Maternal methadone use in pregnancy: factors associated with the development of neonatal abstinence syndrome and implications for healthcare resources

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Objectives The objectives of this study were to investigate factors associated with the development of neonatal abstinence syndrome (NAS) and to assess the implications for healthcare resources of infants born to drug misusing women.

Design Retrospective cohort study from 1 January 2004 to 31 December 2006.

Setting Inner city maternity hospital providing dedicated multidisciplinary care to drug misusing women.

Population Four hundred and fifty singleton pregnancies of drug misusing women prescribed substitute methadone in pregnancy.

Methods Case note review.

Main outcome measures Development of NAS and duration of infant hospital stay.

Results 45.5% of infants developed NAS requiring pharmacological treatment. The odds ratio of the infant developing NAS was independently related to prescribed maternal methadone dose rather than associated polydrug misuse. Breastfeeding was associated with reduced odds of requiring treatment for NAS (OR 0.55, 95% CI 0.34 0.88). Preterm birth did not influence the odds of the infant receiving treatment for NAS. 48.4% infants were admitted to the neonatal unit (NNU) 40% of these primarily for treatment of NAS. The median total hospital stay for all infants was 10 days (interquartile range 7 17 days). Infants born to methadone prescribed drug misusing mothers represented 2.9% of hospital births, but used 18.2% of NNU cot days.

Conclusions Higher maternal methadone dose is associated with a higher incidence of NAS. Pregnant drug misusing women should be encouraged and supported to breastfeed. Their infants are extremely vulnerable and draw heavily on healthcare resources.

Keywords Breastfeeding, health resources, methadone, neonatal abstinence syndrome.

Introduction

Maternal drug misuse is related to socio economic depriva tion, and infants born to drug misusing mothers are recog nised to be at risk of preterm delivery, poor intrauterine growth and the development of neonatal abstinence syndrome (NAS).[1] These problems persist even when drug misusing mothers are managed in specialist units.[2] Substitute prescrib ing of methadone stabilises lifestyle and reduces risk taking behaviour as well as the incidence of preterm birth and intra uterine growth restriction[3–6] but is commonly associated with NAS.[6–9] Preterm infants may be less likely than term infants to exhibit signs of NAS resulting from opiate or opioid expo sure.[10–12] There is conflicting evidence with regard to optimal maternal methadone dose in pregnancy, with some studies showing an association between maternal methadone dose and the risk of NAS and some studies showing no such rela tionship.[9,13–19] Duration of stay may be longer for infants born

to polydrug misusing mothers,[20] and since higher doses of methadone have been associated with less polydrug use, reducing methadone during pregnancy may not be justified.[13] Australian and European data have demonstrated large consumption of healthcare resources by infants born to drug misusing women,[2,8] but there are few data to quantify this within the UK healthcare setting.[20–22]

We present data from infants born over a 3 year period to a large cohort of drug misusing mothers cared for by a specialist service within a large inner city maternity hospital in the UK.

Methods

Local service provision

Princess Royal Maternity provides an established obstetrically led, community based city wide multidisciplinary service for women with social problems including substance misuse.[23] The majority of drug misusing women attending this service use opiates and benzodiazepines. Antenatal care includes substitute prescribing (predominantly with methadone) and is provided in collaboration with social work and addiction services.[24] In common with standard addiction management, all women are prescribed sufficient methadone to eliminate physical withdrawals. Urine is routinely screened at booking to confirm the presence of illicit drugs. Thereafter, to foster a sense of trust and responsibility and to keep women engaged with services, additional urine drugs screens are performed as infrequently as possible in the outpatient setting. A second routine urine sample is collected immediately post delivery, and additional urine screens generally only during periods of hospitalisation to confirm grounds for discharge of difficult women suspected to be using illicit drugs. Social stability is monitored, taking into account factors such as antenatal clinic attendance, general appearance and/or evidence of intoxication and self reported drug use. All women are referred to the clinic addiction worker at booking and assessed to determine the level of social work input required. Postnatally, women are cared for on a dedicated ward by familiar midwifery staff who also provide community review after discharge. Infants are nursed by their mother's bedside unless any specific indication for admission to the neonatal unit (NNU) is present. Breastfeeding is encouraged for all women unless HIV positive. Management of infants is guided by local protocol including a modified version of the Lipsitz Tool.[25] Lipsitz scores of ≥5 on two occasions prompt consideration of pharmacological treatment, particularly if the infant is feeding poorly and/or unusually difficult to console. First line treatment for infants exposed to opiates/opioids is oral morphine solution[21,26] with phenobarbitone as second line, particularly in cases of polydrug misuse.[27–29] Pharmacological treatment for NAS is not an indication *per se* for admission to the NNU, and mother and baby can remain together in the postnatal ward until day 10; thereafter, healthy mothers are discharged home and infants continuing to require pharmacological treatment are admitted to the NNU. Once oral morphine solution has been weaned, infants may be considered for discharge on phenobarbitone. For practical reasons, including the stability of the oral morphine solution available during the time of this review, and the difficulty of supervising 4 hourly administration of oral morphine solution, it is not our practice to discharge infants on oral morphine solution.

