How do premature babies exposed to opiates in utero withdraw?

A comparison of withdrawal symptoms in preterm and term babies exposed to opiates in utero.

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Abstract

Objective:
The aim of this research is to discover the rate and pattern of withdrawal observed in premature babies exposed to opiates (heroin, methadone and buprenorphine) in utero.

Methodology:
To determine the incidence and severity of neonatal abstinence syndrome in term and preterm babies, a retrospective case note review was undertaken of all women who delivered at a tertiary obstetric hospital, from January 2003 to December 2007 inclusive, who were regularly using heroin, or prescribed methadone, or buprenorphine. Neonatal abstinence syndrome (NAS) was diagnosed using the modified Finnegan NAS scoring system. A control group of non-opiate-exposed mothers and babies matched for gestation, gender and postcode as a marker of socioeconomic status were also selected. Their postnatal course and incidence of co-morbidities was compared to the preterm opiate-exposed cohort.

Results:
There were 149 opiate-exposed babies included in our study. 108 were term and 41 were preterm. The overall rate of NAS was 32.9%, with no significant difference between term and preterm babies. The mean gestation of those babies with NAS was 37.5 weeks. Those babies with NAS had significant difficulty in establishing feeding, particularly in the term group. Length of stay between preterm and term babies with NAS was comparable.

Preterm opiate-exposed babies took significantly longer to regain their birth weight when compared to non-opiate-exposed controls. Length of stay in hospital was increased, only if neonatal abstinence syndrome was diagnosed.

Conclusion
Opiate-exposed babies experience withdrawal across gestations. Preterm opiate-exposed babies take significantly longer to return to their birth weight. This could reflect stress, which manifests as poor weight gain.
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A comparison of withdrawal symptoms in preterm and term babies exposed to opiates in utero.

1 Introduction

1.1 Background

Drug use in pregnancy, particularly with opiates, has been discussed and studied at length since the 1960s, as the large numbers of mothers and babies involved became evident. The visible suffering of the affected babies due to drug withdrawal led to further work in both understanding the biological mechanisms that underlie the symptoms and signs of withdrawal, and defining the most effective medical treatment for ameliorating that suffering.

Neonatal abstinence syndrome (NAS) is a constellation of physical signs and symptoms seen in babies exposed to drugs of addiction in utero, and it is most often considered in relation specifically to opiates. It comprises respiratory signs, such as an increased respiratory rate, gastrointestinal signs, such as vomiting, poor feeding, and diarrhoea, as well as central nervous system signs including excessive crying, increased muscle tone, and seizures. The symptoms and signs of NAS were compiled after observation of many drug-exposed babies, who were largely born at term, and used to construct an assessment tool, such as the Finnegan NAS severity score. A modified version of this is used at the Mercy Hospital for Women to assess babies born to mothers known to have taken opiates during pregnancy. The modified Finnegan NAS score is used to determine which babies have NAS so severely that they require treatment, usually with oral morphine.

It has been a long-held view that withdrawal from opiates is less common and less severe in preterm babies, than in babies born at term. There are several reasons why preterm babies may be less vulnerable to in utero opiate exposure than term babies. These include prematurity itself, where there is less overall exposure to
maternal opiate consumption during pregnancy, or the relative immaturity of liver enzymes metabolising methadone so that its breakdown, and therefore the withdrawal process, is far more gradual. Finally, NAS is itself assessed by observations made using recognised assessment tools, such as those created by Finnegan et al4 and Lipsitz5. These tools were originally largely intended for use in term babies. It is possible that preterm babies do develop a neonatal abstinence syndrome that our current methods of assessment are unable to detect. Their expression of opiate withdrawal may be subtle. It may be demonstrated by a delay in reaching recognised neonatal milestones, such as establishing full enteral or suck feeds, or gaining weight, or an increased frequency of common neonatal complications, such as sepsis or apnoea, or congenital anomaly. These factors are outside the scope of the current assessment tools used.

It is clear that the development of NAS is subject to many factors, such as the dose, duration, and type of opiate used in pregnancy6, as well as the effects of polydrug use, including cigarette smoking, and the quality of antenatal care7. There are many external influences, which affect neonatal outcome, such as housing, poverty, and maternal health and wellbeing8. These are all potential confounders in establishing a clear and direct link between gestational age and the rate of NAS.

Without recognising the presence of NAS in babies, term or preterm, we are denying them treatment, which may alleviate the suffering associated with drug withdrawal. There is the possibility that the mother-baby bond may be affected when a perhaps irritable, poorly feeding baby is discharged into the care of a mother, who is herself opiate-dependent, and potentially without adequate support. Once identified as a high-risk baby, there is an opportunity to intervene in the long-term health and wellbeing of this child.

1.2 Aims and Scope

The aim of this research is to discover the rate and pattern of withdrawal observed in premature babies exposed to opiates in utero. The type of opiate used by mothers in pregnancy was limited to methadone and buprenorphine, which are used for opiate maintenance, and heroin. Mothers dependent on other prescribed opiates such as oxycodone were excluded from the study, as these drugs are more
inconsistently documented in patient notes. The study was conducted at the Mercy Hospital for Women, a tertiary metropolitan hospital in Melbourne, with a Level 3 neonatal unit, which accepts referrals from across the state of Victoria. It holds a separate antenatal clinic for opiate-dependant pregnant women, known as the Transitions Clinic, involving a multidisciplinary team of obstetricians, midwives, paediatricians, psychiatrists, and social workers.

1.3 Overview

In Chapter 2, the available literature on neonatal abstinence syndrome in term and preterm infants is examined. Section 2.1 looks at the current theories as to why NAS is thought to be less common and less severe in preterm opiate-exposed babies. The association between opiate exposure and the occurrence of NAS is explored in Section 2.2, and the tools, by which NAS is diagnosed and assessed, are examined in Section 2.3. There are many factors, external to the opiate exposure itself, which may impact on the development of NAS in the newborn, which are not taken into account when only the Finnegan assessment tool is considered. This is discussed in Section 2.4. Section 2.5 describes the metabolism of opiates in mother and baby. Section 2.6 deals with the effects of opiates on the fetus, whilst Section 2.7 looks at the long-term effects of in utero opiate exposure. A discussion regarding the long term effects of in utero opiate exposure is included as it serves to highlight the importance of diagnosing NAS in the first instance, as well as understanding that the consequences of NAS extend beyond the neonatal period.

In Chapters 3 and 4 the formulation of the hypothesis and the research method is described. This involves comparing the withdrawal process in term and preterm opiate-exposed babies, using the current gold standard method of assessment in Australia, which is the modified Finnegan NAS scoring system. The study model also involves exploring factors outside the modified Finnegan scoring system, and their presence in both opiate-exposed and non-opiate-exposed babies.

In Chapter 5 the results of the study are presented in two parts. The first part looks at the results of comparing neonatal abstinence syndrome in term and preterm babies in our study population. The second part compares preterm opiate-exposed and non-exposed babies in terms of growth, feeding, and neonatal complications.
Finally, in Chapter 6 the effects of opiate exposure in preterm and term babies will be further discussed, with regard to their clinical manifestations, and conclusions drawn.
2 Literature Review

2.1 Studies on term and preterm babies with NAS

Despite the presence of numerous studies on neonatal abstinence syndrome\textsuperscript{9,10,11} there is a paucity of information regarding the relationship between preterm birth and neonatal abstinence syndrome, in opiate-exposed babies. Most studies either excluded babies born preterm, or included all opiate-exposed babies, regardless of gestation. There are only two articles specifically investigating NAS due to opiate exposure in both term and preterm populations.

The first study was conducted by Doberczak et al\textsuperscript{12} and was published in 1991. It was a well-designed study, and prospectively followed 212 women prescribed methadone in pregnancy, and their babies, all of whom were admitted to the neonatal special care unit after delivery. Drug exposure was established by maternal self-report and urine drug screens. Information was also gleaned from social services and methadone maintenance programs. Gestational age was assessed by using the Ballard score, with prematurity defined as less than 37 completed weeks of gestation. Babies were assessed using the Lipsitz tool\textsuperscript{5}, which is described further in Chapter 2.3. The Lipsitz tool scores 11 signs, and is usually performed 12 hourly. A score of greater than 4 is required to diagnose NAS and commence treatment. However, for this study, “mild” symptoms were associated with a score less than 6, “moderate” symptoms had scores between 7 and 9, and “severe” symptoms had total scores over 9. Treatment (with either paregoric, Phenobarbital, or both) was commenced with scores equal to or greater than 7, though on how many occasions was unclear. In addition, scores from the central nervous system (CNS) section, such as tremors, irritability, and increased reflexes, were also summed, giving a "CNS score".

Of the 212 women enrolled in the study, 178 delivered at term. The mean gestational age was 39.5 +/- 1.4 weeks. One hundred and forty five (or 81\%) of these babies required pharmacotherapy in response to high scores. The median total severity score was 7. Abstinence-associated seizures occurred in 13 (or 7\%). In the preterm group, 20 of the 34 babies (58\%) required treatment, with a median
severity score of 5.5. The mean gestational age was 34.3 +/- 2.6 weeks. Of note, the article states that the mean methadone dose ‘in late pregnancy’ was the same in both the term (49.7 +/- 23.3mg) and preterm (50.1 +/- 18.3mg) groups. However, it is unclear whether the preterm babies were exposed to 50mg methadone prior to delivery at 34 weeks, and the term babies were also exposed to a similar dose at 34 weeks, or that they were on this dose at term. Regardless, there was a significantly greater incidence of polydrug use in the term population (heroin, cocaine, benzodiazepines, barbiturates and amphetamines), which may have increased the likelihood of withdrawal in this group.

Nevertheless, the conclusions from this study have formed the basis of the current knowledge of how preterm and term babies exposed to opiates in utero behave. Doberczak et al found that preterm babies have a lower rate of neonatal abstinence syndrome than term babies. Neonatal abstinence syndrome is less severe in this group, as shown by the lower peak severity scores, and by the decreased need for treatment with pharmacotherapy. The peak severity scores occurred later in the preterm group, and a significant correlation between gestation and total severity score was found. From this Doberczak et al were able to conclude that the signs of NAS were related to the developmental maturity of the neonate.

There were many theories postulated to explain these findings12,13. The first relates to the developmental immaturity of the preterm baby. Central nervous system immaturity would lead to decreased expression of central nervous system signs such as seizures and alteration in tone. Immaturity of hepatic enzymes would lead to delayed metabolism of methadone, and therefore a later and perhaps milder withdrawal process.

The second theory involves a relationship between maternal methadone dose and the presence and severity of NAS across the range of gestational ages. Doberczak found that there was a significant correlation between peak CNS abstinence severity scores and maternal methadone dose in both term (p<0.05), and preterm (p<0.01) babies. Interestingly exposure to methadone alone (n=42) compared to methadone and heroin (n=107) did not alter the severity of abstinence symptoms. However, the ability to quantify heroin exposure is limited, so this may reflect low heroin intake in this study.
The third theory refers to the appropriateness of using a single scoring system in order to assess NAS in term and preterm babies. The scoring systems are discussed in detail in section 2.3. Clearly, regardless of the scoring system used, it is difficult to assess such things as feeding performance or sleep patterns consistently and meaningfully across gestations spanning 25 to 42 weeks.

In 2007 Dysart et al published a paper outlining the differences in neonatal abstinence syndrome in preterm and term babies exposed to opiates in pregnancy. This was a retrospective study including term and preterm babies whose mothers were on methadone and who were treated for neonatal abstinence syndrome. The primary outcomes were length of stay, and the duration and dose of treatment required to manage the symptoms and signs of NAS. Babies were assessed using a modified Finnegan scoring system and required three scores greater than 8 to warrant treatment. The treatment protocol involved neonatal opiate solution (morphine) to a maximum dose of 1 mg/kg/day, with the addition of phenobarbitone or clonidine at the discretion of the treating physician if symptoms of NAS remained a problem.

There were 53 preterm babies, with a mean gestational age of 34.2 weeks (range 27-36 weeks), and 66 term babies, with a mean gestational age of 38.7 weeks (range 37-42 weeks). They had similar in utero illicit drug exposure, but, critically, there is no information regarding methadone dose. For preterm babies the length of stay was 28.4 +/-13.4 days, compared to 37.8 +/- 19.6 days (p<0.05) for the term babies. Interestingly treatment with morphine for NAS was not a significant predictor of length of stay. Length of treatment in the preterm group was 19.8 +/-12.5 days, compared to 31.8 +/-17.3 days (p<0.05) for the term babies. The maximum dose of morphine used was 0.43 +/- 0.2 mg/kg/day, compared to 0.62 +/-0.28 mg/kg/day in the term group.

Both the dose of morphine required to control the symptoms of NAS and the duration of treatment are difficult to interpret as the management of NAS at the study hospital (Mercy Hospital for Women) is largely protocol-driven, and therefore more standardised. It is customary to commence morphine treatment at 0.5 mg/kg/day, titrating upwards or lower depending on the clinical picture. Weaning the morphine dose is done systematically, 10% every 72 hours, guided by clinical response. It would be expected that the baby’s NAS scores would fall once
treatment had commenced. Should the scores remain high, or continue to rise, the morphine dose could be increased, and/or phenobarbitone could be added.

Dysart et al explained their results in a similar way to Doberczak, i.e. altered methadone metabolism, central nervous system immaturity, and reduced overall opiate exposure in the preterm group were suggested. However, both these studies leave many questions unanswered. Firstly important information regarding maternal methadone dose is missing in both studies. Although the link between methadone dose and neonatal abstinence syndrome has been debated it is difficult to draw conclusions regarding the risk of NAS without having this information available. There is little information provided regarding antenatal care, other neonatal complications, and socioeconomic or demographic data. Secondly, it is possible that opiate withdrawal is present but manifests differently in the preterm population, and further examination of the standardised assessment tools used is necessary. This is addressed in section 2.3.
2.2 **NAS and opiate exposure**

2.2.1 **Methadone**

Methadone has been used as a substitute for illicit opiate use since the early 1960s. It is a synthetic opiate, administered orally, usually daily. It is well-absorbed from the gastrointestinal tract, with peak concentrations being reached at approximately four hours after ingestion. Methadone is largely protein-bound, metabolised in the liver and excreted in the urine as pyrrolidines and pyrroline\textsuperscript{15}.

The use of an opiate substitute, such as methadone is thought to reduce drug-seeking behaviour, and add safety and overall stability to the lives of people with an opiate addiction\textsuperscript{16,17}. Initially its use in pregnant women was considered controversial, as there was concern regarding the safety of the drug for the unborn baby. However, the number of women with opiate addiction of child-bearing age is high, and gradually the positive effects of methadone on pregnancy, such as higher birth weights and decreased risk of preterm birth when compared to that of heroin-users\textsuperscript{16,17}, became evident. By the 1980s and early 1990s, methadone maintenance for women with opiate dependence in pregnancy became standard practice\textsuperscript{17,18}.

