Predicting length of treatment for neonatal abstinence syndrome in methadone-exposed neonates

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Background and Objective

Drug use is prevalent among reproductive-age women. A survey of combined data from 2005 and 2006 reported that 10% of women of child-bearing age used illicit drugs. Intrauterine exposure to opiates may lead to neonatal withdrawal characterized by central nervous system irritability, gastrointestinal dysfunction, and autonomic signs. The constellation of findings is termed neonatal abstinence syndrome (NAS).

Management of opioid dependence with methadone has been used to improve maternal and neonatal outcome. Methadone maintenance is associated with more prenatal care, improved fetal growth, and increased likelihood of discharge to parents' care. Despite its benefits, withdrawal from methadone is more severe than withdrawal from heroin, which translates into lengthier hospital stays, causing a substantial burden on families.

Efforts to reduce the severity of withdrawal have largely focused on methadone administration and treatment of NAS. Initiating pharmacologic treatment for NAS decreases the duration of symptoms but does not subjugate the necessity to decrease the severity of withdrawal through antenatal interventions. The purpose of this study was to determine which maternal variables predict the length of treatment for NAS in methadone-exposed neonates.

OVERVIEW

Methadone and benzodiazepines used together during pregnancy significantly lengthen the duration of treatment for neonatal abstinence syndrome.

Materials and Methods

The hospital medical records database was queried using the International Classification of Diseases codes for antepartum drug dependence (648.33), maternal drug dependence with delivery (648.31), and opioid dependence continuous use (304.01). The inpatient medical records of methadone maintained women who delivered from Jan. 1, 2000, through June 30, 2006, and had urine drug screen (UDS-9) positive for methadone within the 2 weeks preceding the delivery date were reviewed. Neonatal charts were reviewed; only neonates with a diagnosis of NAS and their mothers were included in the study.

All neonates were delivered at Thomas Jefferson University Hospital, at which standard-of-care treatment consists of an initial dose of morphine 0.4 mg/kg per day (in the form of neonatal opium solution) in 6 divided doses with dose escalation of 10% per day for Finnegan scale scores greater than 24 total on either 2 or 3 measures. Infants were weaned from neonatal opium solution (NOS) once they demonstrated control of their NAS as measured by the Finnegan scale for 48 hours.

The following variables were compared with length of treatment for NAS: length of exposure to methadone, trimester of initial exposure, methadone dose at delivery, maternal body mass index (BMI), antidepressant use, benzodiazepine use, tobacco use, alcohol use, gestational age at delivery, race, and maternal age. Methadone dose at delivery was defined as the methadone dose within the 24 hours prior to delivery. Maternal BMI was calculated using weight at delivery. First urine drug screen (UDS) was defined as the first available UDS more than 2 weeks prior to delivery. Last UDS was defined as the composite results of all UDS within 2 weeks of delivery. Benzodiazepine use was defined as last UDS positive for benzodiazepines or a history of prescription benzodiazepine use during the index pregnancy.

Length of treatment was transformed by taking square roots to normalize residuals. The association between transformed length of treatment and various clinical and demographic factors was analyzed using a mixed effects linear regression. Variables significant at the univariate level ($P < .20$) were entered into a multivariate mixed-effects model as fixed effects. A random intercept term was included to account for correlation among infants born to the same mother. The number of neonates included in the multivariate analysis was determined by the number of nonmissing values for length of treatment and the independent variables. Model adjusted least-squares means (using observed marginal sample sizes) were calculated from estimates from the multivariate model and squared to obtain values on the original scale.

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Results

Our cohort consisted of 185 methadone-maintained women and 204 neonates, including 2 sets of twins. The median length of NAS treatment was 32 days. The overall average maternal methadone dose was 127 mg daily. The delivery dose of methadone was greater than 150 mg daily in 31.4% of women and greater than 200 mg daily in 11.8% of women.

In the variable analysis, there was a statistically significant relationship between length of neonatal treatment for NAS and both concomitant benzodiazepine use ($P = .002$) and later gestational age at delivery ($P < .001$). After we had controlled for the possible interaction of significant variables ($P < .2$), including length of exposure, time of initial exposure, methadone dose at delivery, alcohol use, and gestational age at delivery, adjusted mean length of treatment was 14.4 days longer in women who used benzodiazepines (Table).

TABLE
Multivariate analysis of variables $P < .2$ for all births

Variable	Category, n	Adjusted mean LOT (d)[a]	*P* value
Length of exposure, wks			.075
10 or less	27	26.5	
Longer than 10	174	33.4	
Methadone dose at delivery, mg			.090
50 or less	14	31.5	
51-100	61	32.6	
101-150	71	36.7	
150-200	37	26.3	
greater than 200	18	29.7	
Benzodiazepine use			< .001
None	159	29.7	
Any	42	44.1	
Alcohol use			.15
None	184	33.1	
Any	17	26.1	
Gestational age at delivery, wks			< .001[b]
23-32	11	11.9	
33-36	62	26.2	
37-42	128	38.1	

LOT, length of treatment.

[a] Numbers reported are the squares of the model-adjusted means calculated for the square root of length of treatment.

[b] All pairwise group differences were significant (Bonferroni adjusted $P < .05$).

