

# Methadone in pregnancy: treatment retention and neonatal outcomes

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## ABSTRACT

**Aim** To examine the association between retention in methadone treatment during pregnancy and key neonatal outcomes. **Design** Client data from the New South Wales Pharmaceutical Drugs of Addiction System was linked to birth information from the NSW Midwives Data Collection and the NSW Inpatient Statistics Collection from 1992 to 2002. **Measurements** Obstetric and perinatal characteristics of women who were retained continuously on methadone maintenance throughout their pregnancy were compared to those who entered late in their pregnancies (less than 6 months prior to birth) and those whose last treatment episode ended at least 1 year prior to birth. **Findings** There were 2993 births to women recorded as being on methadone at delivery, increasing from 62 in 1992 to 459 births in 2002. Compared to mothers who were maintained continuously on methadone throughout their pregnancy, those who entered treatment late also presented later to antenatal services, were more likely to arrive at hospital for delivery unbooked, were more often unmarried, indigenous and smoked more heavily. A higher proportion of neonates born to late entrants were born at less than 37 weeks gestation and were admitted to special care nursery more often. **Conclusion** Continuous methadone treatment during pregnancy is associated with earlier antenatal care and improved neonatal outcomes. Innovative techniques for early engagement in methadone treatment by pregnant heroin using women or those planning to become pregnant should be identified and implemented.

**Keywords** Linked data, methadone, obstetric, perinatal, pregnancy

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## INTRODUCTION

Many of the negative outcomes associated with the continued use of 'street' heroin, such as poor health and nutrition and susceptibility to blood-borne viruses, can also be transmitted to the developing fetus. As such methadone maintenance is considered the 'gold standard' for treatment of opioid dependence in pregnancy [1–3]. Methadone maintenance treatment reduces many of these negative outcomes through substitution of an illicit substance of uncertain composition and dose (heroin) with a pure substitute at a stable dose (methadone). Stabilization on methadone also avoids the danger of repeated intoxication and withdrawal cycles that can lead to a number of adverse outcomes, including premature labour and spontaneous abortion [4–7].

Attendance at clinics to pick up methadone also affords these women the chance to receive the essential antenatal care and advice necessary for a healthy pregnancy they may otherwise be without [8]. This is a critical feature of methadone treatment in pregnancy, and research has shown that methadone in conjunction with adequate prenatal care reduces maternal mortality, lowers the rates of fetal morbidity, fetal wastage and pregnancy-associated complications and promotes fetal stability and growth [2,3,9,10]. A linear relationship between the length of time in methadone treatment and increased attendance at prenatal care and improved maternal and antenatal outcomes has also been reported [8,11–14]. Factors shown to increase retention in methadone programmes include the type and intensity of treatment, the stabilization dose of methadone, the provision of psychosocial services and the availability of take-home

methadone [15–17]. Longer treatment duration is associated with improved outcomes, while short-term methadone treatment where the goal is detoxification and abstinence has been shown to be relatively ineffective [4,12,18]. Case management and child protection services involvement independently facilitate attendance at drug treatment and increase birth weight among infants [14,17].

Studies examining the relationship between retention in methadone treatment and neonatal outcomes have been based on relatively small samples from single treatment sites [3,14]. Studies from specific treatment agencies are, however, limited in their generalizability due to differences in the services provided by agencies and the different characteristics and drug use patterns of their clients [19]. These studies often also lack the statistical power to detect significant associations due to the small number of pregnant drug-dependent women seen in these agencies.

A relatively new method of examining the impact of substance use during pregnancy at the population level is to use record linkage of large-scale population health databases. Record linkage involves bringing together records from different sources, but relating to the same individual [20]. Previous studies using record linkage have examined topics such as death and hospitalization rates associated with the use of illicit drugs [21,22]. The specific aim of the present study is to expand that body of work by using linked administrative health data to describe the association between retention in methadone treatment of pregnant women and key neonatal outcomes.