Despite it being accepted practice to commence and stabilise women addicted to narcotic drugs on methadone, or in more recent times, on buprenorphine, we still have many unanswered questions. Should a woman be maintained on as little methadone as possible through her pregnancy, leaving her to possibly crave and access illicit drugs, or should the methadone dose be increased as the pregnancy progresses, satisfying her opiate requirement, but possibly leaving the fetus at increased risk of NAS? Although the relationship between maternal methadone dose and neonatal abstinence syndrome has been investigated a number of times, it has never been completely established. The advantage of methadone is its ability to stabilise a drug user's life. At effective doses, methadone can prevent the onset of withdrawal symptoms for twenty-four hours or more. It can reduce or eliminate drug craving, thereby diminishing the need for criminal or drug-seeking behaviour\textsuperscript{18}. As a prescribed medication there are assurances regarding the actual content, quality and quantity of each methadone dose, unlike illicitly purchased drugs. As an oral preparation, there is a degree of safety against blood-borne viruses, such as HIV.
and hepatitis C. Perhaps most importantly, a structured methadone program brings the drug-using pregnant woman into contact with medical and social services to help correct all the other issues of concern, such as maternal infections or illness, anaemia, tailored antenatal care, financial and legal aid, as well as assistance with housing.

There are clearly a number of compelling arguments for the universal prescribing of methadone to pregnant addicts. Certainly, this view is held by the authorities in Sweden, who have taken a more punitive view toward women, who are unwilling, or unable to comply with a program of methadone maintenance, and no other drug use. The rationale for this approach is that the rights of the fetus are paramount. Indeed continued intravenous drug use would produce greatly fluctuating maternal opioid levels, and methadone could protect the fetus from repeated episodes of withdrawal. However, there is no consensus opinion regarding methadone dosage in pregnancy, and the possible increased risk of neonatal abstinence syndrome with methadone has raised concern.

A relationship between the rate of NAS and methadone dosage was investigated by a number of authors. Some found an increased rate of NAS with increasing methadone dose, whilst others detected no such link. However, evidence exists that the rate of NAS is higher in mothers of babies on methadone, compared to those on heroin. If there is a relationship between methadone dose and rate of NAS, this may add weight to the theory that preterm babies have less NAS because their gestation and therefore their duration of methadone exposure, is less. Could it be that those preterm babies that are diagnosed and treated for clinically discernible NAS have a higher methadone dose prior to delivery than those methadone-exposed preterm babies that do not develop NAS?

When one considers the long history of methadone substitution for pregnant drug users, it is interesting that a relationship between methadone dose and the development of NAS has neither been proven nor discounted. If clinicians are coercing pregnant opiate-addicted women to comply with methadone treatment, and if they are choosing between using the lowest possible dose and the dose that best treats the opiate-dependent mother, then the evidence needs to be examined critically.
Dashe et al\textsuperscript{20} studied 70 pregnant opiate-addicted women and their babies between 1990 and 2001, with the aim of finding a relationship between maternal methadone dose and neonatal withdrawal. Women were first offered detoxification, so they would no longer be opiate-dependent at all, or for those who declined or who were unable to complete detoxification, methadone maintenance was either commenced or continued. Of the 70 women, 27 underwent detoxification, and 43 (61\%) were on methadone maintenance. The median methadone dose prior to delivery was 20mg (range 0-150mg), reflecting the many who chose the detoxification path. Although the women were said to not differ in characteristics such as age, ethnicity, or reported substance abuse history, again there are no data regarding socioeconomic status, or duration of heroin or methadone use prior to the detoxification.

In Dashe's study, the women on higher methadone doses were significantly more likely to be also taking heroin (p=0.04). Interestingly, higher methadone dosage was significantly associated with birth weight less than the tenth centile, and positive neonatal drug screens for opiates, and for cocaine (all p<0.05). The argument for prescribing higher methadone doses in later pregnancy has been to promote fetal growth, so this finding is difficult to explain. However, it could be explained by the concomitant heroin and/or cocaine use, and correlate with a more ‘severe’ opiate dependence. With regard to neonatal abstinence syndrome, 46\% of the neonates were treated for withdrawal. Of the 25 women who received 20mg or less of methadone per day, only 3 of their babies developed NAS, but in each of these cases, the women had completed opioid detoxification less than 48 hours prior to delivery.

Further, Dashe found that 90\% of the babies born to mothers on 40mg or more of methadone per day developed NAS. Whilst this is in keeping with previous studies by Doberczak\textsuperscript{23} who linked NAS with increased methadone dose, the relationship is not straightforward. He explains his findings by stating that his team actively encouraged detoxification, so those on higher doses were the more ‘severely’ addicted, and less likely to cease heroin use, regardless of their methadone dose. However because there is only information regarding the maximum methadone dose prior to delivery, we do not know when, or at what gestation methadone was commenced, the rate of dosage increments, or the amount of polydrug use that occurred throughout the pregnancy. It is also worth noting that the number of babies with a dose of methadone of 40mg or greater would have been small (less than 20).
McCarthy reviewed the case notes of 81 methadone-maintained mothers and their babies cared for by a methadone program in California between 1999 and 2003. Methadone doses throughout the pregnancy were increased according to maternal requirements, with a range of 14-190mg/d, generally administered at least twice daily. The cohort was divided into a high-dose (greater than or equal to 100mg/d) and a low-dose (less than 100mg/d) methadone group, and the rate of NAS in their babies was examined. The mean dose was 132mg in the “high-dose” group and 62mg in the “low-dose” group. There was no significant difference in the rate of NAS in the two groups. In the low dose group, 19 babies (51%) required treatment compared to 18 (49%) in the high dose group (P=0.32). The overall rate of NAS across the two groups was 46%. The use of higher doses of methadone in pregnancy, compared to either Dashe or Doberczak, was associated with a lower or comparable rate of NAS in the baby.

The relationship between opiate exposure and risk of severe neonatal abstinence syndrome is not simple. Firstly obtaining accurate information regarding the exact methadone dose taken and at what gestation, is difficult, particularly when concomitant heroin, cannabis, and/or benzodiazepine use, either overtly or covertly, has also to be taken into account. An accurate estimate of overall antenatal drug exposure will help predict the development of neonatal abstinence syndrome. Information regarding drug exposure comes firstly from maternal history, then maternal screening, usually of urine.

In the neonate, screening also most commonly involves testing urine. A urine drug screen is limited by the relatively short elimination half-life of some drugs. It may confirm drug use in the previous one to eight days. Although not always readily available, meconium testing may be performed on the neonate. Because meconium is formed in the fetus from the sixteenth week of gestation, it can reflect drug exposure in the fetus across the last two trimesters. Analysis of hair, either from the mother or baby, can also reflect drug exposure, depending on hair length. In a baby, hair analysis is limited by the size of the hair sample. In the mother, hair analysis is also affected by hair length, racial differences, and chemical treatment.

Nevertheless, Vinner attempted to correlate maternal history of drug use (opiates, methadone, cannabis, cocaine and benzodiazepines) with drug testing results, on
maternal hair and urine, and neonatal hair, urine, and meconium. The study was small, with only 17 mother-baby pairs consenting, of whom 8 developed a neonatal withdrawal syndrome. It was interesting because, despite a negative neonatal urine drug screen, toxicology on meconium and/or hair confirmed prenatal drug exposure. Meconium or hair screening is therefore useful when a neonate exhibits withdrawal signs, but no accurate history of maternal drug use in pregnancy is available.

Another factor potentially influencing the development of NAS is the time at which methadone maintenance was commenced. McCarthy et al.\textsuperscript{25} compared outcomes of 22 babies born to mothers who conceived on methadone, with 35 babies born to mothers who commenced methadone after conception. Methadone dose at delivery was not significantly different between the groups. The dose at delivery was 110 mg for the “conceived on” methadone group compared to 93 mg for the “conceived off” group. There was no significant difference in the rate of NAS requiring treatment between the two groups, even though the “conceived on” group had a longer history of opiate addiction (12.7 versus 7.7 years, \(P=0.0001\)) and the “conceived off” group had more positive urine drug screens, though not statistically significant, in the neonates. There was no evidence to show that the time of commencement, the duration or the total dose of methadone, make any difference to the development of NAS. Once again, the limitation of this study is the small sample size. Nevertheless, it does provide evidence that total opiate exposure in utero, alone, does not directly correlate with the development of NAS.

NAS is said to occur in 30 to 80\% of opiate-exposed babies.\textsuperscript{21} So, why do only some babies exhibit withdrawal? Doberczak et al.\textsuperscript{23} hypothesised that clinically discernible NAS was due to a fall in neonatal plasma methadone levels, classically around day four of life, when withdrawal from methadone usually becomes apparent. In her study there were 21 mother-baby dyads, of whom 14 were polydrug users. Two babies were born prematurely at 35 weeks. Blood samples for methadone levels were taken from the mother after delivery, and from the neonate after birth, and again on day 4. Importantly, only 14 pairs had all three samples taken. 17 of the 21 babies required treatment for severe NAS, based on the Lipsitz assessment tool.

Doberczak found that there was a significant relationship between maternal methadone dosage at delivery and maternal plasma methadone level 16 hours
postpartum. In turn, the relationship between the maternal plasma methadone level postpartum and the neonatal plasma methadone level on day 1 of life was also significant. Further, the relationship between the initial neonatal plasma methadone level and its rate of decline was also found to be significant. She concluded that lowering maternal methadone doses in late pregnancy could be protective against NAS. However, this study is limited by its small numbers, with a complete data set available for only 14 mother-baby pairs. Although the rate of NAS did not differ between those only on methadone and those supplementing with other illicit drugs, notably cocaine, only 7 were not polydrug users. Two of the babies were born prematurely, and it is unclear whether they were amongst the babies withdrawing.

The mean dose of methadone used in the last trimester was 47mg +/- 16mg (range 20-80). The doses, when compared to those in our study, are not high, yet the rate of NAS reported in the study is high (17 out of 21).

In more recent times, Wouldes and Woodward again revisited the issue of maternal methadone dose and its effect on neonatal outcome, in a prospective study based in Auckland. They followed a cohort of 32 methadone-exposed babies and 42 non-methadone exposed babies, from the third trimester of pregnancy to 6 to 7 months corrected gestational age. Methadone dose through the course of the pregnancy was obtained from the maternal medical record, and, in addition, the women were interviewed regarding their drug and alcohol history. 16 of 32 women on methadone conceived on methadone maintenance. The mean daily dose at booking was 58.97 +/- 29.45mg, and at birth was 63.84 +/- 31.17mg. The Finnegan scoring system was applied hourly for the first 24 hours, and then 4 hourly until discharge. Treatment was started if two scores greater than or equal to 8 were recorded.

For analysis, the cohort was divided into three groups: “no” group (not on methadone), “low” group (less than or equal to 58mg/day), and the “high” group (greater than or equal to 59mg/day). In addition to methadone dose, other possible factors influencing neonatal outcome were included, such as maternal demographics, level of education, and obstetric and medical history. Exposure to methadone at “high” dose in pregnancy affected fetal growth as well as neonatal morbidity. The study showed that the “high” dose group weighed less (p=0.001), and had smaller head circumferences and length (p=0.001). This is similar to the results
noted by Dashe\textsuperscript{20}, discussed earlier. 56\% of the infants of the “high” dose group were born prematurely.

The neonatal morbidity in the “high” dose group (n=16) was reflected not only in the 50\% rate of NAS, compared with 19\% in the “low” dose group, but also the increased rate of neonatal complications. Congenital anomalies included one baby with a cardiac defect and one with a cleft palate. Three babies in the “high” risk group died of SIDS by 7 weeks of age. This group also had an increased risk of NICU admissions and an increased length of stay (median 20.5 days range 6-91), compared to the “low” dose group (7.5 days, range 4-22 days), and the “no methadone” group (3.0 days, range 2-34).

There were a number of other associations between high-dose methadone and maternal social factors. This group had lower parental education levels, increased rates of unemployment, and a higher proportion of miscarriages and intrauterine growth retardation in previous pregnancies. More women in this group had positive hepatitis C serology, depression, used other drugs such as marijuana and benzodiazepines, and smoked more than 10 cigarettes per day.

In this study the methadone dose even in the “high” dose group was modest, with a mean of 63.84 +/-31.17mg. However, their results indicate clear dose-related effects of methadone on the fetus and newborn. However the “high” dose group also had a number of confounders such as polydrug use, cigarette smoking and low socioeconomic status, which could influence both intrauterine growth as well as the development of NAS. In addition, the study numbers were small. In its favour is that it is prospective, and the details of these confounders can be examined closely.

Thus, review of the literature evaluating the relationship between methadone use in pregnancy and the risk of developing NAS, gives conflicting results. Some authors finding a dose dependent relationship, whilst others finding none. Further, there is a suggestion that those with the greatest degree of opiate-dependence, those maintained on the highest doses of methadone, with or without polydrug use, may represent a more susceptible group to NAS and other serious complications. Do these women because of their socioeconomic status, smoke more, have a greater opiate/drug-dependence, and predisposition to complications in pregnancy such as smaller babies, prematurity, and neonatal complications? Or is it the drug
dependence per se that creates this situation? It is always difficult to establish drug exposure in utero. Drug screens, of urine, meconium, and hair, are useful adjuncts to maternal interview when establishing drug exposure. However, their use is limited by cost, availability, and the potential to jeopardise a relationship of trust.
2.2.2 **Buprenorphine**

Buprenorphine is an alternative maintenance medication in opiate dependence. It is a semi-synthetic opiate, which acts as a partial agonist to the \( \mu \)-opioid receptor\(^{15} \). It is a newer agent used for opiate substitution. It has been approved for use in pregnancy outside of Australia. Because it is a partial agonist, it may give some protection in the case of overdose. However, it still produces the morphine-like effects desired by those with opiate-dependence. Because it has a longer duration of action, alternate day dosing may be used. When compared to placebo, buprenorphine is found to be better at suppressing heroin use at moderate (8-12mg) and high (16mg) doses, but not at low (6mg or less) doses. When compared to methadone, buprenorphine is less effective at suppressing heroin use, if both are prescribed at moderate doses (i.e. methadone at 60-120mg per day)\(^{27} \). Information regarding its use in pregnancy is reassuring, but at the time of our data collection, buprenorphine had not been approved for use in pregnant women in Australia. Those women on buprenorphine at the time of conception were either changed to methadone or, if they wished to continue on it, signed a form acknowledging that buprenorphine had not been approved for use in pregnancy here.

Jones et al \(^{28} \) conducted a randomised double-blind study comparing the effects on the neonate of methadone or buprenorphine in pregnancy, on the rate of NAS, length of stay, and peak NAS scores using a modified Finnegan scoring chart. Women were enrolled from 16 to 30 weeks gestation as the authors were concerned regarding the possible effects of buprenorphine on the developing fetus. The treating medical staff were blinded to the medications used but were aiming to reach a target dose of either 20-60mg of methadone or 8-12mg of buprenorphine, before titrating the doses according to patient need. Voucher payments were used as financial incentives against concomitant use of other drugs or alcohol. Consequently the results were uncontaminated by the effects of polydrug use. Unfortunately, the study is limited by small numbers, with 11 babies in the methadone group and 9 babies in the buprenorphine group. 5 babies in the methadone group developed NAS, compared with 2 babies in the buprenorphine group. The total length of stay for the methadone-exposed babies was 8.1 days, compared with 6.8 days for the buprenorphine-exposed babies (\( P \ 0.021 \)). There were no birth complications with either medication, and there is a suggestion that buprenorphine-exposed babies may
develop less NAS. Those that do develop NAS may require shorter periods of hospitalisation, which is important from both a maternal and hospital point of view.

