome information.	Retrospective Study 2-tailed t-tests, chi-squared analyses, and Mann-Whitney tests.	High doses of methadone not associated with increased risk for NAS
Kuschel C, Austerberry L, Cornwell M, Couch R, Rowley R. ¹²	Methadone doses were reviewed to determine if higher doses caused an increased risk of NAS.	25 infants	Inclusion: approached at antenatal visits by a midwife affiliated to ADAPT, and gave informed consent for participation in the study. Exclusion: infants delivered prematurely at a gestation of less than 35 weeks.	Prospective Study Student's t test or Mann-Whitney U test, x2 test.	Methadone concentrations taken from cord blood may identify infants at greater risk of neonatal withdrawal and therefore requiring treatment.
Lacroix I, Berrebi A, Chaumerliac C, Lapeyre-Mestre M, Montastruc J, Damase-Michel C. ¹³	prospective follow-up of 34 pregnant women exposed to buprenorphine maintenance for opiate dependence.	31 neonates	Women recruited from drug treatment centers, treated during pregnancy with buprenorphine	Prospective Study	No significant differences in outcomes was observed
Jones H, Johnson R, Jasinski D, O'Grady K, Chisholm C, Choo R, et al. ¹⁴	Compared the neonatal abstinence syndrome in neonates of methadone and buprenorphine maintained pregnant opiate-dependent women and to provide preliminary safety and efficacy data for a larger multi-center trial.	14 pregnant women	Inclusion: opiate-dependent pregnant women and their neonates in a comprehensive drug-treatment facility that included residential and ambulatory care	Randomized, double-blind, double-dummy, flexible dosing, parallel-group controlled trial	There was earlier onset of NAS in neonates born to the methadone (mean 60 hours) than to the buprenorphine groups (mean 72 hours) Further study warranted
Martinez, A, Kastner, B, Tausch H. ¹⁷	To show whether hyperphagia was a clinically significant problem for the infants whose mother received methadone treatment during pregnancy.	44 neonates	Inclusion: all infants born at San Francisco General Hospital to women enrolled in a methadone program during their pregnancy as well as, infants exposed to other opiates Exclusion: if the mother used opiates but was not	Retrospective Study SEM, ANOVA, unpaired 2-tailed t-test, Wilcoxon Rank Sum test, Linear regression analysis	Hyperphagia in the neonatal period may be a useful marker for inadequate control of NAS

			enrolled in a methadone program.		
Lejeune C, Aubisson S, Simmat-Durand L, Cneude F, Piquet M. ¹⁸	Compared the effects of methadone directly to buprenorphine in both the mothers and their neonates	246 neonates	all neonates whose mothers has been maintained during pregnancy on methadone or high dose buprenorphine were included by 34 French perinatal centers	Prospective multicentric study Chi-square goodness of fit test, Poisson distribution and regressions, Estimation and test of significance, and Satterthwaite's method.	statistically significant differences between the groups were: maintenance program was more frequently initiated before this pregnancy for the methadone vs. buprenorphine group ($p < 0.03$);
Doberczak T, Kandall S, Freidmann P. ¹⁹	To assess whether there is a relationship between neonatal opiate withdrawal and maternal methadone usage, maternal and neonatal plasma levels, or the rate of decline of methadone in neonatal plasma	21 neonates	Inclusion: drug-dependent mothers with neonates admitted to NICU where they were observed for at least 7 days in an enclosed incubator, and then swaddled in bassinets for continuing care.	Prospective, observational study Standard deviation or median, Spearman rank correlation coefficient .	careful reduction of the maternal methadone dosage during pregnancy under intensive medical and psychosocial surveillance may benefit the drug-exposed newborn infant clinically
Fischer G, Jagsch R, Eder H, et al. ²¹	Compared the effects of methadone and slow-releasing morphine on NAS.	48 neonates and 48 pregnant women	Inclusion: pregnant women mean age, 26 years and mean gestation, 22 weeks, who were dependent on opioids or abused poly-substances (mean duration, 61 months) and were willing to follow the maintenance program and to avoid using illegal drugs	Randomized, unblended controlled study Finnegan score. Other outcomes were illegal drug consumption and nicotine dependence	Neonates born to mothers in the group receiving methadone and the group receiving slow-release morphine did not differ in the duration of the neonatal abstinence syndrome (16 days in the methadone group vs 21 days in the slow-release morphine group; $P = 0.18$).