## METHODS

New South Wales (NSW) is the fourth largest state of Australia, covering an area of 801 600 km<sup>2</sup> and with approximately 6 million residents has the highest population of all Australian states and territories. NSW also has an expansive methadone programme. As at 30 June 1999 there were an estimated 35 400 opioid-dependent individuals resident in NSW, 11 272 of whom were in methadone treatment [23]. As at 3 June 2005 the number of individuals in methadone treatment had increased to approximately 16 000.

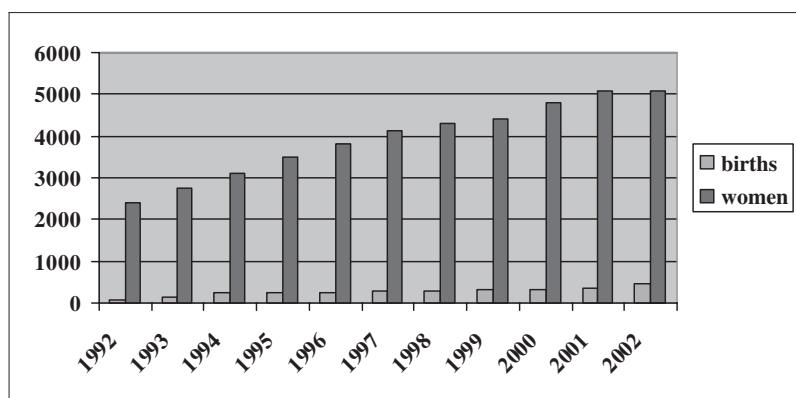
### Linkage

The study used probabilistic record linkage of the client database from the NSW Pharmaceutical Drugs of Addiction System (PHDAS) with the NSW Midwives Data Collection (MDC) and the NSW Inpatient Statistics Collection (ISC). The PHDAS is the system that records when an authority to dispense drugs of addiction in New South Wales (including methadone) by a clinician to a

particular client has been approved by the NSW Health Department. The NSW Midwives Data Collection (MDC) is a collection that provides information about pregnancy care, services and pregnancy outcomes. The collection covers all births in New South Wales of at least 400 g birth weight, or at least 20 weeks gestation. The information recorded in the MDC includes demographics, medical and obstetric information on the mother, and information on the labour, delivery and condition of the infant. The Inpatient Statistics Collection (ISC) is a census of all admitted patient services provided by New South Wales public hospitals, public psychiatric hospitals, public multi-purpose services, private hospitals and private day procedures centres. The information reported includes patient demographics, diagnoses and procedures using *International Classification of Diseases* version 9 (ICD-9) and ICD-10AM codes. ICD-10AM codes are an Australian modification to the World Health Organization ICD-10 classification of diseases and health-related problems. Coding involves the allocation of a code for each relevant diagnosis/condition/disorder/health status and a code for each relevant procedure and treatment that a patient encounters during an in-patient hospital stay. Prior to 1998 20 ICD-9 codes were allowed for each admission and from 1998 onwards 40 ICD-10AM codes were allowed.

Prior to matching the records in these data sets, address details and names were standardised using Autostan. This involved breaking addresses, suburbs, given names and surnames into standardized components derived from existing patterns. In matching, the PHDAS was chosen as the reference file. Matching variables included components of name, address and hospital number. Following linkage, the files were supplied to the researcher as separate de-identified unit record files with a project number to allow for merging.

To establish whether a woman was actively on the NSW Methadone Program at delivery, the MDC records were merged by the researcher to the PHDAS file and records selected where a baby's date of birth occurred between a start and end date of a treatment episode. A new episode of treatment is counted each time an application to prescribe methadone to a particular client is approved by the Director-General of the NSW Health Department or when a client changes their methadone prescriber. This means that, although a woman may have been retained continuously in methadone treatment prior to delivery, she may have more than one episode of care during that time. Continuous treatment was defined as a situation where, if a woman was on multiple programmes, there was at most a 7-day break between programmes and retention in continuous treatment therefore calculated as the number of days in continuous treatment prior to delivery.