Kakko reported rates of NAS of any severity of 60-80% in neonates exposed to methadone in utero. NAS was defined as a single score of 8 or greater, using the Finnegan scoring chart, with three consecutive scores of 8 or greater constituting "NAS requiring medication". His study was based in Stockholm, in the unit where all babies born to mothers with opiate dependence are managed. In this study the outcome in pregnancies of women maintained on methadone were compared with those maintained on buprenorphine. The methadone maintained group was derived from a retrospective review of all methadone-exposed babies and their mothers between 1982 and 2006. There were 26 women, who delivered 36 babies in this arm of the study. The buprenorphine group were prospectively recruited, consisting of 39 women and 49 babies. In 27 of the pregnancies, buprenorphine was started before conception, and 20 after. 8 women became pregnant twice, and 2 women became pregnant with twins. The mean dose of buprenorphine given was 15.4 +/- 6.4mg (range 2-32mg). The mean dose of methadone given was 71.3 +/- 27.3mg (range 20-120mg).

The study showed that methadone-exposed babies have a higher rate of NAS (52.8% compared to 14.9% for buprenorphine-exposed babies, P =0.0004), and a longer length of stay (19.7 +/- 18.8 days when compared to 9.4 +/- 8.4 days in the buprenorphine group, P=0.0009). Interestingly, women on buprenorphine commenced prior to conception had a trend towards lower rates of NAS (7.4%) than those commenced later in pregnancy (25%; P=0.11). As far as intrauterine growth is concerned, birth weights in the methadone-maintained group were lower, with the proportion of babies born below 2500gm being significantly higher than in the buprenorphine group (25% versus 6.4%, P=0.03).

The benefits to the neonate of buprenorphine over methadone, in pregnancy in this study, are at odds with those presented by Lejeune in 2006, who found no difference. However, Kakko argues the benefits of using adequate doses of buprenorphine decrease the need for illicit drug use, which could explain the increased rate of NAS in babies exposed to buprenorphine in Lejeune's study. In that study the mean buprenorphine dose was 5.4 +/- 4.5mg (range 0.4-24mg), which is associated with a low rate of maternal retention in treatment, and a high rate of
illicit drug use. In addition Kakko’s study was undertaken in Stockholm, where there is a designated hospital unit with a multidisciplinary team to offer support to the mother and baby. This is in the context of Sweden’s policy of “zero tolerance” to illicit drugs in pregnancy, which states that women may be committed to involuntary residential care if they are unable to comply with a policy of taking only prescribed methadone or buprenorphine in pregnancy.

Kahila et al conducted a prospective study in Finland following 66 women who were on buprenorphine, and their 67 pregnancies. 9 of the women were already on buprenorphine maintenance at the start of the pregnancy, and 24 were commenced on buprenorphine maintenance. In the remaining 34 pregnancies the women were said to have a chaotic lifestyle and did not commit to outpatient therapy. They had poor antenatal attendance. 9 women were on a program of weaning dose and were off buprenorphine completely by the end of their pregnancy. 18 (27%) infants had drug-free urine screens and did not withdraw. 45 babies had buprenorphine-positive urine samples, and 38 withdrew, requiring morphine for NAS. The study concluded that neonatal abstinence syndrome was common among babies exposed to buprenorphine in utero.

In summary there is no clear and irrefutable dose-response relationship between prescribed opiate dose and development of NAS. This may be due to confounders such as polydrug use, or the availability of supportive antenatal care. However, managing opiate-dependent women in pregnancy is best achieved by a multidisciplinary team, providing holistic care, and the prescription of maintenance opiates to decrease drug-seeking behaviour. Individual variation in response to the same prescribed dose of opiate raises the question of possible individual vulnerability to opiates and the development of a withdrawal syndrome in the newborn.
2.3 **Assessment Tools for NAS**

Review of the literature has a clear line of demarcation, dividing those studies of the neonatal abstinence syndrome that pre-date the design of a formal assessment tool, to those that utilise it. Despite the multiplicity of assessment tools being used, their value lies in the fact that the staff involved in caring for drug-exposed babies are directed to observing the whole baby, at regular intervals, using a checklist. Even if the staff vary from shift to shift, at least in theory, the same symptoms and signs are being observed. Not only can babies with NAS be compared within one institution, but because most institutions worldwide use either the modified Finnegan NAS score or the Lipsitz tool, it allows babies to be compared across institutions.

The inventory of opiate withdrawal symptoms and signs outlined in the Finnegan NAS scoring system are often drawn upon when assessing any baby thought to have been exposed to drugs in utero. Even if the drug exposure is known to be that of methadone, the spectre of polydrug use has to be considered. Depending on the drug in question, the withdrawal process may be altered clinically. Most studies of neonatal withdrawal rely on maternal disclosure, at least in part, as drug screening of urine is not universal, and meconium testing is not readily available. Thus, reported rates of NAS may be coloured by the effects of other drug exposure. Studies such as Kuschel et al argue that obtaining data in centres such as Auckland, where polydrug use is thought to be lower than that in bigger countries such as the United States, could reduce the effect of polydrug use as a confounder in research related to neonatal opiate withdrawal.

2.3.1 **Finnegan Scoring System**

In 1975 Finnegan wrote of the problem of neonatal drug withdrawal, of the growing numbers of affected babies identified in neonatal nurseries across the United States, and the role of paediatricians, each with varying experience, in managing and treating the condition. The lack of a standardised approach in assessment, management, and, if required, treatment of babies with NAS has led to under- or overtreatment of these babies, with medication, which often varied in type and dose. Finnegan recognised the difficulty in comparing data derived from other centres.
when the assessment process was so subjective. She was one of the first to pool together the expertise in the different medical specialities involved in caring for the pregnant drug-using mother, and her baby. This holistic multidisciplinary approach (Obstetrics, Paediatrics, and Psychiatry) is used in many centres today.

The Finnegan Neonatal Abstinence Severity Score was created to better assess the neonatal abstinence syndrome, and also to evaluate the efficacy of different treatment options. It involved drawing on the authors’ own experience of the signs and symptoms of NAS, as well as those described in the literature, to arrive at the twenty most commonly seen. These symptoms were grouped, and ranked, with a score of “5” for a symptom with “the greatest potential for clinically adverse effects”, and a score of “1”, for the symptom “with the least pathological significance”\(^4\). It worked on the premise that the greater the number of symptoms experienced by the baby, and the more severe these appeared, the higher the total abstinence score achieved. Therefore a higher score would reflect a more severe abstinence syndrome in the baby. Based on clinical experience and observation, Finnegan’s group judged that a score of 7 or less would not warrant drug treatment, and that the baby would settle with simple measures, such as swaddling and demand feeding. A baby with a score of 8 or greater would be prescribed medication. In the original study, this medication was either Phenobarbital or paregoric.

In evaluating the neonatal abstinence syndrome, the Finnegan score was used not only to determine whether a baby was withdrawing, but also, whether the withdrawal syndrome was of sufficient severity to warrant treatment, and whether the response to treatment was adequate. Finnegan goes further and questions whether the scoring system improves on a paediatrician’s clinical acumen alone. She compared two groups of drug-exposed babies observed in the nursery. Group I infants were treated using “standard clinical approaches”, whilst Group II infants had their medication for NAS regulated using the scoring system. In the group that was assessed purely on clinical grounds, only 30% were managed without drug treatment. In contrast, 46% of the group using the abstinence scores were managed without drug treatment. For those babies requiring medication for NAS, the average number of days of treatment was 8 in Group I, and 6 in Group II. The length of stay in hospital for babies in Group I was 21 days, and 15 days for those in Group II\(^3\).
There are problems associated with the Finnegan scoring system. Firstly, the symptoms and signs outlined were those which the researchers had encountered most frequently in babies with neonatal abstinence syndrome, and which were also described in the literature of the day. However, many of the signs and symptoms are non-specific, such as fever, or vomiting, and subjective, such as "poor feeding" or "excessive sucking". They also have limited relevance in babies born preterm (i.e. less than 37 weeks).

Secondly, Finnegan describes how "further validity of the abstinence score was attempted" by looking at "objective" measures of newborn behaviour (Finnegan used sucking), whilst simultaneously scoring the baby. Sucking was used as a measure because it was felt that it reflected the baby’s level of CNS excitation or depression. In addition, there had been reports in the literature regarding the use of sucking as a means of assessing drug effects in newborns. They were able to compare the rate of sucking (in sucks per minute), and percentage sucking time (describing the total time of active sucking in the allotted time, given as a percentage). This was tested using milk formula from a special teat, whereby sucking pressures could also be measured. However, no control group information is given, so comparison of how a well, non-drug-exposed baby, matched for gestation, would perform is not readily discernible. The study showed that for those babies undergoing withdrawal, as identified by either the scoring system or clinical grounds, the ability to suck was best when treatment with paregoric was used, worst when treatment with Phenobarbital or no medication was given. This was not surprising, given the sedating effects of barbiturates.

Overall, the symptoms and signs listed in the Finnegan NAS score are not validated as sensitive or specific for neonatal abstinence syndrome, nor are the individual scores assigned to each symptom or sign. Indeed, our experience has been that there are certain signs that are documented with increased frequency whenever severe NAS is considered, though they are not ascribed a high enough value on the chart to be always considered clinically relevant. The decision to use “8” as the cut-off at which treatment should be instituted is based on Finnegan’s observations of the 200 or so babies with NAS in her series. Further, we have more sensitive and specific ways of assessing babies with or without a history of drug exposure in utero at our disposal, some thirty or more years on, so we can re-visit many of the assumptions of the past.
The third issue centres on the inter-rater reliability of the Finnegan neonatal abstinence score. This was addressed, by Finnegan, in her original article, whereby she describes a training process which included an initial detailed explanation of the scoring system. After this, the nursing staff were supervised when scoring babies undergoing various stages of withdrawal. Inter-rater reliability was 0.82, having been tested by asking 4 randomly selected pairs of nurses to score babies at set intervals. Nevertheless, in our pilot study we found significant errors both in the way NAS was assessed practically on the ward, using the scoring system, as well as errors in recording, such as wrong total, wrong score, infrequent recording, or times not recorded. Further, the original scoring system was based on these babies being placed in a nursery, and away from their mothers, which is not routine practice in nurseries in Melbourne. Finnegan scored the newborns hourly, for the first 24 hours, every two hours for the next 24 hours, and then four hourly for the first five days of life. This is very unrealistic in our current practice where babies are demand fed, and largely cared for by their mothers, under supervision. It also puts considerable demands on the time of nursing staff each shift.

Zimmerman-Baer et al sought to determine if the Finnegan NAS scoring system was specific for identifying babies with NAS. The scoring system was applied to newborns with gestations greater than 34 weeks who had no history of opiate exposure. 102 babies were scored at eight-hourly intervals for the first three days of life (cohort one). Their urine and meconium were screened for drugs if the baby scored greater than 8. 26 of the 102 babies were then scored again at age 5 to 6 weeks (cohort two). Drug screening of urine and meconium was again performed on those babies who scored greater than 8. Babies were excluded from the second cohort if they had feeding problems, had had recent vaccinations, or were unwell. For cohort one the median score was two, but with the 95th percentile of the scores increasing from 5.5 on day 1 to seven on day 2. Five infants had scores between 8 and 11 on one assessment, but the meconium drug screen was negative for opiates, methadone, cocaine, benzodiazepines, and amphetamines. The most frequent signs recorded were high-pitched cry, shortened sleep period, vomiting, and sneezing. Signs recorded infrequently were exorision of skin, myoclonic jerks, sweating, frequent yawning, mottling, and tachypnoea. Examining the scores obtained in weeks 5 to 6 revealed a marked diurnal variation. Scores were higher during the daytime (5 = 50th percentile, 8 = 95th percentile, P=0.02), than at night (2 = 50th
percentile, 6=95th percentile). This was attributed mainly to the longer duration of night sleep.

There are several important facts raised in this study. The scores tended to increase with age, probably reflecting an increase in developmental maturity in the baby, particularly with crying, sleep and feeding patterns. If this is true after birth, could similar aspects of maturity influence the scoring of premature babies, such that withdrawal is under recognised? Finnegan's threshold for instituting treatment for NAS was above a score of 8. This appears to be appropriate, as the 95th percentile never exceeded 8.

D’Apolito and Hepworth 37 acknowledged that many women on the methadone program were polydrug users. Their study looked at the most prominent symptoms and signs noted in the babies of mothers on methadone who were polydrug users, using the modified Finnegan scoring system. They found that increased tone was the most frequently observed CNS sign, with increased respiratory rate, disturbed sleep, fever, excessive sucking and loose/watery stools all occurring often. They compared these results to previous work by Finnegan and Ehrlich38, who looked at the most common symptoms and signs seen in methadone-exposed babies. Finnegan and Ehrlich in a series of 43 methadone-exposed babies, found the most prominent withdrawal symptoms were tremor when disturbed, increased muscle tone, fever, mottling, nasal stuffiness, and increased respiratory rate. This demonstrated that there is some overlap in presentation of withdrawal between opiate-exposure alone, and exposure to other drugs with opiates, and that some signs such as “tremor when disturbed” are more frequently observed amongst babies exposed to opiates alone in utero.

2.3.2 The Lipsitz tool

Worldwide, there are other assessment tools used. The Lipsitz tool5 was developed at a similar time to the Finnegan scoring system. It aimed to simplify the process of assessing opiate-exposed babies. First Lipsitz identified the most common or prominent symptoms and signs of withdrawal. He included tremors, irritability (excessive crying), hyperreflexia, increased muscle tone, and tachypnoea as the most striking signs. These were therefore ranked highest. Other common clinical manifestations of withdrawal were also added, and included: explosiveness of stools,
skin abrasions, repetitive sneezing, repetitive yawning, vomiting, and fever. These signs were all scored, with the maximum score achievable being 20.

Lipsitz then engaged two paediatric residents to score a series of newborn babies, twice daily for one week, or until discharged. The residents were blinded to the infant's clinical history. The babies were then divided into 5 groups. Group A were 11 term babies, with Apgar scores greater than 7, whose examination scores ranged from 0 to 3. Group B consisted of 10 term babies with Apgar scores less than 7, and examination scores between 0 and 4. Group C had 7 babies with gestations ranging from 33 to 37 weeks, who had examination scores between 0 and 4. Group D had 5 term babies who were small for their gestational age (SGA), with examination scores from 0 to 4. Finally the 8 babies in Group E were babies of opiate-dependent mothers with gestations ranging from 35 to 40 weeks, and with scores ranging from 0 to 9.

The study conducted by Lipsitz, and the assessment tool he created, provide important information. Firstly, regardless of gestation, non-opiate-exposed babies did not display the symptoms and signs identified in the study as commonly associated with opiate withdrawal. Since none of these babies (Groups A through to D) scored more than 4, this was suggested to be the natural clinical cut-off for identifying babies with possible opiate exposure or withdrawal. For Group E, assessment of the 8 opiate-exposed babies generated 89 scores in total. 22 of these 89 scores (or nearly 25%) were greater than 5. In comparison, for Groups A to D, almost 80% of the total 201 scores were either 0 or 1.