Studies and Research Methods

Thirteen studies are presented that attempted to determine the effectiveness of methadone compared to alternatives such as buprenorphine. The studies are relatively small and collectively suggest similar safety of buprenorphine as compared to treatment with methadone in opiate addicted mothers and subsequent neonatal abstinence syndrome.

The studies vary widely in terms of design and research questions, limiting any collective judgements on outcomes. However, they do appear to demonstrate the usefulness of buprenorphine as an alternative to methadone in the treatment of opiate addicted mothers and neonates who develop NAS.

DISCUSSION

Methadone is a long-acting opioid that is similar to morphine and is commonly used to treat opioid dependence. Therefore, a pregnant woman undergoing treatment for opioid dependence with methadone or alternative drugs to control her addiction places her unborn child at risk for the development of complications after birth, especially NAS.⁴ In the studies conducted, methadone and an alternative drug, buprenorphine, were used to treat mothers during their pregnancies.

The trials noted above demonstrate that 30 to 50% of the methadone or buprenorphine exposed neonates developed NAS of a severity that requires treatment of the neonate.^{1,3,5,8,10,11,13,14} The length of stay (LOS) for methadone exposed neonates is harder to determine and quite variable among the studies. According to Lainwala et al., the median LOS was 40 days, but in Kuschel et al., the median LOS was only 15 days.^{5,12} The range of average LOS for neonates likely relates to a number of variables including fetal maturity at delivery, availability of prenatal care, and dosage of methadone or buprenorphine required for maintenance in the mother.

The McCarthy et al. study compared mothers requiring high dose methadone to low dose methadone in order to determine if dosage effected neonatal outcomes.¹¹ According to the study, there were no significant differences in the incidence of treated NAS. However, higher doses of methadone prenatally had a positive effect on subsequent maternal drug abuse. In the Kuschel study, cord blood was sampled from the neonate to determine if there is an increased risk of NAS with higher concentrations of methadone.¹² Maternal methadone dose had no effect on the risk of NAS. A lower dose might be more harmful than beneficial in the neonate and mother by still causing NAS but not adequately treating the maternal drug dependence.

In the Doberczak et al. study, venous blood samples were collected from both mothers and their neonates within 24 hours of birth.¹⁹ At 16 hours, the maternal plasma methadone level was 183 +/- 118 ng/ml and the neonatal level was 26+/-8 ng/ml. The neonates had a rate of decrease of methadone in their plasma that averaged 0.2 +/- 0.3 ng/ml/hour. Of the 21 neonates, 17 had moderate to severe NAS that required pharmacological treatment. They found that higher initial methadone levels were associated with a more rapid decline of drug levels in the neonates. The rate of decrease in serum methadone levels correlated with the acuity of the CNS withdrawal signs. Animal studies have shown that methadone accumulates in the non-human primate brain. Exposure of the fetal brain to the opiates promotes regional development of specific opiate receptors and suppresses neurotransmitter formation and function. Therefore, a more rapid decline in methadone levels can lead to an availability of opiate receptors as well as replenishment of neurotransmitters. The increased sites and replenishment of neurotransmitters can produce the neuronal excitability which clinically manifests as tremors, hyperreflexia and possibly seizures. The researchers recommended reducing methadone dosages late in pregnancy to reduce the severity of neonatal withdrawal.

In the Fischer et al. study, slow-release morphine was compared to morphine.²¹ The 48 women enrolled were split evenly with 24 in each group. There was no significant difference in the duration of NAS between the two groups (16 days in the methadone group vs. 21 days for the slow-release morphine) or the doses they received. Also, the slow-release morphine did not reduce the likelihood of developing NAS any more than the methadone.