**Figure 1** Number of births to women on the NSW Methadone Program at 30 June, by year (1992–2002)

### Comparison groups

Maternal and neonatal outcomes were compared for three groups of women: first, a group who entered continuous treatment at least 1 year prior to birth, the 'early entrant' group; secondly, a group who entered continuous treatment in the 6 months prior to birth (with any previous programme ending at least 1 year prior to birth), the 'late entrant' group; and thirdly, a group whose last treatment programme prior to birth ended at least 1 year prior to the birth, the 'previous treatment' group. In order to compare longer-term outcomes between these groups, we selected births occurring after 1994 for this analysis. To examine neonatal abstinence syndrome (NAS), neonates were flagged as positive for NAS if they recorded an ICD-9 code of 779.5 prior to 1998 (drug withdrawal syndrome in the newborn) or an ICD-10 code of P96.1 (neonatal withdrawal symptoms from maternal use of drugs of addiction) from 1998 onwards.

### Statistical analysis

The data were analysed using the SAS statistical package version 8.2 [24]. Statistical tests between groups using dichotomous variables used  $\chi^2$  tests. Student's *t*-tests were used to compare means of normally distributed variables and Wilcoxon's rank sum tests for those variables with non-parametric distributions. Logistic regression using backwards elimination was used to examine the relationship between retention in treatment and key neonatal outcomes after adjusting for covariates. In the case of multiple births (e.g. twins), the first birth was used. To avoid the effect of multiple pregnancies only first pregnancies were used in the logistic regression analysis.

### Ethics

Ethics approval for the project was granted by the NSW Department of Health Ethics Committee. All data were provided to the researchers only once full

de-identification of records had taken place. De-identified data were held on a password-protected computer with firewall protection.

## RESULTS

Overall, 2993 women were on the NSW Methadone Program at delivery. Figure 1 shows that the number of births rose steadily from 62 in 1992 to 459 in 2002. During this time the majority of mothers had just one birth (64%), 26% had two or more, 8% had three and 2% had four or more births.

### Maternal and neonatal characteristics by retention in treatment

Table 1 compares the characteristics of women who entered methadone treatment at least 1 year prior to delivery (early entrants), those who entered in the 6 months prior to delivery (late entrants) and those whose last recorded treatment episode ended at least 1 year prior to delivery (previous treatment). Late entrants smoked most heavily (62% smoked more than 10 cigarettes per day), followed by early entrants (55% smoked more than 10 cigarettes per day) and those in previous treatment (44% smoked more than 10 cigarettes per day) ( $P < 0.001$ ). Late entrants were also most likely to first access antenatal services later in their pregnancies (at more than 20 weeks gestation ( $P < 0.001$ )). After adjusting for covariates late entrants were 2.3 (95% CI: 1.7, 3.2) times more likely than those in the previous treatment group to attend their first antenatal visit at more than 20 weeks pregnant (Table 2). Late entrants were also younger and less likely to have had a previous pregnancy of  $> 20$  weeks gestation ( $P < 0.001$ ) (Table 1).

With respect to neonatal outcomes, there was a significant difference between the three groups with respect to the proportion of neonates whose birth weight was in the lowest tenth percentile [small for gestational age

**Table 1** A comparison of the characteristics of births to women in the late entrant, early entrant and previous treatment groups.<sup>1</sup>

	Late entry n = 306		Early entry n = 1213		Previous treatment n = 711		P-value
	%	n	%	n	%	n	
Age (years)							< 0.001
< 25	53.7	144	27.2	291	28.4	199	
26–39	39.9	107	56.0	600	55.6	390	
40 +	6.3	17	16.8	180	16.0	112	
Indigenous†	13.0	21	7.0	39	8.6	48	0.04
Cigarettes per day in 2nd half of pregnancy							< 0.001
None	16.1	42	17.9	187	32.6	223	
1–10	22.2	58	27.3	285	23.4	160	
> 10 per day	61.7	161	54.8	572	44.0	301	
% Attending first antenatal visit > 20 weeks gestation	51.9	139	34.4	368	31.5	221	< 0.001
Not booked admission	11.2	30	10.0	107	9.4	66	0.71
Previous pregnancy > 20 weeks gestation	57.4	154	76.5	819	70.6	495	< 0.001
Gestational age of neonate < 37 weeks	28.0	75	18.3	196	14.1	99	< 0.001
Median birth weight (g)	2823		2940		3094		< 0.001
Birth weight% < 10th percentile adjusted for gestational age	29.5	79	30.0	322	21.1	148	< 0.001
Neonate admitted to neonatal ICU†	12.0	19	11.3	63	4.9	27	< 0.001
Neonate admitted to special care nursery†	58.9	93	61.2	342	30.0	167	< 0.001
NAS	20.5	55	23.4	251	4.0	28	< 0.001

†Data from 1998 onwards. <sup>1</sup>Cell numbers may not add to totals where there are missing data.