Secondly, Lipsitz included term, preterm, small for gestational age (SGA) babies, as well as opiate-exposed babies in his study. It was helpful to see the tool used amongst all babies. Indeed, the opiate-exposed (group E) babies included preterm babies. Doberczak\(^3\) used the Lipsitz tool in her study, though the opiate-exposed babies in Lipsitz's study were of 35 to 40 weeks' gestation. Although unclear, it appears the babies were assessed twice per day. This makes the tool more amenable for use on a busy ward, as there are less components to assess and score. For this reason the Lipsitz tool is recommended for use by the American Academy of Pediatrics \(^39\).
Diagnosing NAS rests largely on a high index of suspicion, maternal disclosure of drug use, and recognising symptoms and signs consistent with the syndrome of opiate withdrawal. These symptoms and signs reflect not only opiate withdrawal, but, with the varying prominence of one clinical feature over another, also reflect the effect of polydrug use on the withdrawal process. The modified Finnegan scoring system is the commonest scoring system used in Victorian special care nurseries. Fundamentally, regardless of the tool used, a scoring system provides a unified approach to regularly assessing a baby for symptoms and signs of withdrawal.
2.4 **Other factors that may impact on the fetus exposed to opiates in utero and affect the rate of NAS in the newborn**

There will always be debate regarding whether it is opiate use per se that contributes all or most of the detrimental effects seen in babies of substance-abusing mothers, or whether poverty, poor general health and nutrition, as well as mental health issues and lack of housing are equally to blame. These factors are difficult to investigate in isolation, as all these issues often co-exist.

The Maternal Lifestyle Study (MLS) was conducted between May 1993 and May 1995 and involved four centres in the United States (University of Miami, Brown University, University of Tennessee, and Wayne State University), with the aim of studying women exposed to opiates and/or cocaine during pregnancy. They also included a control group with no evidence of cocaine or opiate use, either in history or by urine drug screen. A cohort of 11,811 women (70% of those eligible) were recruited. Black women were over-represented in the cocaine-opiate-exposed group compared with controls (74.7% versus 47%). The drug-exposed group (n=1185) had a greater incidence of medical complications including sexually transmitted diseases, and psychiatric and emotional disorders.

Whilst the sample size in this study is impressive, each of the four sites had different maternal characteristics. However, overall 93% of the cocaine-opiate-exposed group admitted to alcohol, tobacco, or marijuana use, compared with 42% of the non-exposed (control) group (P<0.001). Regarding quality of antenatal care, in the exposed group, 77.3% accessed antenatal care, with a median of 7 visits, compared with 97% of the non-exposed group accessing antenatal care with a median of 11 visits. Despite this, the number of hospitalisations, during pregnancy, between the two groups, were very similar (11.5% in the exposed, compared with 10.8% in the non-exposed), and were largely involving the cocaine-exposed group.

From this study there is evidence, at least in the United States, that women with drug dependence, including opiates, form an obstetrically high-risk population. The issues of concurrent medical problems, polydrug use, and possibly poor antenatal attendance contribute to the difficulties in adequately caring for the mother and baby.
A study carried out in Western Australia by O’Donnell et al\textsuperscript{41} used cross-government data linkage between the Health and Child Protection Departments to retrospectively review all live births in Western Australia between 1980 and 2005 that were also coded for “Neonatal Withdrawal Syndrome” (NWS), or NAS. They also reviewed the maternal records of babies born between 1970 and 2005. The maternal records were reviewed for maternal risk factors and characteristics, but also for evidence of assault, domestic violence, and mental health issues. O’Donnell found 906 infants were coded for NWS in the study timeframe. There was increased prevalence of NWS from 1992 to 2002, and, for every year, on average there was 16.4% increase in children born with NWS (95% CI: 15.2%-17.4%; \( P< 0.001 \)).

O’Donnell found that those babies with NWS were more likely to be preterm and/or show evidence of poor intrauterine growth. Aboriginal mothers (n=104) had twice the risk of having a baby with NWS than non-Aboriginal mothers (27.3 versus 13.4 per 10000 live births). For both Aboriginal and non-Aboriginal mothers, smoking, having a low skill level, and having a previous admission for mental health issues, were risk factors for having a baby with NWS.

Children with NWS had an increased risk of a child maltreatment allegation (OR: 5.7 [95% CI:4.8-6.9]), a substantiated allegation (OR: 10.5 [95% CI:8.4-13.1]), and a period of care (OR: 10.5 [95% CI:8.4-13.1]), compared with children without NWS. Most of the allegations (72%) related to neglect. In addition, in this cohort, for those children with NWS, the substantiated allegation of child maltreatment occurred earlier, at a median of one year, compared with three years for children without NWS.

This study does not delve into the level of opiate exposure these babies had in utero. Despite this, there are clearly powerful external factors contributing to the likelihood of NAS (or NWS) developing. The role of good antenatal care and adequate and long-term surveillance of these babies clearly play a part in the overall care of this vulnerable dyad.

A similar linkage study was done by Burns in New South Wales\textsuperscript{42}, involving three databases. These were PHDAS (the NSW Pharmaceutical Drugs of Addiction System), which records when an authority to dispense methadone is given, the NSW Midwives Data Collection, and the NSW Inpatient Statistics Collection. Data from 1992 to 2002 were collected regarding methadone prescribing, birth data, and
maternal demographic, medical, and obstetric information. Information regarding diagnoses and admissions into hospital was also collected. There were 2941 live births to women on methadone in that period, with 27% being diagnosed with NAS. The mean length of stay for a baby with NAS was 16 days (median 12; range 0-64 +/-12.5 days). Mothers of babies who developed NAS were more likely to have a normal vaginal delivery, smoke heavily, identify themselves as of Aboriginal or Torres Strait Islander descent, and have had at least one previous pregnancy greater than 20 weeks gestation. What is most interesting about this study is the very low rate of NAS recorded. The author explains this as possibly due to the symptoms and signs of NAS being mistaken for other pathology, such as fever, sepsis, or even seizures.

Sharpe et al\textsuperscript{43} conducted a study to investigate whether prescribing methadone for opiate maintenance affected the rate of NAS, compared to when methadone was prescribed for the management of chronic pain. Is there something inherent in the drug-using population, be it socioeconomic factors or polydrug use, that compound the opiate effect of methadone, to affect fetal growth and influence the severity of withdrawal symptoms? He explored this by reviewing 19 cases of mothers prescribed methadone for chronic pain and reporting neonatal outcome. Two women in this group had a history of drug or alcohol use and two had depression as co-morbidities. In comparison, he also reviewed 24 cases where the mothers were prescribed methadone for narcotic addiction.

In this study, only 11\% in the “pain group” required treatment for neonatal abstinence syndrome, compared to 58\% in the methadone “maintenance group”. However, methadone was commenced later in the pain group (median gestation 30 weeks, range 0-35 weeks), after other options for pain relief had been exhausted, and were prescribed smaller doses (median 40mg, range 10-180mg), and generally for a shorter duration (median 5 weeks, range 1-36 weeks). Of note, in the “pain group” 11 infants were delivered prematurely, 3 required some respiratory support, 5 developed jaundice requiring phototherapy, 9 had feeding problems, 1 had hypoglycaemia, and 1 had documented sepsis. This is in contrast to the neonates born to mothers in the “maintenance group” who, apart from neonatal abstinence syndrome, had little other pathology. However, infants in the “pain group” had significantly greater birth weights and head circumferences than the maintenance group babies.
Before concluding that methadone given in the context of narcotic addiction gives babies NAS, but little else in the way of co-morbidities, we need to look more closely at the populations used. Firstly the characteristics of the women in the pain group were not clearly described, so it was difficult to assess their socioeconomic status. Information such as housing, relationships, employment, and level of education were not outlined. The causes of their chronic pain were diverse, and included back, pelvic, or abdominal pain of different aetiologies. In general the pain had preceded the pregnancy and these women had been through a clear pathway of escalating analgesia options, ending in short-acting opiates, before methadone was prescribed. In addition to the methadone, these women were on a number of other medications, such as amitriptyline, clonidine, mexiletine, and other anti-depressants and analgesics, which in themselves could have contributed to neonatal pathology. Of the 11 preterm births, only 4 were spontaneous.

If NAS is less evident in preterm babies, then of course the babies in the “pain group” (11 of 19 were preterm), would be said to have less. A link between methadone dose and NAS has never been clearly established, and without uniform drug screening, it is difficult to establish the role of illicit drug use in either group.

Polydrug use is a major confounder when trying to establish a link between exposure to a single opiate (methadone, buprenorphine, or heroin) and neonatal morbidity, such as prematurity or neonatal abstinence. Not only do illicit drugs contribute to neonatal morbidity, but tobacco use is also a factor. Cigarette smoking itself is associated with prematurity, lower birth weights, intrauterine growth retardation, and smaller head circumferences. Choo et al. looked at the influence of in utero tobacco exposure in neonatal withdrawal on babies whose mothers were on methadone. A withdrawal syndrome has been described in both adults and babies, when nicotine exposure is abruptly discontinued, though the critical amount of exposure (number of cigarettes, duration of exposure) remains unclear. However, these authors estimate approximately 90% of pregnant women treated with methadone report cigarette smoking in pregnancy.

Choo recruited 29 mothers on methadone (mean dose 77mg/day +/-19.4mg) who smoked cigarettes. 16 were described as “light smokers” (LS) and smoked 10 or less cigarettes per day (mean 8.4 cigarettes/day +/- 2.3). There were 13 women
classified as “heavy smokers” (HS) and smoked 20 or more cigarettes per day (mean 21.5 cigarettes/day +/-5.5). There was also evidence on urine toxicology of concomitant illicit drug use in both groups, particularly cocaine use (93%). The mean methadone dose between the two groups at delivery was 75.6mg/day +/-22.9 for LS, and 78.8mg/day +/-14.9 for HS.

19 babies were born at full term. Babies were assessed using a modified Finnegan NAS scale, and a peak NAS score was defined as the highest score a neonate received during the course of the admission. Treatment was started for NAS if there were 2 consecutive scores greater than 8. There was no significant difference between the HS and LS groups regarding delivery toxicology (t(27), P=0.66). 3 babies from the LS group displayed no NAS signs, but they were all born prematurely (26, 28, and 36.5 weeks gestation). 12.5% of the LS group and 23% of the HS group required treatment for NAS. The study showed that babies in the HS group had higher peak NAS scores (9.8 +/-4.8 range 4-19, compared to 5.6 +/-3.8 range 0-13, P=0.014), and took longer to reach their peak scores (113.8 +/-90 hours compared to 37.8 +/-33.8 hours), compared to the LS group.

Choo postulated that cigarette smoking, along with using other drugs, among women on methadone, may have contaminated previous studies investigating a link between methadone dose and neonatal abstinence syndrome. A contributory effect of cigarettes and alcohol, on opiate withdrawal in the neonate, was acknowledged as a possibility by Doberczak, but because they do not require a prescription, their use is often difficult to reliably quantify.

Breast milk is thought to ameliorate the symptoms and signs of neonatal abstinence syndrome. In a study by Abdel-Latif et al, 190 drug-dependent mothers and their babies were retrospectively studied, looking at Finnegan NAS scores, need for medication, and the predominant type of milk used for feeding. 85 babies were fed mainly breast milk, and 105 were mainly formula-fed. Feeding with breast milk was associated with less NAS requiring treatment (52.9% vs 79%, p<0.001). This is presumably at least partially explained by the presence of methadone in breast milk. Similarly McQueen et al found the scores for breast milk fed babies were reduced, compared to formula-fed babies.
Opiate exposure, polydrug use, exposure to maternal cigarette smoking, and socioeconomic factors may explain why NAS develops in one baby and not the other. Liu et al. conducted a review of 228 medical records of women on methadone and their 232 live-born babies, over a 6-year period from 2000 to 2006. Opioid use was limited to methadone, as the dose prescribed immediately prior to delivery was clearly identifiable, and the rationale for prescribing methadone maintenance in pregnancy had not changed in the study period. The catchment area, for the hospitals at which these women delivered, was in the lower deciles areas reported in the Australian Bureau of Statistics Socio-Economic Indexes in 2006. The researchers collected 74 parameters, that were readily extracted from the medical records of mother or baby, and that had any possible biological or social link to NAS.

172 of 232 methadone-exposed babies developed NAS (74%). The mean gestational age was 38.42+/−2.19 weeks. 66 babies were born prematurely (<37 weeks), with a mean gestational age of 36.8+/−3.3 weeks. Liu found that higher gestational age (P<0.001) and higher maternal methadone dose (75mg IQR 50-105) were associated with an increased need for treatment for NAS. He also found that delivery by Caesarean section was associated with a decreased risk of the baby requiring treatment for NAS. However, this advantage was no longer significant once the baby reached 38 weeks gestation. Having established in his model that higher maternal methadone dose, gestation, and delivery by Caesarean section were all key factors associated with severe NAS, Liu applied this to a second cohort of 188 mothers on methadone maintenance and their babies. He confirmed that the risk of severe NAS requiring treatment could be calculated based on the methadone dose, gestation and delivery mode. For example, a baby born at 35 weeks gestation by normal delivery to a mother on 20mg/day of methadone would have a risk of withdrawal of 30 to 40%. This risk decreased to less than 10% if the baby was delivered by Caesarean section.

Liu argues that the figures underlying his calculations are reliable despite being retrospective, as they rely on data routinely collected on all babies in all hospitals. He cautions that his findings relate specifically to methadone. Interestingly polydrug use was not mentioned in the article as an important confounder. Finally, there is the acknowledgement that the diagnosis of NAS in both the term and preterm populations was based on the modified Finnegan chart, which was not specifically designed to be used in the preterm population. Nevertheless, in those preterm
babies who were diagnosed and treated based on the scoring system, their outcomes were better than term babies with NAS.

In summary, the development of NAS is multifactorial. Many social issues are associated with opiate use, and these may confound the clinical picture, and make a direct link between degree of opiate exposure and development of NAS difficult to establish.
2.5 Methadone metabolism

Methadone has long been considered the drug of choice for opiate substitution in pregnant women. With the promise of a regular fixed dose of opiate from a reliable source, both mother and baby are relatively protected from recurrent episodes of withdrawal. However, methadone is associated with a higher rate of neonatal abstinence syndrome than heroin\textsuperscript{11}. Investigation of the relationship between methadone dose and rate of neonatal abstinence has produced inconsistent findings, with some studies finding a clear link\textsuperscript{20,22,23,46,48}, and others finding none\textsuperscript{19,21,30}. The relationship is complex, but there may be individual "internal" factors, either maternal or fetal, that alter the metabolism of methadone, as well as external factors, such as polydrug use and duration of exposure to methadone, that in combination cause the severe withdrawal symptoms associated with NAS.

The pharmacokinetics of methadone are altered during pregnancy. Ethical limitations make investigating fetal, placental and maternal metabolism of the drug more difficult. Nekhayeva et al\textsuperscript{49} studied the role of the placenta in the metabolism and pharmacokinetics of methadone in mother and fetus. To do this, the authors used perfused placental lobules from fresh term human placentas as a model, and infused known concentrations of radioactive $[^3H]$ methadone to mimic maternal concentrations measured in previous studies, based on a mean dose of 50mg of methadone (range 10-90mg/day). Samples were taken from the ‘maternal’ and ‘fetal’ sides, and the amount of methadone retained in the placental lobule was also measured.