Buprenorphine has increasingly been used as an alternative to methadone in the UK since being licensed there in 1999.⁹ Buprenorphine was tested in two studies. The Fischer et al. study showed that there is no significant difference between the two treatments. The study was limited because of its small size. Three out of the six methadone babies developed NAS and three out of eight buprenorphine babies developed it. However, in the methadone neonates, on average, they began treatment 12 hours earlier (mean 60 hours, range 52-68) and their treatment lasted a mean duration of 5.3 days (range 4 to 7 days).¹ The buprenorphine neonates began treatment at around 72 hours (range 35-109) and their duration of treatment lasted a mean of 4.8 days (range 1 to 8 days). During the treatment period, it was noted that the mothers on buprenorphine maintenance had a considerable rate of additional consumption of opiates as compared to the methadone-treated group. The Lejeune studies were the largest studies conducted.^{10,18} A total of 260 neonates were studied, with 101 neonates on methadone maintenance in utero and 159 neonates on buprenorphine maintenance in utero.¹⁰ Methadone and buprenorphine were compared on several parameters including intrauterine growth retardation (IUGR) and length less than the 10th percentile. Thirty-eight percent of the methadone neonates compared to 31% of the buprenorphine neonates had IUGR. Fourth-six percent of the neonates on methadone maintenance were less than the 10th percentile in length compared to only 34% of buprenorphine neonates. The mean birth weight was 2822g with 2790g mean for methadone and 2843g mean for buprenorphine. The mean Apgar score for both methadone and buprenorphine were 9.9 and 9.8 respectively.

The second Lejeune et al. study included 246 women, 93 on methadone maintenance and 153 on high-dose buprenorphine.¹⁸ There was no neonatal mortality with either drug. The only statistically significant differences between the methadone and high-dose buprenorphine groups were that prematurity was 18% for the methadone group versus 9% for high-dose buprenorphine group. Also, the mean age of the maximum Lipsitz score (measuring NAS symptoms) was hour 92 for the methadone group compared to hour 70 for the high-dose buprenorphine group.

Jones et al. conducted a study comparing buprenorphine to methadone.¹⁴ Although 30 women enrolled, only 20 completed the study. Eleven women were treated with methadone and nine with buprenorphine during pregnancy. Of the 20 neonates, 20% of buprenorphine-exposed and 45.5% of methadone-exposed neonates were treated for NAS. The amount of medication administered to treat the NAS in the methadone-exposed neonates was three times greater than for the buprenorphine exposed neonates. Buprenorphine exposed neonates remained in the hospital for a significantly shorter period of time (1.3 days difference) than methadone-exposed neonates. Also, on average, buprenorphine-exposed neonates weighed 528 g more than the methadone-exposed group and buprenorphine exposed neonates were discharged from the hospital 1.3 days earlier than methadone-exposed neonates.

In a review of this topic by Oei and Lui,¹⁶ the effects of drug abuse on neonates is assessed using various studies. In one study, amphetamine usage was compared to methadone usages with 46% of amphetamine exposed infants developing significant NAS compared to 80% methadone-exposed infants. They compare studies testing buprenorphine effects on neonates. The frequency of severe NAS due to buprenorphine exposure appears to be variable and ranges from zero to around 50%. They also found that the peak age at which symptoms of buprenorphine withdrawal occurs seems to be about the same time as withdrawal from methadone, approximately 40 hours. However, peak NAS scores seem to occur later with buprenorphine at about 70 hours of age. The authors also report that methadone withdrawal symptoms can first occur up 4 weeks after birth with subacute symptoms lasting up to six months of age. Several studies were used to determine whether the dosage of methadone had an effect on NAS. Studies were contradictory stating that both low and high doses may increase the severity of NAS. No definite conclusions can be determined based on the studies they reviewed. However, they indicated that a rapid decline in the neonatal methadone serum concentrations can increase the severity of the withdrawal symptoms. The neonates requiring pharmacological treatment for NAS had an undetectable serum methadone level at 48 hours after birth.