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Comment

Benzodiazepine use and gestational age at birth were the 2 maternal variables identified by our study that predicted the length of treatment for NAS. Neonates exposed to benzodiazepines and those born at term had a significantly longer length of treatment when compared with unexposed neonates or with those born at less than 37 weeks of gestational age. Our results also demonstrate that, with regard to length of treatment, there is no significant relationship to maternal methadone dose prior to delivery. Length of neonatal treatment could not be predicted by any of the other variables studied.

One strength of our study is that our cohort's mean and maximum doses of methadone are among the highest reported in pregnancy in the English literature.

The association of benzodiazepine use with longer length of treatment confirms earlier studies in smaller samples at our center and others. Symptoms of benzodiazepine withdrawal may confound neonatal abstinence scoring during treatment because of delayed onset as late as day 12 to day 21. Duration of withdrawl may be prolonged, as well.

The other major finding in our study was the direct association between later gestational age at birth and longer length of neonatal treatment for NAS. The association between gestational age and length of treatment is also explained by several biologically plausible mechanisms. One theory is that incomplete dendritic developmental may alter clinical expression of NAS. Another explanation is slower weaning due to delayed hepatic and placental metabolism of methadone in premature neonates. A final explanation is increased placental transfer of methadone to the neonatal circulation at term.

The appropriate methadone dose is controversial. Our results demonstrate that, with regard to length of treatment, there is no relationship to maternal methadone dose at delivery.

In conclusion, the main findings of our study were that benzodiazepine use and later gestational age at birth increase length of neonatal treatment for NAS. Clinicians should not be hesitant to use higher doses of methadone to ameliorate withdrawal in symptomatic women.

CLINICAL IMPLICATIONS

- Of the maternal and antenatal variables studied, only benzodiazepine

use and later gestational age at birth were significantly associated with increased length of neonatal treatment for neonatal abstinence syndrome.

- Clinicians should not hesitate to use higher doses of methadone to ameliorate withdrawal in symptomatic women.
- Consideration should be given to avoiding benzodiazepines in methadone-maintained mothers when a suitable alternative is available. ■

Intracranial magnetic resonance imaging findings in the surviving fetus after spontaneous monochorionic cotwin demise

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Background and Objective

Demise of a cotwin in a monochorionic pregnancy places the surviving twin at significant risk for neurologic sequelae. Intracranial abnormalities after cotwin demise have most commonly been detected sonographically. Few case reports of fetal magnetic resonance imaging (MRI) findings after cotwin demise are present in the literature. The purpose of this study was to evaluate intracranial abnormalities in the surviving fetus after a cotwin demise using fetal MRI.

OVERVIEW

Fetal magnetic resonance imaging can detect ischemic, developmental, and/or hemorrhagic abnormalities in the developing brain of survivors of monochorionic cotwin demise and is a valuable tool in this setting.

Materials and Methods

Forty-seven cases of cotwin demise in monochorionic twin pregnancies were identified from a database consisting of all fetal MRI examinations performed at the University of California, San Francisco (UCSF), from 1997 through 2007. Of these cases, 25 were associated with an intervention (fetal radiofrequency ablation or placental ablation) and were excluded from the study. An additional case was excluded because of the lack of a comparison ultrasound after cotwin demise. Our study group comprises the remaining 21. One case has been reported previously.

A 1.5-T MR magnet was used to obtain ultrafast (single-shot fast spin echo) T2-weighted images of the fetal brain. Fetal MR images were retrospectively reviewed in a blinded manner by a pediatric neuroradiologist with expertise in fetal MRI.

Results

The mean gestational age at the time of cotwin demise was $19^{6/7}$ weeks (range, $12^{4/7}$ weeks-$26^{5/7}$ weeks) with an average interval of $4^{3/7}$ weeks between the time of cotwin demise and fetal MRI (range, 0-$12^{1/7}$ weeks). Intracranial abnormalities were visualized by antenatal MRI after cotwin demise in 7 of the 21 cases, for the majority of which ultrasound scans were normal. These abnormalities included a unilateral infarct with developing polymicrogyria (Figure), small focal injury in the left parietal lobe associated with shallow sylvian fissures and dilation of the adjacent ventricle, bilateral germinolytic cysts in the region of the ganglionic eminence, and shallow sylvian fissures. In 3 of the 7 cases, an ultrasound scan was abnormal, although MRI detected additional abnormalities. The gestational age at the time of cotwin demise ranged from $15^{5/7}$ weeks-$26^{2/7}$ weeks (mean age of 20 weeks) in the 7 cases with an abnormal fetal MRI.

Only 9 of 21 cases in our series carried the diagnosis of twin-twin transfusion syndrome (TTTS). Another 4 carried a probable diagnosis of TTTS by ultrasonographic findings after cotwin demise; 2 had twin reversed arterial perfusion (TRAP); and the remaining 6 had no diagnosis other than the presence of cotwin demise. The majority, 71%, of intracranial MRI abnormalities occurred in association with confirmed or probable TTTS, 14% in conjunction with TRAP and 14% in cases without additional diagnosis.

Comment

The ability to predict neurologic sequelae of a surviving twin prenatally by sonographic findings was first reported in 1989. Since then, several studies have

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