This study found that firstly, the methadone itself did not damage the placental lobule or affect its viability. Secondly there was bidirectional transfer of methadone between the mother and fetus. However, the transfer of methadone from the fetus to the maternal circulation is greater than from mother to fetus. This was thought to be due to the presence of a transporter glycoprotein, P-gp which is present in syncytiotrophoblast cells and is probably designed to protect the fetus from any xenobiotics in the maternal circulation. Methadone is retained by placental tissue, as is buprenorphine.
Nekhayeva et al confirmed that methadone, being highly lipophilic, is transferred first by uptake of tissue, and then by release into the circulation. Transfer across the human placenta is by passive diffusion, and is limited by flow. The placental enzyme CYP 19 (aromatase) is thought to be primarily responsible for the metabolism of methadone in the placenta. Both P-gp and CYP 19 aromatase have varied activity, according to gestational age, genetic and metabolic factors. These may affect the concentration of methadone in the fetal circulation, and therefore affect the incidence of NAS.

Pond et al studied the pharmacokinetics of methadone in 9 pregnant women. They collected urine and blood samples at four points: phase I (20-34 weeks gestation), phase II (35-40 weeks gestation), phase III (1-4 weeks post partum), and phase IV (8-9 weeks post partum). The women were on methadone for a minimum of 2 months (mean 1.4 +/- 0.9 years).

As the pregnancy progressed, maternal weight was significantly greater, and serum albumin concentrations significantly lower, than postpartum. All babies were born at term, with 5 developing NAS requiring treatment. There is no information regarding how the diagnosis was made. Methadone doses were again not high, 30mg+/-8 at Phase I, 22mg+/-9 at Phase II, 28mg+/-12 at Phase III, and 36mg+/- 22 at Phase IV. Mothers whose babies withdrew were taking 0.40+/- 0.17mg/kg of methadone per day, and the dose for the 4 mothers whose babies did not withdraw was 0.28+/- 0.15mg/kg. The differences between the doses was not statistically significant. Only one mother had evidence of illicit drug use.

Each mother completed a questionnaire prior to receiving her methadone dose at each of the phases, asking about symptoms of withdrawal. Although the peak plasma concentration was achieved at a similar time and did not differ with the phases, the trough plasma concentration of methadone was significantly lower in all the subjects during pregnancy, compared to postpartum. Completed questionnaires for all four phases were available for 6 women. Of these, three women described withdrawal symptoms in pregnancy, and four requested an increase in methadone dose.

There was evidence of increased clearance of both total and unbound methadone in pregnancy, compared to postpartum. This was thought to be due to increased
metabolism of the drug during pregnancy. Methadone is metabolised in the liver, but metabolism in the placenta and fetus also play a part. The authors concluded that the methadone dose needs to be increased in the latter half of pregnancy.

In her discussion, Pond points out the positive obstetric outcome achieved by using methadone stabilisation. All pregnancies were carried to term, with all babies well-grown (3.3 +/- 0.5kg). The pharmacokinetic evidence from this study suggests that methadone metabolism during pregnancy is increased, given that the clearances of both total and unbound methadone were greater during pregnancy than postpartum, and that absorption was unlikely to be altered. In the study, the methadone dose was given to a fasting participant, who was kept fasting for a 4 hour period post-dose. However, this means that higher doses of methadone are required as pregnancy progresses, if one wishes to ameliorate any maternal withdrawal symptoms, and decrease the need to use illicit drugs. Giving the methadone in two divided doses may also assist in managing withdrawal symptoms developing at the end of the dosing interval. Again, this study is limited by small numbers.

Kuschel et al\textsuperscript{21} in Auckland in 2004 investigated a link between methadone concentrations in cord blood and serum in the neonate and the development of NAS. He recruited 25 babies whose mothers were on methadone during pregnancy. Four babies were born to mothers who were on methadone for chronic pain, with the remaining 21 babies born to mothers who were part of a drug and alcohol program. Four women admitted to using illicit opiates in pregnancy, but all but one had ceased prior to 6 weeks before delivery. Of the 20 study babies who had urine drug screens, only one tested positive for illicit opiates. Two women were still taking diazepam at the time of delivery. Nine women admitted to cannabis use in pregnancy. Twelve of the 25 study infants required treatment for NAS. The median methadone dose at delivery was 55mg (range 15-105mg). However, there was no significant difference in maternal methadone dose between requirement for treatment (47.5mg) and no requirement (65mg; \( p=0.14 \)).

Due to difficulties with sampling, there were 17 paired blood samples available, the first taken from cord blood and the second at a median of 49 hours after birth. The relationship between cord methadone concentration and maternal methadone dose was significant (\( R^2=0.59, p<0.0001 \)), indicating that the greater the dose of methadone taken, the higher the cord methadone concentration. In addition, for
those babies who developed NAS requiring treatment, their cord methadone concentrations were significantly lower than those who did not (31ng/ml compared to 88ng/ml, p=0.029). At 48 hours, all 9 babies requiring treatment for NAS had low or undetectable serum methadone concentrations. The authors suggested that either cord methadone concentration and/or the rate of elimination of methadone by the neonate may determine the severity of withdrawal. Further, this study suggested that maternal methadone dose was not a predictor of NAS.

In summary methadone is metabolised hepatically, as well as in the placenta. Requirements for methadone increase during pregnancy, and it is likely that pregnant women will need their methadone dose increased to avoid withdrawal symptoms. Methadone undergoes some metabolism by the fetus and the fall in methadone concentrations as reflected by cord blood levels may predict severe NAS requiring treatment in the newborn. Maternal methadone dose at delivery is not a useful predictor of severity of NAS.
2.6 Effects of in utero opiate exposure on the fetus and newborn

Concern for the developing fetus has underpinned much of the interest regarding maternal drug use in pregnancy. The concept that the fetus is a rapidly changing, growing being is important because this growth and change leaves the fetus vulnerable to agents that interfere with normal patterns and processes of growth at critical times. Malanga and Kosofsky\textsuperscript{51} described drugs of abuse as "behavioural teratogens". Although the long-term outlook for opiate-exposed babies is thought to be good, there may be more subtle effects on attention and affect.

The development of the central nervous system begins by day 28 post-conception with the formation of the neural tube. It continues throughout the pregnancy and into childhood. Biological vulnerability to teratogens exists throughout pregnancy, and the developmental consequences depend on the timing and nature of the insult. Drug use in pregnancy may alter the actual formation of normal neuronal circuits, thereby disturbing normal brain development. This is in contrast to an adult drug user, who starts using drugs after brain development is complete.

All drugs of abuse act either by mimicking the action of endogenous neurotransmitters or by changing the activity of endogenous neurotransmitter systems. Drug-induced alterations of transmitter signals that are required for normal brain development may lead to structural changes in the brain that may have subsequent effects on brain function and behaviour. Genetic influences as well as local factors, such as neurotransmitter activity are involved in the development of mature neurological pathways. Exposure in utero to cocaine, opiates, and ethanol has been found to result in impairment of brain growth and in disruption of the cellular structure of the cerebral cortex. Opiates cause a reduction in size and density of neurons. Cocaine and ethanol have effects on cortical structure. These findings suggest the possibility of a final common pathway of drug action for these agents\textsuperscript{51}.

Many studies looking at the effects of opiates on the fetus are based on animal models. Farid et al\textsuperscript{52} summarised the findings of effects on the central nervous system development, pointing out that the positive aspect of animal models is that the socioeconomic factors influencing fetal growth are no longer a confounding
factor. Interspecies differences are the obvious limitations of these studies. They reported 11 animal studies describing decreased brain and cerebellar weights. Decreased birth weights are associated with opiate, particularly heroin, use. The question also raised is whether low birth weight is also a result of maternal factors, such as poor nutrition. Effects on reflexes and motor coordination have also been noted in rat models after methadone exposure.

Jansson et al\textsuperscript{54} suggested that the symptoms and signs of NAS represent autonomic dysfunction in the newborn resulting from in utero opiate exposure. They studied the electrocardiographic (ECG) data of 64 babies in the first 4 days of life who had been exposed to methadone in utero, with a mean dose of 76.17 mg at delivery. Forty-eight (75\%) of the infants developed NAS requiring treatment. The development of severe opiate withdrawal in this study was unrelated to opiate dose, but was thought to reflect the effect of prenatal methadone on disruption of autonomic functioning in the developing fetus. This was thought to result in decreased fetal heart rate variability, as well as disrupted maternal autonomic functioning.

The effects of methadone on maternal vagal tone, including respiratory sinus arrhythmia, were studied by Jansson. A relationship between a marked maternal vagal response to methadone administration and an increased rate of NAS was found\textsuperscript{55}. She postulated that babies with lower vagal tone (as manifested by faster heart rates) postnatally represented a maladaptive response to alterations in maternal vagal tone on methadone administration in utero. What was possibly an appropriate response by the baby in utero may result in the manifestations of severe NAS following cessation of methadone exposure in the extrauterine environment.

A biological vulnerability making an individual more susceptible to the effects of drugs of addiction has been put forward for some time. Many researchers are looking for a genetic cause for the individual variation in severity of opiate withdrawal. Lieb et al\textsuperscript{56} studied the possession of the 825C>T polymorphism of the G-protein beta 3 subunit gene. This is said to influence sympathetic activity and could be a factor in increased heart rate seen in opiate withdrawal among some opiate-dependent people carrying the T-allele.
Polydrug use is a major confounder when trying to establish a link between a single opiate exposure (methadone, buprenorphine, or heroin) and neonatal morbidity, such as prematurity or neonatal abstinence. Chasnoff et al. investigated whether babies exposed to methadone alone had a different outcome, in terms of somatic growth, incidence of malformations, development of neonatal withdrawal, and neonatal behaviour, than those babies exposed to maternal polydrug use, or non-drug-exposed controls. His three study groups, a methadone group (group I), a polydrug group (group II), and a control group (Group III), were not statistically different with regard to mean maternal age, education level or gravidity.

The methadone group consisted of women who presented to antenatal clinic on heroin, and who were stabilised on a low dose of methadone (5-40mg, mean 14.6+/–10.2mg). The maintenance methadone dose was determined once the third trimester was reached, and not increased any further until delivery. Those in group II used two to five of the following drugs: Phenobarbital, diazepam, marijuana, pentazocine and pyribenzamine, phencyclidine, and codeine. They were not prescribed methadone. Group III were consecutively born babies whose mothers had no history of drug and alcohol use. The authors determined that groups I and II were of similar socioeconomic status, as they met with these mothers on a daily basis and were aware of the similarities in the issues that they faced. All three groups had similar educational levels. Group I had a significantly smaller proportion of black women.

The methadone exposed babies of group I had a significantly lower weight and length than control infants, and had a statistically smaller head circumference than those in either group II or III. Birth weights, head circumferences, and lengths of polydrug exposed babies did not differ significantly from control babies. Fetal growth and maternal nutrition were closely supervised in all three groups during the pregnancy. Therefore the authors concluded that the effects on growth, in the methadone group, were directly related to opiate exposure. Of note, the doses of methadone prescribed were low in this study. Chasnoff goes on to hypothesise that there is a spectrum of effects from in utero drug exposure, whereby opiate exposure, as seen in group I, is at one end, group III with its controls, at the other, and the polydrug-exposed (group II) in the middle.
As part of the Maternal Lifestyle Study, Bada et al.\textsuperscript{58} looked at the symptoms and signs of withdrawal from cocaine, opiates, or combinations of both. There were 100 babies exposed only to opiates, confirmed by maternal history and assay of meconium. Assessment of the infants was performed by research nurses blinded to the drug exposure of the baby. The major limiting factor was that the babies were term, and so were discharged from hospital before one could reasonably expect withdrawal symptoms to become obvious. Opiate-exposed babies were more likely to exhibit withdrawal signs than those exposed to cocaine only (44.8% versus 28.2%). The most common signs reported in the opiate-exposed group were tremors, irritability, high-pitched cry, and hypertonia, representing the effects of opiate withdrawal on the infant’s central nervous system and autonomic nervous system.

Opiates have effects on the developing fetus, which after birth, may manifest as alterations in growth, behaviour and development, as well as a withdrawal syndrome. If developing neonatal abstinence syndrome were simply related to the size of the opiate exposure, or the dose of the methadone prescribed, then it would be a simple matter to predict which babies would develop NAS. The lack of consistency in results, from studies performed with varying opiate exposure, suggest a more complex relationship. Animal models may be useful in determining which effects are largely pharmacological, and which are influenced by host or external factors, such as maternal nutrition, or antenatal care.
2.7 **Long term effects of opiate exposure**

The well-known effects of opiate exposure in utero centre around fetal growth and the risk of developing a withdrawal syndrome. However there are other consequences of opiate exposure both long and short term which have been investigated. The potential for impairment of development and growth, have raised concern for many years. They are discussed here to highlight that the consequences of in utero opiate exposure extend beyond the neonatal period.

The results of earlier studies reporting the effects of opiate exposure other than NAS may reflect the absence of good affordable healthcare, or a non-punitive, multidisciplinary approach. Ostrea and Chavez\(^59\) studied neonatal outcome, other than NAS, in 830 methadone and/or heroin dependent mothers, and 400 control mothers who were not known to use drugs. Both groups were "public" patients of lower socioeconomic status, with a high percentage (90% in the drug group, 86% in the control group) of black women. Polydrug use with barbiturates, amphetamines, and benzodiazepines was known to commonly occur in the drug dependent group.

The results of the study showed preterm delivery (18.5% versus 9.8% in controls, \(P<0.01\)), being small for gestational age, and having low Apgar scores were more common in the drug group. Because of a high incidence of meconium-stained liquor at delivery, and a high incidence of Caesarean section for fetal distress, the authors postulated that fetal asphyxia, possibly secondary to maternal withdrawal, was an important risk. This study also found an increased rate of congenital malformations, such as hydrocephalus, and cardiac defects, (2.4% vs 0.5% in controls, \(P<0.01\)). However, the authors felt a causal relationship was unlikely, as there were so many confounders, such as polydrug use and poor nutrition, involved.

Abdel-Latif et al\(^60\) looked at all the infants of substance-using mothers (ISM) admitted to one of the ten tertiary neonatal intensive care units (NICU) in New South Wales and the ACT between 2001 and 2003. Indications for admission included: prematurity (<32 weeks gestation), birth weight less than or equal to 1500gm, requiring respiratory support (continuous positive airway pressure (CPAP) or
intermittent mandatory ventilation (IMV)) in the first 28 days, or needing major surgery in the first 28 days of life. There were 310 ISM who met these criteria. He also included 5810 control babies who were consecutively admitted to the NICUs and also met the above criteria, but were thought to be drug-free, based on maternal self-report. The authors defined “substance use” as maternal report of use of cocaine, heroin, marijuana, methadone, amphetamines, or any other drugs of dependence during her current pregnancy. 167 of the 310 substance-using mothers were identified as using heroin (n=54) or on methadone (n=113).

Given that both the study (ISM) group and the control group are considered high risk, it was interesting to compare their neonatal course. In the substance-using group, the mothers tended to be younger (26.8+/−6.5 versus 29+/−5.8 years, P<0.001) and more likely to be of Aboriginal descent (20.6% versus 2.6%, P<0.001), and had more perinatal complications such as chorioamnionitis (13.2% versus 7.4%, P<0.001) than the control group.

More ISMs were born prematurely (84.6% versus 74.4%, P<0.001), with lower birth weights and head circumferences than controls of similar gestation. Those ISMs born less than 32 weeks’ gestation did not show evidence of poor fetal growth, which would suggest that the differences in growth (birth weight and head circumference) between the study and ISM groups occurred in the third trimester. 165 ISM were born less than 32 weeks gestation, and there was a trend toward a lower mortality in this group (7.9% versus 12.7%, OR 0.59, 95%: 0.33-1.05, P=0.090). This was particularly true of those babies born between 22 and 26 weeks.