**Table 2** Adjusted odds ratios and 95% confidence intervals measuring the association between key neonatal outcomes and retention in treatment.<sup>1</sup>

	Early entrants	Late entrants
Small for gestational age <sup>2</sup>	–	–
First antenatal visit > 20 weeks <sup>2</sup>	–	2.3 (1.7,3.2)
Admitted to neonatal ICU <sup>2</sup>	–	–
Admitted to neonatal SCN <sup>2</sup>	3.3 (2.4,4.5)	2.8 (1.9,4.1)
Gestational age < 37 weeks <sup>2</sup>	–	2.6 (1.5,3.3)

<sup>1</sup>Previous treatment entry is the referent category, first births are used to adjust for the effect of multiple pregnancies. <sup>2</sup>Adjusted for smoking (none/1–10 per day, more than 10 per day in second half of pregnancy) and maternal age (< 25; 25–39; 40+).

(SGA)] [25,26], with the previous treatment group having the lowest proportion of SGA neonates ( $P < 0.001$ ). No significant association between SGA and treatment was retained, however, once covariates (see footnote Table 2) were entered into the model. Neonates born to late entrants were also most likely to be born at less than 37 weeks gestation ( $P < 0.001$ ). In comparison to the previous treatment group, after controlling for

covariates neonates born to late entrants were 2.6 (1.5,3.3) times as likely to be born prematurely (Table 2). Similarly, neonates born to late entrants were more likely to be admitted to either NICU or SCN ( $P < 0.001$ ). Once covariates were adjusted for, neonates born to early entrants were 3.3 (2.4, 4.5) times as likely and late entrants 2.8 (1.9, 4.1) as likely to be admitted to SCN (Table 2).

## DISCUSSION

This study is the largest yet undertaken to examine the characteristics of births to women on a state-wide methadone programme. Using this method the estimated number of births to women actively on the NSW Methadone Program was 2993 in the 11-year period 1992–2002, with annual increases from 62 in 1992 to 459 in 2002. As previous research has shown, approximately one-third of the population of heroin-dependent users are in treatment we would expect the number of births to opioid-dependent women to be significantly higher than this [23].

A particular strength of our large sample size was the ability to examine the effect of treatment retention on key neonatal outcomes. Among mothers on methadone at delivery, early commencement on methadone was associated with increased antenatal care and reduced prematurity. This is consistent with previous research that has shown that methadone in conjunction with adequate prenatal care promotes fetal stability and growth [3,6,9,27]. As prematurity is a key predictor of future health, this suggests that strategies should be put into place to encourage pregnant opioid-dependent women to enter treatment as early as feasible in their pregnancies. Previous research has shown, however, that injecting drug use quadruples the risk of amenorrhoea and it may therefore be that a number of heroin-using women confuse their pregnancy status with amenorrhoea and subsequently come into treatment later on in their pregnancy [28,29]. If so, this signals the need to develop models of care that emphasize the education of drug dependent women about pregnancy planning, identifying early signs of pregnancy as well as engaging them in services as early on in their pregnancies as possible. Equally, it may be the case that the current configuration of services or treatment policies are unsuitable for this significantly younger cohort, who may require more flexible and innovative engagement strategies.

Interestingly, we found previous treatment (i.e. the last programme prior to birth ending at least 1 year prior to delivery) was associated with most improvement in maternal and neonatal outcomes, suggesting that for a subgroup of women methadone treatment may be used as a pathway to a lower-risk life-style. This proposition is supported by findings that neonates born to mothers in the previous treatment group had the lowest admission rate to special care nursery and neonatal intensive care and were least likely of the three groups to have a diagnosis of NAS recorded. However, it may also be the case that this group had lower levels of dependence initially or had greater access to services, this requires further examination.