Study design

This was a retrospective cohort study of singleton infants born to drug misusing women prescribed substitute methadone and delivered at Princess Royal Maternity in Glasgow over the 3 year period from 1 January 2004 to 31 December 2006.

Mothers were identified on admission to the postnatal ward and information extracted from case notes after discharge. Completeness of data was ensured by cross checking ward admission diaries, controlled drug books, hospital discharge and paediatric outpatient clinic records. Details of maternal methadone prescription and additional illicit drug misuse were obtained from case notes, hospital prescription charts and urine toxicology as detailed above. Social deprivation was measured by postcode derived Carstairs deprivation scores.[30] NAS was defined as signs of withdrawal that had been considered severe enough to require pharmacological treatment according to local protocol (*vide supra*). Data were anonymised prior to analysis. The local research ethics committee approved this anonymised retrospective study.

Statistical analyses

Univariate analyses were performed to investigate possible predictors of NAS. Significant predictors were then entered into a multivariate logistic regression model, and backwards selection was performed to determine independent variables associated with NAS. All analyses were performed using Minitab (version 15) at a significance level of 5%. Methadone was categorised according to daily dose into four groups (1–29, 30–59, 60–89 and ≥90 mg).

Results

Four hundred and fifty singleton infants were delivered to 450 methadone prescribed drug misusing women over the 3 year period. Two further women delivered two live sets of twins; their data are not included. Six infants were stillborn (at 25, 32, 34, 34, 35 and 37 weeks of gestation, respectively). The postnatal courses of the remaining 444 infants were reviewed. Data were complete for 437 infants (98.4%) and 440 mothers (97.8%). The remaining case notes could not be traced, although basic demographic data including birthweight, gestation and duration of hospital stay were obtained from hospital electronic records for all deliveries.

Maternal characteristics and pattern of drug misuse

Maternal characteristics are detailed in Table 1. The median maternal age at delivery was 28 years (range 15 41 years), and the median parity was 1. 18.2% of women had a history of depression, two thirds of whom were on antidepressants. The vast majority regularly smoked tobacco; by contrast, recog nised excessive alcohol consumption during pregnancy was relatively uncommon. Ninety percent of mothers were offered and accepted antenatal hepatitis C screening; almost one third had evidence of hepatitis C virus in the blood (poly merase chain reaction [PCR] positive). One mother was HIV positive, diagnosed prior to pregnancy. Social deprivation was prevalent with 77.8% of the women assigned Carstairs scores 6 or 7. The median daily prescribed dose of methadone at delivery was 50 mg (range 5 150 mg). There was no associ ation between prescribed dose of methadone and antidepres sant use. Combining self reported drug misuse and results of urine toxicology, at least 80% of the women used illicit drugs during their pregnancy (Table 1). The drugs most frequently used were benzodiazepines and heroin. Cannabis misuse was relatively common, and a significant minority of women also used cocaine. Amphetamine use was uncommon.

Table 1. Maternal characteristics (n 450)

Age (years)	
Median (range)	28 (15 41)
Parity	
Median (range)	1 (0 7)
Social deprivation Carstairs category[30]	**%**
1 2	2.7
3 5	19.1
6 7	77.8
Tobacco smokers, *n* (%)	395 (87.8)
Known excess alcohol consumption, *n* (%)	21 (4.7)
Hepatitis C serology, *n* (%)	
Hepatitis C antibody positive*	203 (50.4)
Hepatitis C PCR positive**	124 (33)
History of depression, *n* (%)	82 (18.2)
On antidepressant treatment at time of booking***	55 (12.2)
SSRI	32
Tricyclic/related	17
Other	6
Illicit drug use, *n* (%)	360 (80)
Benzodiazepines	272 (60.4)
Heroin	230 (51.1)
Cannabis	82 (18.2)
Cocaine	32 (7.1)
Amphetamines	7 (1.6)

*86% of women tested.
**85% of women tested.
***Categorised as per British National Formulary.