One could postulate that these fetuses are perhaps subjected to more in utero stresses, related to maternal drug use, which may enhance their maturity. However, in this same group, a non-significant increase in neonatal complications such as chronic lung disease, NEC, PDAs was also noted. ISMs had a longer length of stay in hospital (67.2+/−53.7 days) than control babies (56.9+/−35.8 days, P=0.016). Because the data for this study were extracted retrospectively from a database, the authors could not determine a reason for this. Commonly, the increased duration of hospitalisation could be due to NAS, or social reasons, but also could be due to complications such as difficulty in establishing suck feeds.
This study found that ISM made up 5.1% of NICU admissions, although substance-use in the pregnant population was reported in only 1.3%. The authors go on to suggest that ISM are over-represented in the NICU population. Further, if this group have a greater length of stay, then they may consume a greater proportion of resources than similar high-risk newborns.

Kaltenbach and Finnegan published a case series of 85 babies born to women on methadone maintenance treatment, 65 of whom developed NAS requiring treatment. At 6 months of age, the developmental status of the babies was assessed using the Bayley Scale for Mental Development. Those babies requiring treatment were divided into four groups depending on the medication they received (paregoric, phenobarbital, more than one agent, and no agent). At 6 months of age, all the babies scored within the normal range for development, and there was no significant difference between the groups. They concluded that appropriately treating babies with severe NAS may have allowed these babies to develop in a similar pattern to those babies with methadone exposure but not requiring treatment for NAS.

However, there is no background information on the babies, such as birth history, or overall methadone or other drug exposure. It may be that this group of 85 babies who returned for follow-up at 6 months, represented the more organised and compliant of mothers on methadone treatment. Still, the fact that all these babies scored within the normal range for development using this tool does suggest that the effects of intrauterine exposure to methadone may be limited to the neonatal period. Also of note is the high rate of withdrawal quoted in this study.

Wilson, Desmond, and Wait prospectively compared the health, development, and social outcomes, of heroin and methadone exposed infants. These authors compared three groups of women and their babies. Group A had 29 predominantly black, untreated heroin-dependent mothers and their 30 babies (one set of twins). Group B had 39, predominantly white methadone-treated women and their babies, and group C had 57 drug-free women and their 58 babies (one pair of twins). Group C were matched for maternal age, race, socioeconomic level, marital status, and gestation at the time antenatal care was commenced.
This study found that methadone-maintained women were more likely to comply with regular antenatal care than those on heroin, with the rate of antenatal care comparable to that of controls (group C). However, the babies exposed to methadone in utero (group B) were significantly smaller than controls (P<0.01). Although there was evidence of polydrug use amongst the group B women, the rate of NAS was similar in the heroin and methadone exposed groups. However, the duration of treatment required was longer for group B (t=2.76, P<0.01).

119 of 127 babies were followed up at one year. Mothers on methadone reported more minor accidents and more presentations to hospital. The authors commented that this more frequent contact with medical staff as being overly concerned about their child’s welfare. They were more likely to be admitted for illnesses such as gastroenteritis as the attending staff were concerned regarding the mother’s ability to cope when the baby was ill. These mothers also report more excessive crying and babies that took longer to establish a sleep routine. Assessment by an examiner blinded to the baby’s grouping, using the Bayley Scales of Infant Development, was performed and found the mean Mental Development Index was within the normal range for all groups. However, methadone infants performed significantly worse than drug-free controls on the Psychomotor Developmental Index (F=4.160, P<0.018) and on assessment of fine motor coordination (χ²=8.80, P<0.01).

At one year 80% of methadone infants were living with their biological parent/s. In contrast, only 52% of untreated drug-dependent women had custody of their baby. All babies in the control group remained with their families. The authors suggested that this may be the most important benefit of being maintained on methadone. Although remaining with their biological parents did not necessarily mean they received good parenting, it does suggest some degree of stability in the family home.

Hunt et al64 conducted one of the few case control studies looking at long term effects of maternal opiate use in pregnancy. There were 133 babies, with a mean gestation of 37.7 weeks whose mothers were on the methadone program. 33 (25%) were born preterm. 74 (56%) required treatment with morphine. Babies with no history of opiate exposure were recruited as controls. Psychometric assessments
were performed at 18 months and at 3 years of age. They found on assessment of cognitive function and social maturity that scores for opiate-exposed children were significantly lower than for controls. All control babies remained with one or both parents during the follow-up period. In contrast, in the opiate-exposed group, 57 of 79 children were with a biological parent at 18 months (72%), and 46 of 67 children (68%) at 3 years. 16% were in foster care or adopted at 18 months, and 25% at 3 years.

Van Baar et al\textsuperscript{65,66} conducted a study using 35 infants of drug-dependent mothers (heroin, cocaine, and methadone) and 37 control infants born at term to drug-free mothers, and compared their neurobehavioural development in the first year of life. Babies were tested at 3, 6, 9, and 12 months, using standardised assessment tools such as the Bayley scales of infant development. Their motor development, temperament, and behaviour were also assessed at these points. In addition, electroencephalographic (EEG) recordings were obtained at 12 months. The only important difference detected was at 3 months of age, when the drug-exposed infants were significantly more active than controls. This was attributed to a period of subacute withdrawal, as 80% of the drug-exposed babies required treatment for severe NAS. Otherwise, development was within normal limits regardless of drug-exposure. A longer period of observation is required to detect deficits which appear later. In addition, 9 of the 35 drug-exposed babies were born preterm, and 7 were not living with either biological parent by 12 months.

Soepatmi\textsuperscript{67} in another study based in Amsterdam, followed 157 opiate-exposed children after discharge from hospital. There were difficulties in locating and engaging families beyond the first year of life. However, opiate-exposed children had reduced weight, length, and head circumference at one month of age and at 2 years of age, compared with the Dutch-Caucasian population generally. This difference was not significant beyond 2 years. Difficulties with behaviour and social competence were also noted, particularly in boys aged 4-5 years (p=0.011), and girls aged 6-11 years (p=0.009). There was an association with difficulties with behaviour at home and at school and an IQ <85, and being in foster care.
Clearly there are a number of potential confounders in these findings, some of which the author alludes to. The oldest children in the study fared the worst. However, since they were recruited into the study at its earliest point, their circumstances may have been different to younger children. Further, there is no clear description of how many children were in each age bracket. As with all studies spanning several years, maintaining adequate rates of follow-up is very difficult.

The Maternal Lifestyle Study\(^{41}\), described in section 2.4, sought to overcome the difficulties associated with assessment of the outcome of opiate-exposed babies. A large initial cohort allows for the fall in numbers with subjects being lost to follow-up, and increases the likelihood of discovering truly significant findings. Multiple sites create a more representative sample of drug-exposed babies and their families. They used a specific developmental assessment tool designed to be appropriate for identifying any possible neurological effects of drug exposure (the NICU Network Neurobehavioural Scale, NNNS)\(^{66}\). Sophisticated screening of urine and meconium allowed for more accurate delineation of fetal drug exposure, rather than relying on maternal self-report alone.

However, there are again issues regarding our ability to extrapolate their findings to drug-exposed babies in Australia and elsewhere. Their cohort across four states consisted of black, poor, Medicaid patients, largely cocaine users, with maternal age significantly older than their controls. Nevertheless, no other study has had the opportunity to so closely scrutinise mother and baby. Detailed assessment of drug and lifestyle factors showed more mothers in the opiate- or cocaine-exposed groups used tobacco, alcohol, and marijuana, and had less years of education than controls. Perhaps these findings are not unexpected. However, more subtle changes in arousal and quality of cry in the babies were also detected, and found to be different, depending on if exposure was to opiates or cocaine. Are these factors developmentally significant? The authors’ response was to describe an “at risk” infant. This is an infant who, because of its intrauterine exposure coupled with its environment, is vulnerable, to abuse, neglect, and possibly subtle brain injury.

The Maternal Lifestyle Study, also evaluated a different cohort of cocaine and opiate-exposed babies at ages between 1 and 3 years\(^{69}\), using the Bayley Scales of Infant
Development II. Only 50 of the 1227 infants were exposed to opiates alone, and there were 655 controls. Adjustments for co-variates such as birth weight, socioeconomic status, maternal education, race, and prenatal alcohol, cigarettes, and marijuana were made, after careful and detailed assessment of all these potential confounders. They found that in utero opiate exposure was associated with deficits in psychomotor development, but after correcting for confounding factors, the association was not significant. The authors comment that, in their sample, however, opiate use was associated, on the one hand, with “disruptions in maternal care”, and on the other hand with greater scores on questionnaires regarding the home environment and maternal vocabulary. This creates a mixed picture of the background of the opiate-exposed children. It then raises the question that this sample of purely opiate-exposed babies may not be truly representative of opiate-exposed babies worldwide. Alternatively, opiate-exposed children across the world may not represent a homogeneous sample, and so the discrepancies in rates of NAS, and developmental outcome can be at least partially explained by this.

If there are subtle but detectable differences in the development of opiate-exposed babies at 3 years of age, could it be that with age and with increasingly more complex activities being attempted, more differences will become evident? The Maternal Lifestyle Study has continued to follow this cohort and is now at phase IV of their research project. Their final results may shed more light on the long-term consequences of in utero drug exposure.

Rosen and Johnson prospectively studied 61 babies of methadone-maintained mothers and 31 methadone-free comparison babies, matched for maternal race, socioeconomic status, sex, birth weight, and gestation, over a 7-year period. Comparison mothers were significantly younger than controls, and those mothers on methadone were more likely to smoke more than one pack of cigarettes per day. The mean methadone dose was 42+/−3mg/day, and 56% were known to use multiple drugs. Using a modified Finnegan scoring system, 75% of methadone-exposed babies were diagnosed with NAS. It is not stated how many required pharmacological treatment. Assessment of behaviour and development, growth, and general health were done at regular intervals.
It seems that the major differences between methadone-exposed and control children are evident in the first three years of life. More methadone-exposed children have head circumferences below the 3rd centile. Eye disorders such as strabismus were associated with opiate exposure in utero. Scores both for motor and psychomotor development using the Bayley Developmental Scales were significantly lower than controls, and neurological assessment showed difficulties in language development and fine motor coordination. There was no relationship between severity of NAS and developmental outcome, with the only factors relating to poor developmental outcome being exposure to methadone in utero (regardless of dose), and gender.

At seven years, the differences between the two groups were diminishing. Those in the methadone group who were identified earlier as having problems with development continued to have difficulties in school. Conversely, those in the methadone group who were developmentally appropriate on initial testing, tended to continue to follow that path. Those children in the control group, who were matched to the methadone-exposed children for socioeconomic status, had a more variable outcome. Once at school their performance tended to fall as postnatal environmental influences came into play. Regardless, methadone exposure in utero was associated with a higher prevalence of gross and fine motor coordination difficulties, hyperactivity, poor attention span and speech and language delays. In both groups maternal education and family stability were protective factors.

McGlone et al describe abnormal visual evoked potentials (VEP) in methadone-exposed infants. Visual evoked potentials are electrical impulses from the visual cortex that occur in response to a visual stimulus. If they are normal, then the visual pathway is intact. Abnormal VEPs are known to occur in adults on methadone, which is thought to be due to an opiate effect on neural transmission in the visual cortex. VEPs have been used to predict poor neurological and visual outcome in term and preterm babies following birth asphyxia or intraventricular haemorrhage (IVH) and/or periventricular leucomalacia (PVL).

McGlone compared the visual evoked potentials of methadone-exposed and control babies in the first few days of life, and one week later. 100% of the control babies
had normal VEPs to a ‘flash’ visual stimulus. In contrast, only 76% of methadone-exposed babies had detectable ‘flash’ VEPs, which had immature and low amplitude waveforms than in controls. There was some improvement in their VEPs at one week, but still remained low amplitude, when compared to controls. The authors postulated that the effects of opiates, or drugs of abuse, on the visual system were sequential. There is an immediate effect at birth due to the presence of the circulating drug. This occurs also in adults taking methadone. McGlone then describes possible effects due to the withdrawal process, as seen in animal studies. Thirdly they postulate there may be long term effects due to the teratogenic nature of the drug on visual development.

In summary, in utero exposure to opiates has some effect on the long-term growth, development and well-being of children. Determining whether this is due to the social environment in which these children live or a pharmacological effect, or a combination of these, is difficult to ascertain. Finding the correct tool to assess these children is fundamental in identifying differences in how these children grow, behave, and develop. Later studies, with the appropriate selection of controls, have identified early differences in growth and development. From school age, there is no clear difference in developmental outcome between those children with opiate-exposure in utero and controls, as factors in the home environment exert more influence.
3 Hypotheses

3.1 Development of the hypothesis

Based on the work by Doberczak\textsuperscript{12} it became the widely held belief that prematurity itself reduces the incidence and severity of neonatal abstinence syndrome in the newborn baby, exposed to opiates during pregnancy. This work was then replicated, to some extent, by Dysart et al\textsuperscript{13}. This was discussed further in Section 2.1, where these authors put forward four possible mechanisms, as to why this was so.

Firstly, central nervous system immaturity in the preterm baby may limit the demonstrable symptoms and signs of opiate withdrawal. However, this immaturity should be evident in other aspects of the baby's postnatal life, such as difficulty feeding. “Difficulty feeding” could encompass poor or incoordinate suck. This could be manifest as a delay in achieving “full suck feeds”. These signs may be more prominent when compared to preterm babies of similar gestation with no opiate exposure.

Opiate-exposed preterm babies have a lower incidence of neonatal abstinence syndrome, and it is said to be less severe, and this may be attributable to being exposed to opiates for a shorter period of time. This explanation seems overly simplistic, as firstly there is a considerable variation in the prescribed dose of methadone in particular. It is difficult to establish whether the risk of NAS for a newborn whose mother is on 100mg of methadone for 30 weeks will be less than if the mother was on 20mg for 40 weeks. Secondly it may suggest there is a link between methadone dose, and rate of neonatal abstinence syndrome. This relationship has never been unequivocally established.

In Section 2.5 the metabolism of methadone was discussed. It has been suggested that the relative immaturity of hepatic enzymes leads to the delay in breakdown of methadone in the preterm infant. Therefore, rather than an abrupt cessation of methadone to the baby at the time of delivery, there is a gradual decrease in methadone levels. This theory is supported by work done by Kuschel\textsuperscript{21}. Methadone levels in cord blood and at 48 hours of age were measured in 17 babies whose mothers were on methadone during pregnancy. 12 babies who required treatment
for neonatal abstinence syndrome had significantly lower cord blood methadone concentrations than those who did not require treatment, and the postnatal sample in 11 of the 12 babies had undetectable methadone concentrations. This may indicate that the ability to metabolise methadone soon after birth produced a significant fall in methadone concentrations postnatally, which was associated with the development of NAS. Babies born before 34 weeks gestation were excluded from this study.

Both Doberczak and Dysart used assessment tools to objectively diagnose NAS, and to determine the need for treatment and its efficacy. Doberczak used the Lipsitz scoring system, whilst Dysart used the modified Finnegan chart. The use of scoring systems has been discussed in detail in Section 2.3. The modified Finnegan NAS score was not specifically designed to be used with preterm babies. Consequently it is possible that preterm babies are experiencing withdrawal, but they do not manifest the symptoms and signs measured by the scores. If we postulate that in utero opiate exposure must have some effect, then we need to look at how the postnatal course of opiate-exposed preterm babies differs from that of preterm babies of similar gestation, with no history of opiate exposure.