There was also a difference in maternal smoking patterns across the groups (62% in the late entrants, 55% in the early treatment group and 44% in the previous treatment group smoked more than 10 cigarettes per day). Women in the previous treatment group also had the lowest number of low birth weight neonates. As maternal smoking remains a major predictor of poor growth this suggests, as noted by other researchers, that antenatal care opportunities associated with methadone treatment should be used more effectively to introduce treatments to reduce smoking among these women [30–32]. Even though the outcomes for the previous treatment group were improved, almost one-third of this group attended their first antenatal visit late in their pregnancy, at more than 20 weeks gestation. Although our study did not assess the reasons for this, it may be that factors such as past negative experiences with generalist antenatal services, reliance on public transport and location of services and a high number of dependent children make access to services more difficult for these women [33,34].

Measuring the impact of methadone treatment in pregnancy is complicated by polydrug use, not captured in this data set. A number of US studies report that compared to those exposed to cocaine or narcotics alone, neonates exposed to both heroin and cocaine *in utero* were more likely to experience neonatal abstinence syndrome, require medication and show a significantly higher rate of perinatal morbidity (e.g. intrauterine growth retardation, prematurity and fetal distress) [35–37]. The use of alcohol is associated with additional effects such as facial anomalies and mental retardation [38]. Variations also arise from individual differences in metabolic processes, which may be affected by the mother's drug habits and history of drug abuse, number of cigarettes smoked, regularity of eating and sleeping and general health. It may therefore also be the case that the levels of polydrug use differ across the groups in our sample and contributed to the differences in outcomes and this will be the subject of future work.

There were no significant differences in the proportion of neonates transferred to special care nursery (SCN) or neonatal intensive care unit (NICU) between women who entered treatment early or late. Overall, approximately 60% of neonates born to mothers on methadone were transferred to neonatal special care unit and 12% to neonatal intensive care. This is not unexpected, as neonates in both groups were exposed to opiates *in utero*. Previous research has shown a major reason for transfer of neonates born to opioid-dependent women to specialist units is for the treatment of neonatal abstinence syndrome and that this treatment is extensive and costly, and may hinder the development of attachment between the infant and her family [39,40]. Preliminary data to be published in forthcoming work supports this finding as

approximately 40% of these admissions were primarily for the treatment of neonatal abstinence, 30% for conditions related to prematurity or low birth weight and the remaining 30% for a variety of other conditions. Overall, the high and increasing number of babies born to women on methadone therefore suggests the need to develop treatments that will improve the outcomes of these neonates and reduce the need for them to be separated from their primary care givers for lengthy periods of time.

### Limitations

In interpreting these findings it should be noted that neither the Midwives Data Collection or the Pharmaceutical Drugs of Addiction Database were designed for the purposes of examining the impact of drug use in pregnancy, and for this reason there are a number of limitations to the present study. A major limitation was the lack of reliable information on methadone dosage or treatment policies, critical factors affecting both retention and hence outcomes. Findings from linked data studies such as these should therefore be used to direct future prospective research in this area. In a similar light, these data sets do not contain data that may also influence outcomes; for example, hospital or methadone clinic policies that dictate length of stay or treatment regimen for NAS. Neither are predictive variables such as income, violence and other measures of disadvantage included.

The current study controlled only for confounding variables on main neonatal outcomes and future work will examine relationships between variables in more depth. The nature of the study is also cross-sectional and cannot determine cause and effect. Finally, there will always be a unquantifiable proportion of linkages that are false or missed between the two data files [41], and this may be particularly so when linkage is reliant on matching the names and addresses of a drug-using population where transience and the use of aliases is more common.

### Implications

Overall, the present study has shown record linkage to be a powerful and cost-effective means of enhancing our understanding of the impact of methadone in pregnancy. Specifically, the estimation of the number of births born to women on methadone and the definition of key maternal and neonatal outcomes can provide important direction to the planning and implementing of appropriate services for this most disadvantaged subgroup of women.

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