Infant characteristics

Infant characteristics are outlined in Table 2. The median gestational age was 38 weeks. 20.3% of infants were born before 37 weeks of gestation compared with 9.4% for the hospital as a whole (chi square, $P < 0.001$). Twenty three percent of infants weighed less than the ninth centile includ ing 7.4% weighing less than the second centile. Head circum ferences were correspondingly low. 68.9% of infants were born by spontaneous vertex delivery (SVD) compared with 58.1% for the hospital as a whole (chi square, $P < 0.001$) and fewer required instrumental vaginal delivery (6.3 versus 12.3%, chi square, $P < 0.001$). Sixteen infants were born before arrival at hospital. Seven (1.6%) infants had significant congenital anomalies. All but two infants survived to dis charge; one male infant died aged 7 days of complications of prematurity and another infant with multiple anomalies died of renal failure. One term infant died suddenly at home aged 25 days; this death was unexplained after postmortem examination. Breastfeeding was initiated in 27.7% of infants, and a further 19 infants received mother's own expressed breast milk. 11.3% of the total cohort was still breastfeeding, at least in part, at discharge.

Neonatal abstinence syndrome

45.5% infants received pharmacological treatment for NAS. Median age at commencement of treatment was 3 days (range 1 13 days), and this was not related to the pattern of maternal drug misuse. Duration of oral morphine therapy ranged from 1 to 44 days (median 11 days), and this was not different among infants exposed to selective serotonin reuptake inhib itors (SSRIs) *in utero* ($n = 32$). Of the infants who required second line treatment ($n = 42$), just over half (22) were dis charged home on phenobarbitone, eight of these to foster

Table 2. Infant characteristics (n 444)

	Mean	SD	Median	IQR
Gestational age (weeks)	37.8	2.5	38	37 40
Birthweight (g)	2713	550	2730	2344 3080
Occipitofrontal head circumference (cm)	32.6	1.9	32.9	31.5 33.8
Mode of delivery, *n* (%)				
Spontaneous vertex	306 (68.9)			
Instrumental	28 (6.3)			
Emergency caesarean section	74 (16.7)			
Elective caesarean section	36 (8.1)			
Congenital anomalies, *n* (%)	7 (1.6)			

IQR, interquartile range.

care. A further three infants who had been discharged home without treatment were commenced on phenobarbitone in the outpatient clinic at 3, 5 and 8 weeks of age, respectively. Total duration of phenobarbitone therapy ranged from 2 to 140 (median 25) days. Ninety three percent of the infants who required phenobarbitone had been exposed to polydrug misuse *in utero*.

Factors associated with development of NAS

Maternal use of benzodiazepines in addition to prescribed methadone significantly increased the likelihood of NAS requiring treatment (OR 1.73, 95% CI 1.17 2.55; $P = 0.006$) (Table 3), but there was a strong positive correlation between prescribed maternal methadone dose and polydrug misuse ($P < 0.001$). After multivariate logistic regression analysis, only prescribed maternal methadone dose independently influenced the likelihood of an infant receiving treatment for NAS ($P < 0.001$). This is illustrated in Figure 1. Breast feeding for ≥72 hours significantly reduced the odds of receiv ing treatment for NAS (OR 0.55, 95% CI 0.34 0.88; $P = 0.013$). Neither gestational age (OR 1.00, 95% CI 0.93 1.08; $P = 0.954$) nor prescription of SSRI (OR 1.3, 95% CI 0.63 2.7; $P = 0.479$) affected the odds of an infant receiving treatment for NAS.

Table 3. Factors predictive of receiving pharmacological treatment for NAS

Variable	*n*	OR	95% CI	*P* value
Univariate analysis				
Gestation (weeks) (analysed as continuous variable)	444	1.00	0.93 1.08	0.954
Methadone				
30 59 vs 1 29 mg	166 vs 98	1.58	0.94 2.66	0.082
60 89 vs 1 29 mg	135 vs 98	1.78	1.04 3.04	0.037
≥90 vs 1 29 mg	43 vs 98	5.09	2.32 11.18	<0.001
Mother only used methadone in pregnancy	27	0.40	0.16 0.96	0.041
Methadone plus benzodiazepines	272	1.73	1.17 2.55	0.006
Methadone plus other drugs except benzodiazepines	76	1.33	0.81 2.17	0.264
Mother on SSRI	32	1.30	0.63 2.70	0.479
Breastfed ≥72 hours*	99	0.52	0.33 0.83	0.006
Multivariate analysis				
Methadone				
30 59 vs 1 29 mg	166 vs 98	1.57	0.93 2.65	0.089
60 89 vs 1 29 mg	135 vs 98	1.72	1.00 2.96	0.049
≥90 vs 1 29 mg	43 vs 98	4.82	2.18 10.64	<0.001
Breastfed ≥72 hours*	99	0.55	0.34 0.88	0.013

*Includes preterm infants receiving mother's own expressed breast milk.