### 3.2 Hypotheses

- Preterm infants exposed to opiates during pregnancy manifest less symptoms of withdrawal, as determined by the use of the current standard assessment tool used in Victoria, the modified Finnegan NAS scoring system, compared to term opiate-exposed infants. They have a decreased need for pharmacological treatment than their term counterparts.

- Preterm infants exposed to opiates during pregnancy have a more complicated inpatient course and are at an increased risk of co-morbidities of prematurity, as compared to infants of similar gestation and socioeconomic status, with no documented exposure to opiates during pregnancy.

Our aim was to determine how preterm babies exposed to opiates in utero demonstrate withdrawal. From the work of Dysart and Doberczak, the study design had to incorporate term and preterm opiate-exposed babies. In order to obtain
adequate preterm opiate-exposed babies in our sample, as well as to obtain information on neonatal outcome within a practical timeframe, the study design is retrospective.

If we consider the effects of in utero opiate exposure, which may not be detected by the standard scoring tools, then data regarding such factors as weight gain and loss, and establishment of feeding would also need to be recorded. These factors occur in all preterm babies, within a predictable timeframe. As such, comparison to well, gestation-matched babies, with no history of opiate exposure is useful, as they provide a “normal” control group.

Collecting data on antenatal drug exposure was vital, but for those mothers on methadone and buprenorphine, in addition to the maximum opiate dose prescribed, it is important to record the changes in dosage throughout the pregnancy. A link between maximum opiate dose at delivery and development of NAS is yet to be adequately established, and perhaps the presence or absence of fluctuations in prescribed opiate may also be a factor. Although Doberczak used the Lipsitz tool in her study, the modified Finnegan NAS score is used most commonly throughout Australia, and is therefore used in our study.

Lam\textsuperscript{47} in his study looking at the effects of opiates amongst the Hong Kong Chinese women and their babies failed to allow for socioeconomic factors when selecting his controls. This biased his analysis of neonatal outcomes, when comparing women on heroin, methadone, or both, to their non-opiate using controls. The postcode of residence at the time of booking could be a useful marker of socioeconomic status, when compared to a list of all Victorian postcodes, divided into quintiles based on socioeconomic data compiled by the Australian Bureau of Statistics\textsuperscript{73}. The selection of a gestation and gender matched non-opiate-exposed baby could be further matched by having a postcode of residence, which falls in the same quintile as the opiate-exposed study baby.
4 Method

4.1 Sampling frame

The medical records of all women who delivered at the Mercy Hospital for Women in Heidelberg, Melbourne, between January 2003 and December 2007 inclusive, who were known to be regularly using heroin, or prescribed methadone, or buprenorphine, were accessed. The Mercy Hospital for Women is a tertiary obstetric hospital in metropolitan Melbourne, with a Level 3 Neonatal Unit. The hospital receives transfers from all over the state of Victoria. It runs a specialist obstetric clinic for a high-risk population of young mothers, those with known drug and alcohol use, and for indigenous women.

The women included in our study were identified by their coding during admission, as F11.2 (mental and behavioural disorders due to use of opioids, with a dependence syndrome), based on the ICD 10 coding system. Additional babies (n=10) were identified through "snowball sampling", when examining maternal records revealed siblings also born whilst their mother was prescribed methadone or buprenorphine, or using heroin during pregnancy. Only one baby was identified by ICD 10 coding P96.1, as the baby was transferred to the neonatal unit from another hospital with a diagnosis of neonatal abstinence syndrome.

4.2 Research instruments used

Case notes of women on methadone, buprenorphine or heroin in pregnancy, and their babies, were reviewed retrospectively to determine:

- The incidence and severity of neonatal abstinence syndrome (determined by use of the modified Finnegan NAS scoring system) in opiate-exposed preterm infants, compared to opiate-exposed infants born at term.
- The postnatal course and incidence of co-morbidities in opiate-exposed preterm infants compared to a gestation-matched cohort of preterm control infants with no known opiate exposure.
The first part of the study compares preterm opiate-exposed babies to term opiate-exposed ones. The primary outcome is the rate of treatment, with morphine and/or phenobarbitone, in each group. Other outcome measures include duration of treatment and length of stay. In this study our criteria for diagnosing severe NAS requiring treatment with morphine was three consecutive scores greater than or equal to 8, using the modified Finnegan scoring system.

The second part of the study compares preterm opiate-exposed babies to preterm control babies with no known opiate exposure. The primary outcome measure is length of stay. Other measured outcomes include time to establish full enteral and suck feeds, as well as rate of weight gain. “Full enteral feeds” is defined, in this study, as taking all feeds without supplementation with intravenous fluids or total parenteral nutrition. Other studies have varying definitions, with some attaching a specific volume (in ml/kg/day) or a specific caloric intake (in kcal/kg/day)21 to our definition. “Full suck feeds” is defined, for the purpose of this study, as five consecutive feeds taken orally, by bottle or breast. Morris69 defined “full suck (‘nipple’) feeds” as the first day that all nutrition was taken by “nipple” feeding. The Mercy Hospital for Women did not have a specific policy regarding the cessation of intravenous nutritional supplementation. This was governed by the clinical condition of the baby. Introduction of suck feeds were determined by the maturity of the baby, as well as the clinical condition. Thus, having a gestation-matched control baby is a useful guide to determine whether these milestones are delayed.

We estimated the rate of withdrawal requiring treatment to be 30% in the term group, and 10% in the preterm group. This was based on the data of Kuschel et al21. The absolute effect size is therefore 20%. With a α value of 5% and β value of 10%, the sample size required to show a difference was 82 babies in each group. The percentage of babies requiring morphine in each group was compared using chi-square tests.

Doberczak12 had 178 term and 34 preterm opiate-exposed babies in their study, of whom 81% of the term, compared with 58% of the preterm babies, required treatment. A greater proportion of the opiate-exposed babies, both term and preterm, required treatment in this study, than we expected to find in ours. There are a number of possible reasons for this. Firstly, there was a high rate of polydrug use in both groups, but particularly those babies born at term. Of the 178 term babies in the study, in addition to
the maternal methadone exposure, 68% used heroin, 28% used cocaine, as well as diazepam, barbiturates and amphetamines in lesser numbers.

There is a difference between developing withdrawal symptoms consistent with neonatal abstinence syndrome, and developing symptoms severe enough to require treatment. The criteria for diagnosing NAS requiring treatment varies from study to study. With the requirement for treatment comes an increase in length of stay, and an increase in health costs. Consequently there may be a reluctance to commence morphine therapy in babies whose scores may be borderline, when one is committing mother and baby to an increased length of stay in hospital. At the Mercy Hospital for Women all babies diagnosed with severe NAS requiring treatment with morphine are managed as inpatients until fully weaned off morphine. After stabilisation on morphine the dose is weaned by 10% every 48 to 72 hours, as guided by the Modified Finnegan NAS severity scores. This is protocol-driven.

Finally, Doberczak used the Lipsitz tool, which requires 12 hourly assessment of the baby, which may not accurately reflect the baby's behaviour throughout the day. Dysart conducted a retrospective study including only methadone-exposed babies who required treatment with morphine. The diagnosis was made by using a modified Finnegan scoring system, but there is little further information regarding how many scores were taken, and how often. The clinical course of 53 preterm babies with NAS was compared with 66 term babies with NAS admitted over a five-year period.

The study of Dysart included a preterm opiate-exposed group, whose gestation spanned 27 to 36 weeks, with a mean gestational age of 34.2 +/- 2 weeks. Doberczak had 34 preterm babies in their study population, with a mean gestational age of 34 weeks, with a range of 25 to 36 weeks gestation. We expected the mean gestational age for this study to also be 34 +/- 2 weeks. Dysart recorded a length of stay of 28.4 +/- 13.4 days for his preterm, opiate-exposed group.

In the second part of the study we compared the clinical course of our preterm opiate-exposed babies recruited in the first part of the study to the clinical course of a preterm opiate-free baby of similar gestation, gender, and socioeconomic status. When comparing the length of stay for opiate-exposed preterm babies to controls, we estimated the mean length of stay for controls born at 34 weeks gestation to be 17 days, with a range of 11 to 23 days. To show a difference in length of stay between the two
preterm groups of at least seven days, the sample size required was small (less than 10 in each group). The 82 preterm babies included in the first part of the study were adequate. Non-paired two-tailed t tests were used to determine differences in length of stay in each group.

De-identified data collected included the following: mother’s year of birth, postcode of residence at first presentation, highest level of education and employment status (if available), general antenatal history (including parity and medical and psychiatric history), gestation at first antenatal presentation, and number of antenatal visits. The number of antenatal visits attended reflected the quality of antenatal care received, whilst the number of “failure to attend” or “FTAs” perhaps reflected the level of maternal organisation.\textsuperscript{8,77} Involvement with protective services (the Department of Human Services) was also noted to reflect the stability of the home environment.\textsuperscript{42}

In addition, all documented drug, alcohol and tobacco use, including intensity of use immediately prior to presentation, and intensity of use during pregnancy, where available, were recorded, as well as documented maximum prescribed methadone or buprenorphine dose at time of delivery, agreed gestation and mode of delivery. Identifiable data (the hospital medical record number) was temporarily held in order to access and link with the related neonate’s records, and deleted immediately thereafter. Draft data collection sheets were shown to academic supervisors and practising clinicians, and modifications made. Once data collection had commenced, recurrent threads such as maternal mental illness and domestic violence became apparent, as well as the need for clearer recording of alcohol and cigarette exposure and the Finnegan scores, both totals and components. A request to amend the data collection proforma was made to the Mercy Hospital for Women Human Research and Ethics Committee, and approval given.

Information concerning the participant’s drug use is reliant on what is told to the midwife or doctor interviewing the patient, and what is then recorded in the medical record. The reliability of self-report among drug users has been studied by Darke et al.\textsuperscript{78} and found to be both reliable and valid. Darke was able to compare self-reported drug use declared to two different investigators, at two different times, by the drug user themselves, as well as independently interviewing their sexual partner, and found there was concordance in the information that was given. Indeed a drug-user’s own description of their drug use is the mainstay of most research into illicit drug use. The
data collected from the medical histories was information gained by the doctor or midwife in the antenatal clinic. There were no standardised questionnaires regarding drug and alcohol exposure included in the medical record, so the information documented varied in its detail. Supplementary information was gleaned from interviews conducted by social workers or psychiatrists, that were documented in the medical record.

The medical records of the babies were then accessed. De-identified data collected included the following: gestation at delivery, birth weight, length and head circumference, Apgar scores and resuscitation required, need for admission to Special Care Nursery, indication for admission to the Special Care Nursery, method of feeding, maximum weight loss, time to regain birth weight or maximum weight gained prior to discharge, maximum 3 consecutive NAS scores, age in hours when each of these scores were achieved, need for medical therapy for NAS (and maximum dose per kg), and duration of hospital stay.

The Finnegan NAS scores, including their components scores, were collected for each baby, over several days, if scoring was performed. All the term opiate-exposed babies were nursed with their mothers on the postnatal ward. They remained in hospital for seven days, so that an adequate period of observation in hospital was achieved, and the babies were scored from birth to discharge. Scoring was thus done by the midwives caring for them. The midwives performing the scoring did not have specific training regarding this. Babies were scored after a feed. Breastfeeding was encouraged, and supplementary feeds given if breast milk supply was inadequate. Babies were admitted to the Special Care Nursery if their scores were greater than 8 on more than 3 occasions, or they were to commence treatment with morphine, or for other medical reasons, such as prematurity.

The neonatal abstinence severity scores (NAS scores), both the total as well as the component scores were recorded for every baby who was scored, from its initiation until either scoring was ceased or for a minimum of 28 scoring events. Because the number of scores performed each day, and for each baby, varied, the number of scores recorded for each case varies. In addition, the modified Finnegan NAS scoring system is prone to error both in the allocation of an appropriate score and in the addition of the scores. Where the maximum three consecutive scores are recorded, where there is an error, the score used is that which appears in the medical records, as this would have
been the figure by which clinical decisions would have been made. Also, the time and date on which the three consecutive maximum scores occur, are recorded, and this may not reflect the time and date that treatment may have been instituted, if it was instituted at all.

In addition, further information regarding postnatal course and incidence of co-morbidities were gathered, with de-identified data collected including the following: time to establish full enteral feeds, time to establish full suck feeds, average daily weight gain (mg/kg/day) across the admission, frequency of apnoea, presence of hypoglycaemia, feeding problems, vomiting, diarrhoea, documented sepsis, and respiratory distress, as well as the need for respiratory support. "Preterm" was defined as being born before 37 completed weeks of gestation. Complications such as “apnoea” or “feeding problems” are included when they were listed in the medical record by the attending medical team as such.

A control group was selected from hospital birth records. The control babies were matched for gender, gestation and socio-economic status based on postcode. Records of potential controls were reviewed to confirm no documented opiate exposure in utero. An attempt to contact mothers in the control group was made. If consent was given, or they were uncontactable, their medical record was accessed, and their course in hospital was then compared. The medical records of the control group of preterm babies were then accessed, and de-identified data collected as described above, with the exception of the need to collect data related to monitoring for NAS.

All information collected is in a de-identified form, after linkage of maternal and neonatal records. For the purpose of this study, only women with documented opiate use (heroin, methadone or buprenorphine) were included as the target population. Heroin use was difficult to quantify, and was established either by maternal self-report, or in the neonate, by a positive urinary drug screen for opiates, if available.

4.3 Ethics approval

Approval from the Mercy Hospital for Women Human Research and Ethics Committee was obtained. As a condition of Ethics approval, prior to the medical record being accessed, an attempt to obtain verbal consent was made, using the most recent telephone number held by the hospital. Because the study is retrospective, and because
of the chaotic lifestyle associated with this patient population, contacting these women was extremely difficult. We were permitted to access their records without their consent if they proved to be un-contactable by telephone.

Telephone contact to obtain verbal consent was attempted for all identified mother-baby dyads. Of the 150 paired samples collected, contact was made with only 13 mothers. 12 consented, with one mother requesting further information. Despite written information and a consent form being sent to her nominated address, the researcher was unable to contact her either by telephone or mail again. Therefore this case was excluded from our study, and no data was collected. Contact was attempted with all the mothers in the control group. Only in two cases were we able to speak with the mothers, both of whom gave verbal consent. Lack of opiate exposure could only be ascertained by the information given in the medical record, and could not be verified by any other means.

The data collection sheet was modified primarily for ease of data collection. It became evident that there were common factors that required more detailed information to be recorded in order to maintain accuracy. This was particularly so for maternal mental health issues. The Human Research and Ethics Committee of the Mercy Hospital for Women was approached and approval to use the amended data collection sheets obtained.

4.4 Data Collection

Ethics approval was granted in September 2008, and data was collected between November 2008 and May 2010. All data were collected by one researcher (NP). The medical record numbers were kept in order to identify mother-baby pairs, and to ensure all records with the ICD coding F11.2 in the selected timeframe were accessed. They were then destroyed. Mother-baby pairs were given a unique code, and no names were recorded. Cases were excluded if there was no evidence of opiate use with methadone, buprenorphine or methadone in pregnancy. One baby was stillborn, and so excluded from our final analysis.
5 Results

5.1 NAS in term and preterm opiate-exposed babies

5.1.1 Maternal demographic factors

Every woman who was on methadone, buprenorphine, or heroin during her pregnancy, who delivered at the Mercy Hospital for Women between January 1\textsuperscript{st} 2003 and December 31\textsuperscript{st} 2007 was eligible for inclusion in this study. Two were excluded as it was clearly identified from documentation in their record that they did not want their medical record accessed. One woman was approached by telephone and requested further written information about the study. Despite further attempts at contact by both letter and by telephone, she was not contactable, and was excluded from the study.