In another review article by the "Committee on Drugs", they also compare studies on dosage of maternal methadone.²⁰ Most studies demonstrate that higher dosages later in pregnancy were associated with greater neonatal concentrations and an increased risk for withdrawal. The larger dosages were associated with faster declines in neonatal serum concentrations and more severe withdrawal in 21 infants. Several of the reviewed studies have found that there is a lower incidence and decreased severity of NAS with lower maternal maintenance dosages, which is why some practitioners have recommended gradually reducing the methadone dose prior to delivery.

Lacroix et al. compared several studies using buprenorphine maintenance.¹³ Most of the studies are retrospective or include neonates at birth; assessing for NAS. Eleven trials with a total of 244 neonates were studied and assessed. Of the 244 neonates, 32 were born with a form of withdrawal symptoms rated from mild to severe. Also, there were four premature neonates, six with fetal growth retardation, three with fetal distress, and one with convulsions. The remaining 212 neonates were born without complications being reported. The prospective studies were follow-ups of pregnant treated women and only evaluated small numbers of women. Thirty-six neonates were assessed after birth, 13 had withdrawal complications with one premature neonate and one with growth retardation. The remaining 23 neonates were healthy babies without complications.

Dashe et al.³ performed a retrospective cohort study comparing dosages of methadone. Women enrolled were started on 20mg per day and adjusted accordingly as needed in 5mg intervals. After birth, the neonates were hospitalized for five to seven days for observation. Neonatal abstinence scoring was used with a score exceeding 8 on two occasions, indicating the need for treatment. Increasing the methadone dose was associated with lower birth weights below the tenth percentile, positive neonatal toxicology screen for opioids, and positive screen for cocaine. Forty-six percent (46%) were treated for withdrawal, increasing from 12% whose mothers received less than 20mg a day to 90% whose mothers received 40mg or more a day. Only three neonates were treated for withdrawal symptoms of the 25 women who received less than 20mg a day. The higher the methadone dose administered each day correlated to both a high neonatal abstinence score and a longer LOS.

The transplacental transfer of a drug may explain why there are differences in the severity of NAS.¹⁵ Nanosvkaya et al. studied the amount of buprenorphine transferred into the fetal circulation, its metabolism, and its effect on the tissue. An ex-vivo technique of dual perfusion of placental lobule has proven to be a valuable tool for obtaining such information. According to the study findings, "less than 10% of the buprenorphine was found in the fetal circulation, and the remainder was found in the tissue." The concentration ratios of the drug in tissue/maternal and tissue/fetal were 13 ± 6.5 and 27.4 ± 0.4 . The drug sequestered did not have any adverse effects on placental tissue viability and functional parameters. Less than 5% of the perfused buprenorphine was metabolized to nor-buprenorphine during the 4 hours of perfusion and the metabolite was distributed between the tissue, and maternal/fetal circulation. These data suggest that the therapeutic levels of buprenorphine in the maternal circulation may have no indirect effects (via the placenta) on the fetus. The observed low transplacental transfer of buprenorphine to the fetal circuit may explain the moderate/absence of neonatal withdrawal in the limited number of reports on mothers treated with the drug during pregnancy.¹⁵

Methadone withdrawal symptoms not only occur in the first days of life, but also weeks or months after. Hyperphagia, described as excessive oral intake greater than 190 cc/kg/day, is listed as one of many clinical findings in infants withdrawing from opiates.¹⁷ In a study conducted by Martinez, Kastner, & Taesch¹⁷, hyperphagia is evaluated in 44 neonates exposed in utero to methadone. The mean birth weight for the neonates was 2804g. By day 20, the neonates had reached a mean oral intake of 202 cc/kg/day. 26% were hyperphagic by day 8 with 56% hyperphagic by day 16. However, they found no correlation between the oral intake and maternal methadone dose. Also they found that the median withdrawal score for the hyperphagic infants at day 28 was 12 compared with 5 for non-hyperphagic infants; there had been no differences before day 28. There was no increase in

gastrointestinal symptoms, vomiting, diarrhea, drooling, abdominal distention, or aspiration found between the hyperphagic neonates and the non-hyperphagic neonates. Even though they found that neonates withdrawing from methadone were more likely to become hyperphagic, there were few differences or complications.