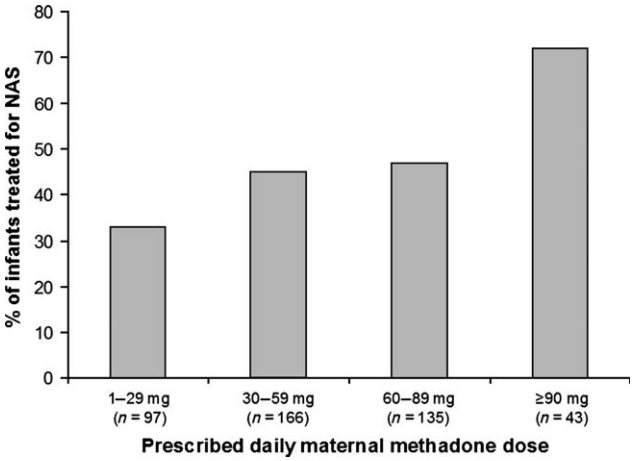

Figure 1. Relationship between maternal methadone dose and develop ment of NAS.

Hospital workload

48.4% infants were admitted to the NNU where duration of stay ranged from 1 to 108 (median 13) days (Table 4). Rea sons for admission included prematurity (15.8%), respiratory distress (12.6%) and a variety of social reasons (13%). Forty percent of admissions were primarily for continuing treat ment of NAS, almost exclusively term infants. Premature infants and infants with respiratory distress remained in the NNU for a median of 20 and 16 days, respectively, reflecting their increased medical needs. Nonadmitted term infants remained in hospital with their mothers for a median of 7 days (interquartile range 6 9 days). Duration of hospital stay was longer for infants born to polydrug misusing women (median of 11 days [interquartile range 7 19 days]) compared with infants born to mothers who took only prescribed meth adone (median 8 days [interquartile range 6 10 days]) ($P < 0.001$). Infants born to drug misusing mothers represented 2.9% of hospital births but occupied 18.2% of the total NNU cot days for the period.

Table 4. Infant lengths of stay

	n	NNU stay days (IQR)	Total hospital stay days (IQR)
Whole group	444		10 (7 17)
Infants admitted to the NNU (all gestations)	215	13 (6 22)	18 (13 26)
Term infants admitted to the NNU	147	12 (5 20)	17 (12 26)
Infants not admitted to the NNU	229	Not applicable	7 (6 9)

IQR, interquartile range.

Discharge and follow up

Almost all women were allocated a named social worker dur ing pregnancy, and all families were assessed by the social work department prior to discharge. Forty two (9.5%) infants were discharged to foster care, and a further 15 were dis charged to the care of family members on a voluntary basis. Outpatient appointments were offered to 182 infants, of whom 51.1% failed to attend on two or more occasions.

Discussion

Our data concur with some previous reports illustrating the vulnerability of infants born to drug misusing mothers. Even with specialist multidisciplinary antenatal care[31] and good maternal compliance during pregnancy, these infants are of low birthweight and at increased risk of preterm delivery.[2,6,8] The stillbirth rate of 1.3% was almost double that seen in the hospital as a whole, although the incidence of congenital abnormality was not increased.[32] Undoubtedly, the effects of drug misuse upon the unborn child are confounded by social deprivation and maternal health and lifestyle. We assessed social deprivation using a scoring system based on four standard variables taken from census data including adult male unemployment, lack of car ownership, low social class and overcrowding:[30] three quarters of our population of mothers lived in areas classified as the lowest two Carstairs categories (6 and 7) compared with 50% for the hospital as a whole. The vast majority of mothers regularly smoked cig arettes, and 4.7% were recognised to have consumed excessive amounts of alcohol during pregnancy. It is impossible to estimate the relative contributions of drug misuse, cigarette smoking, alcohol consumption, poverty and maternal ill health upon fetal growth.

The increased frequency of SVD is consistent with the observations of Kelly *et al.*[2] and may be explained in part by smaller birthweight and head circumference but may also reflect reluctance of labouring drug misusing mothers to admit themselves early to hospital. It is our experience that many of these women prefer to manage early labour them selves at home, often with illicit top up drugs. This would also explain the increased likelihood of delivery occurring before arrival at the maternity hospital.