There were limiting factors in many of the studies, such as finding a large enough sample size and participants that met the inclusion criteria. However, in the studies compared, information gathered can be used to determine a good starting point. The data collected indicates that methadone is helpful in the treatment of opiate addictions, but the effects on neonates can be severe. Withdrawal symptoms are prevalent and seem to increase the LOS and complications. However, the complications start in utero with IUGR and premature births. Compared to methadone, buprenorphine seems to offer some slight improvements. Buprenorphine is shown to have NAS complications, as well as other complications in utero and at birth. However, the LOS for buprenorphine-exposed neonates appeared to be shorter, with lesser degrees of NAS and a quicker recovery.

Another problem with the studies was controlling the other possible influences on neonatal outcomes. Smoking cigarettes is very common during treatment, and the nicotine from the cigarettes has its own effects on the fetus. Therefore, it is hard to completely determine which complications, such as IUGR, were the results of which substance. Further studies need to address and control other substances used by the mothers. Buprenorphine seems to be an effective alternative to methadone, but future studies would need to be conducted with larger populations.

CONCLUSIONS

Methadone is proven to have potential adverse effects on the neonate.^{2,3,5,6} However, it is more appropriate for a pregnant opiate-addict to obtain this treatment during her pregnancy rather than continuing heroin use. Methadone has been proven to help opiate addicts, yet for pregnant opiate addicts, there must be concern for the effects on the unborn child.^{3,4} This review brought together several studies that attempted to assess the effects of methadone on the neonate. These studies have proven inconclusive on the appropriate dosage that will benefit the mother yet keep the neonate safe.^{3,11,19,20} As an alternative to methadone, buprenorphine has proven effective in Europe for helping the mother as well as possibly lessening the effects on the neonate.^{1,9,10,13,14,18} Case studies have been reassuring and rates of NAS were slightly reduced overall. Also, the severity and duration of NAS seem to be improved.⁹ However, most studies conducted prove to be inconclusive about whether methadone should be used or a new alternative such as buprenorphine should be seriously considered.

Since the population of opioid addicted mothers is rather small, it is hard to create large trials. An attempt to pool similar data from across the country would provide the numbers needed to determine the best choices for the mother and the fetus or neonate. The studies reviewed suggest that there may be some benefit from treatment with buprenorphine over methadone in terms of less severity of NAS and shorter LOS, but the results are not clear enough to state conclusively that buprenorphine should be used in place of methadone. For now, methadone seems to be an effective treatment as long as the mother also receives the medical care she needs to have a healthy pregnancy with a healthy neonate.

Methadone can have many effects on neonates after birth, such as hyperphagia. Most symptoms tend to be limited to the first few months of the neonates life. There are few studies that follow up on the children throughout their childhood to see if there are long term effects. Hyperphagia appears to be a result of methadone withdrawal, and this may be a useful marker for sub-clinical or impending NAS. Currently, the studies all conclude that methadone, buprenorphine, and other alternatives cause NAS, but future studies are needed to determine what the long-term effects might be, if any.

It is important to remember that methadone treatment by itself cannot control all of the life issues associated with pregnancy and heroin addiction. In addition to medications, the patient needs a comprehensive program which includes prenatal and medical care, nutritional counseling, and attention to resolving their many medical, personal, and social problems.⁷ A large, multi-dose comparison of methadone and buprenorphine is needed to determine which is more appropriate in the treatment of opioid-addicted mothers and withdrawal-prone neonates.

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