The reported incidence of NAS is dependent on local pol icies for diagnosis and/or treatment as well as the pattern of maternal drug use, hence the marked variation (16 91%) reported between centres.[2,3,7,8,27,28] In a recent survey, only 55% of NNUs had a written policy for management of NAS.[33] We defined NAS by a requirement for pharmacolog ical treatment, commenced according to a reasonably strict local policy incorporating the Lipsitz scoring system as rec ommended by the American Academy of Pediatrics.[34] While we concede that some interindividual differences exist with regard to commencement of pharmacological treatment, we believe that our policy minimises this. Our data agree closely with Dashe *et al.*[9] who reported treatment rates of 44% in a subgroup of infants born to women receiving 20 39 mg methadone per day. Cigarette smoking may have contributed to the development of NAS in some infants, but this cannot be quantified.[35] Within this cohort, maternal SSRI prescription did not affect either the odds of developing NAS or the sever ity of the condition as measured by duration of treatment.[36]

Previous studies investigating the influence of prescribed maternal methadone dose upon the development of NAS have yielded conflicting results.[9,13–19] The largest of these studies included 100 infants.[15] Other studies have spanned more than a decade and been confounded by cocaine and heroin use.[9] Within our cohort of 444 infants, we observed a strong positive association between prescribed maternal methadone dose and the development of NAS. The trend towards higher rates of illicit drug misuse among women prescribed higher doses of methadone was contrary to that observed by Berghella *et al.*[15] but consistent with the findings of Dashe *et al.*[9] The latter study did not, however, separate the effects of increasing methadone and supplemental heroin upon the odds of the infant developing NAS. Within our study cohort, polydrug misuse, although likely in women pre scribed higher doses of methadone, was not an independent predictor of NAS.

Two studies have reported lower rates of NAS among pre term infants compared with term infants, postulated to be due to developmental immaturity or reduced total drug exposure during the intrauterine period.[10,12] Brown *et al.*[11] reported greater levels of irritability in preterm infants exposed to cocaine *in utero*. In our large cohort, we observed no relationship between the gestation and the development of NAS.

Breastfeeding ≥72 hours was independently associated with a halving of the odds of the infant receiving pharmacological treatment for NAS. This is consistent with previous reports,[37,38] but the magnitude of the effect has not previously been quantified. The act of breastfeeding soothes agitated infants,[39] and drugs taken by the mother are excreted in vary ing amounts in breast milk, thus ameliorating the effects of withdrawal.[38,40] The benefits of breast milk extend to preterm infants unable to suckle.[37] Breastfeeding rates in our group were low but must be seen against a breastfeeding rate for the hospital as a whole of 34% by day 5. It is our impression that the majority of our drug misusing mothers who choose not to breastfeed do so as a result of deeply engrained social preju dice and not because of polydrug misuse. With the exception of the small group of women who are HIV positive, we rec ommend that all drug misusing mothers should be encour aged to breastfeed their infants. Rooming in helps to facilitate this.[41]

We believe that a prolonged postnatal stay is important to observe for signs of NAS and also to support breastfeeding

and provide the intense parenting support required by many of the mothers. An extended postnatal stay also facilitates comprehensive social work assessment prior to discharge and organisation of support in the community when required. It is expensive at an estimated cost of £540 per mother/baby postnatal day[42] but compares favourably with NNU (non intensive) costs of £676 per infant per day.[42] The median cost of accommodating a term infant who did not require admission to NNU was £3780, whereas for admitted term infants, the median cost from birth to hospital discharge was £10,812. Consistent with the increased odds of develop ing NAS, duration of hospital stay was longer in infants born to polydrug misusing mothers compared with those taking only methadone.[20] Our cohort represented 2.9% of hospital births but used almost one fifth of the neonatal cot days during the period of the study.

Over half the infants given appointments for the outpatient clinic defaulted on two or more occasions, reflective of the complex lifestyle of many drug misusing parents. Poor atten dance at clinics has been reported by other workers and underpins the need for provision of appropriate support serv ices in the community.[43] We have now adopted a more selec tive follow up policy, with stringent efforts to communicate directly with the health visitor and GP. This is facilitated by a community liaison midwife and by copying all correspon dence to the Social Work Department.

Conclusions

Development of NAS is related to prescribed maternal meth adone dose and may be ameliorated by breastfeeding. Preg nant drug misusing women should be maintained on the lowest dose of methadone compatible with stability and encouraged and supported to breastfeed their infants. Infants born to drug misusing women are highly vulnerable and draw heavily on healthcare resources.

Disclosure of interest

None.

Contribution to authorship

C.D. collected and analysed data and completed the first draft of the manuscript. D.Y. performed statistical analyses and commented upon the manuscript. M.H. assisted with provision of maternal data and reviewed the manuscript. H.M. suggested the review, collected and analysed data and reviewed the manuscript.

Details of ethics approval

The local research ethics committee approved this anonymised ret rospective study.

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