There were 149 opiate-dependent women included in the study. 108 women had babies born at term, 41 delivered preterm. The ages of the women, whose babies were born preterm, were not significantly different from those women who delivered at term. The median age overall was 29.9 +/- 5 years. The median maternal age in the term baby group was 30.1 +/- 5 years. In the preterm baby group the maternal age was 29.5 +/- 5 years. Parity in both the term and preterm groups were also very similar, with the mean parity in the term group being 1.4, compared to the preterm group, which was 1.5.

22 of the 108 opiate-exposed term babies (20\%) were born to Aboriginal women. In the preterm group, 5 of the 41 babies (12\%) had mothers who were Aboriginal. Aboriginal women are known to have a worse obstetric outcome\textsuperscript{79}. The Mercy Hospital for Women Transition Clinic provides an obstetric service, sensitive to the needs of Aboriginal women, with Aboriginal liaison workers who assist in engaging the women to attend antenatal care through the clinic. The difference in the numbers of Aboriginal women in each group was statistically significant.
Information regarding gestation at booking, number of antenatal appointments, and the number of times the mother failed to attend antenatal appointments was also recorded. These were used to indicate the adequacy of antenatal care as well as a marker of a chaotic lifestyle. The mean parity at booking in both groups was similar, at 1.4 in the term group and 1.5 in the preterm group. A Mann-Whitney U test revealed no significant difference in the number of antenatal appointments that the mother failed to attend (FTAs) in the NAS (Md 1.50, n=46), and no NAS (2.00, n=94) groups, U=1905, z=-1.162, p= 0.25. Similarly, there was no significant difference, in the number of antenatal appointments attended (9 visits in the NAS group versus 10 visits in the no NAS group, p=0.48), nor in the gestation at booking (median 19 weeks in the NAS group compared to 16 weeks in the no NAS group, p=0.25).

Table 5-2 Antenatal care (ANC) by NAS status

<table>
<thead>
<tr>
<th></th>
<th>NAS</th>
<th>No NAS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number ANC visits</td>
<td>9</td>
<td>10</td>
<td>0.48</td>
</tr>
<tr>
<td>Number FTAs</td>
<td>1.5</td>
<td>2.0</td>
<td>0.25</td>
</tr>
<tr>
<td>Gestation at booking</td>
<td>19</td>
<td>16</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Postcode of residence at the time of booking was also collected, and expressed as quintiles, with "one" being the highest. The quintiles were derived from information from the Australian Bureau of Statistics, who collected data regarding such factors as employment status, level of education, and income to categorise each postcode in Victoria. We have used the quintiles as a proxy for socioeconomic status. DHS
involvement, polydrug use, and housing were other factors considered. There was no significant difference in the SES quintiles of those babies who developed NAS and those babies who did not (p=0.73). In both the commonest SES quintile was 5, which was the lowest.

Data regarding factors such as maternal education, employment, housing, and presence of domestic violence were collected where available. However often these factors were not consistently recorded, particularly when the mothers were in utero transfers from outside Melbourne. Much of this information was found in entries made by social workers or psychiatrists, and did not form part of the routine prenatal assessment of every pregnant woman with a history of opiate use. This information is displayed in Table 5-3. 54 of the 149 babies were born to mothers who had some DHS (Department of Human Services) involvement at booking. DHS involvement did not differ significantly between preterm and term groups.

### Table 5-3 Maternal socio-economic factors by NAS status

<table>
<thead>
<tr>
<th>Factor</th>
<th>NAS group</th>
<th>%</th>
<th>No NAS group</th>
<th>%</th>
<th>Data available for:</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed secondary school (yr 12)</td>
<td>5/9</td>
<td>56</td>
<td>11/20</td>
<td>55</td>
<td>29/9 with NAS 20 with no NAS</td>
<td>ns</td>
</tr>
<tr>
<td>Employment</td>
<td>14/39</td>
<td>36</td>
<td>16/70</td>
<td>23</td>
<td>109</td>
<td>ns</td>
</tr>
<tr>
<td>Housing</td>
<td>33/48</td>
<td>69</td>
<td>69/95</td>
<td>73</td>
<td>143</td>
<td>ns</td>
</tr>
<tr>
<td>In a relationship</td>
<td>43/48</td>
<td>90</td>
<td>79/99</td>
<td>80</td>
<td>147</td>
<td>ns</td>
</tr>
<tr>
<td>Domestic violence</td>
<td>14/21</td>
<td>67</td>
<td>22/41</td>
<td>54</td>
<td>62</td>
<td>ns</td>
</tr>
<tr>
<td>DHS involvement</td>
<td>19/48</td>
<td>40</td>
<td>35/95</td>
<td>36</td>
<td>143</td>
<td>ns</td>
</tr>
</tbody>
</table>

"ns" denotes Not Statistically Significant at p<0.05 level
5.1.2 NAS in babies exposed to methadone, buprenorphine, and heroin

In the study period there were 149 opiate-exposed babies born to mothers on methadone, buprenorphine, and heroin. 108 were born at term, with a mean gestation of 39.1 +/- 1.2 weeks, and a mean birth weight of 3002 +/- 470gm. The 41 preterm babies had a mean gestation of 33.7 +/- 3.2 weeks, and a mean birth weight of 2072 +/- 640gm. The gestations in the preterm group ranged between 25.5 to 36.6 weeks at delivery.

Amongst the term group (n=108), 83 babies (77%) were born to mothers on methadone. 17 babies (16%) were born to mothers on buprenorphine, and 8 (7%) had mothers who were on heroin alone. In the preterm group 36 of the 41 babies (88%) were exposed to methadone in utero. There were 3 preterm babies with mothers on buprenorphine (7%), and 2 preterm babies (5%) whose mothers used heroin through pregnancy. The type of opiate exposure did not differ significantly between the term and preterm groups.

The rate of NAS by maternal opiate used is shown in Table 5-4. The overall incidence of NAS in our study was 32.9%.

Table 5-4 Rate of NAS by maternal opiate used

<table>
<thead>
<tr>
<th></th>
<th>Methadone (n=119)</th>
<th>Buprenorphine(n=20)</th>
<th>Heroin (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAS</td>
<td>34</td>
<td>20</td>
<td>50</td>
</tr>
</tbody>
</table>

119 babies had mothers on methadone, of which 40 (34%) developed NAS. For babies whose mothers were on buprenorphine, 4 of the 20, or 20%, developed NAS. They were all term babies. The mean maximum buprenorphine dose prior to delivery was 13.4mg (InterQuartile Range – hereafter IQR 9.25mg to 16mg ), and this was not statistically different between those babies born preterm or at term. There were only 10 women who were solely on heroin, but 50% of their babies developed NAS. There was no significant difference in the rate of NAS between the methadone and buprenorphine groups (using p<0.05 as indicator of significance), based on maternal opiate used.

However further examination of heroin use and NAS with a larger cohort would be of interest. In addition, heroin exposure is difficult to quantify, so we are unable to comment on whether these ten women were particularly heavy heroin users.
For the 40 methadone-exposed babies who developed NAS, the median methadone dose at delivery was 62.5mg. For the 79 methadone-exposed babies who did not develop NAS, the median methadone dose at delivery was 65mg. The Mann-Whitney U test revealed no significant difference in maternal methadone dose in babies who did or did not develop NAS (U=1576.5, z=-0.020, p=0.98). Further, this would suggest that maternal methadone dose prior to delivery did not affect the baby’s chance of developing NAS.

We compared the incidence of NAS among the term and preterm babies, regardless of which opiate they were exposed to. 36 of 108 term babies (33%), and 13 of 41 preterm babies (32%) developed NAS. There was no significant difference in the incidence of NAS between the two groups (p=0.85). In our study methadone was the most common opiate to which the babies were exposed. Of the 119 methadone-exposed babies, 40 developed NAS, 27 of whom were born at term. There was no significant difference in the number of babies developing NAS, based on being born term or preterm (p=0.70). This is shown below in Table 5-5.

<table>
<thead>
<tr>
<th></th>
<th>Term (n=83)</th>
<th>Preterm (n=36)</th>
<th>Total (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAS</td>
<td>33%</td>
<td>36%</td>
<td>34%</td>
</tr>
</tbody>
</table>

As in other studies, the incidence of polydrug use is difficult to estimate. We were largely reliant on maternal self-report. However, 49 babies had urine drug screens, and these results were used to identify any additional illicit drug use by their mothers in pregnancy, or to corroborate their history. 10 women were known to be on heroin without opiate maintenance treatment. However, heroin use was associated with a significant increase in the incidence of NAS, with 27 of the 49 babies with NAS known to be exposed to heroin (p=0.05). Similarly, concomitant cannabis use at booking was also associated with the development of NAS (p=0.03).

If one compares illicit drug use amongst the overall term and preterm opiate-exposed groups, the results are similar. The preterm group had significantly more mothers who were using cannabis (p=0.02) than the mothers who had babies born at term. There was no significant difference in exposure to benzodiazepines or heroin between the term and preterm groups.
Table 5-6 Rate of exposure to illicit drugs in babies with NAS by term/preterm

<table>
<thead>
<tr>
<th></th>
<th>Term babies with NAS % (n=38)</th>
<th>Preterm babies with NAS % (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin*</td>
<td>53</td>
<td>35</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Cannabis</td>
<td>29</td>
<td>40</td>
</tr>
</tbody>
</table>

*Heroin numbers include those taking heroin alone (n=10) as well as those also taking prescribed opiates (methadone or buprenorphine)

NAS was determined by the modified Finnegan NAS scoring system. Three consecutive scores greater than 8, or the mean of three scores of 8 or greater were an indication to commence treatment with morphine. Of the 149 babies, NAS scores were available for 138. For 11 babies initial scores were not available. 6 of these babies were born preterm, and had concomitant respiratory distress syndrome requiring ventilation. 3 babies were transferred to another tertiary unit as they had significant congenital anomalies requiring surgery, one of whom subsequently developed NAS requiring treatment. Two were very unwell and died.

We recorded the three consecutive highest NAS scores from the baby's medical record. Because these scores could include a very low score followed by two high scores to make a high total, it was more appropriate to use the sum of these scores, rather than the mean, or one individual peak score. For the term opiate-exposed babies, scores were available for 104 babies. The median value of the sum of the peak scores was 20.0 (IQR 14 to 30). In the preterm group the median value for the sum of the peak scores was 24.0 (IQR 15 to 28.4). Scores were available for 34 preterm babies. When comparing the two groups, the mean value for the sum of the peak scores was not significantly different (p=0.08). Peak scores were reached at 2.54 +/- 1.96 days in the term group, and 2.59 +/- 1.83 days in the preterm group. This was not significantly different (p=0.51).

We had initial NAS scores for 47 babies requiring treatment for NAS, 34 term and 13 preterm. When comparing the sum of their three consecutive peak NAS scores, a Mann-Whitney U test revealed a significant difference between the term (median 38, n=34) and preterm (median 30, n=13) babies diagnosed with NAS, U=124.0, z=-2.310, p=0.02, r=0.33.
Figure 5-1 Summed peak NAS scores, where NAS was identified, by term/preterm

Length of stay was greatly increased once treatment for NAS was required. Overall, the median length of stay for those opiate-exposed babies who did not develop NAS was 7 days (IQR 6 to 8 days). This reflects the standard period of observation in hospital required for these babies. In the NAS group the median length of stay was 30 days (p<0.0001). When comparing the length of stay of preterm babies with NAS, the median length of stay was 30 days, compared with 12 days (IQR 6.75 to 26.50 days) for those babies who did not develop NAS (p=0.01). Term babies who developed NAS also had greater lengths of stay (median 30.50 days, compared to median 7 days for those who did not require treatment, p<0.001). Yet the length of stay between term and preterm babies with NAS was very similar, with a median length of stay of 30.5 days (IQR 19 to 38.5 days) in the term group, and 30 days (IQR 18.5 to 35.0 days) in the preterm group (p=0.84). Term babies with NAS had a prolonged admission due to their treatment with morphine, and the process of weaning in hospital.
Table 5-7 Median length of stay (days)

<table>
<thead>
<tr>
<th></th>
<th>NAS  n=49</th>
<th>No NAS n=98</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term</td>
<td>30.5</td>
<td>7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preterm</td>
<td>30.0</td>
<td>12</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Figure 5-2 Frequency of NAS by gestation

Figure 5-2 shows the frequency of NAS by gestation at delivery. For the babies with NAS, the mean gestation at delivery was 37.8 weeks. NAS is defined as three scores greater than 8, using the modified Finnegan NAS scoring chart.

For those babies with NAS requiring treatment with morphine, data regarding duration of treatment was available for 42 babies, 32 term and 10 preterm. This was due to babies being transferred to other hospitals on morphine, or being transferred to the Mercy Hospital for Women with treatment having been commenced. The mean duration of treatment was 22.6 days in the term group, compared to 18.0 in the preterm group. A Mann-Whitney U test found no significant difference between the two groups, U=125.0,
z=-1.034, p=0.30. 6 babies required the addition of phenobarbitone in order to adequately treat the severe NAS.

We collected data regarding the time taken for the babies to establish full enteral feeds as well as full suck feeds. As this hospital is a tertiary referral centre, many babies were transferred to a local centre when the baby was stable and able to be cared for in a level 2 Nursery. Consequently there are data missing. Generally it would be expected that healthy term babies would establish both full enteral feeds and suck feeds at birth. In those babies who developed NAS (n=49), data regarding full enteral feeds were available on 48 babies. Breastfeeding and the use of expressed breast milk was encouraged at the Mercy Hospital for Women. Artificial feeds were used if breast milk was unavailable.

There were 35 term babies with NAS, who took a mean of 22.4 days until full feeds were established, compared to 30.2 days in the preterm group (n=13, p=0.05). With regard to establishing full suck feeds, term babies with NAS (n=35) took a mean of 20.5 days compared to 31.6 days in the preterm group (n=10, p=0.01). This is an expected result. Preterm babies often require intravenous fluids or total parenteral nutrition, and/or nasogastric feeds before achieving full suck feeds. However the length of time taken for opiate-exposed term babies to be able to fully feed is markedly increased, if compared to term babies with no history of opiate exposure.

If the preterm opiate group are examined alone, there are a total of 41 babies. Information regarding the time taken to achieve full enteral feeds and suck feeds is available for 31 babies. A Mann-Whitney U test revealed no significant difference in either the time taken to achieve full enteral feeds in those preterm babies who developed NAS (mean=16.8 days, n=13) and those who did not (mean=20.2 days), U=127.5, z=-0.933, p=0.35). Similarly, there was no significant difference in the time taken to achieve full suck feeds between those who developed NAS (mean=17.2 days, n=10), and those who did not (mean=15.4 days, n=21), p=0.61.

Overall birth weight between babies who developed NAS and those who did not were comparable. For those babies who did not develop NAS, the mean birth weight was 2717 grams, compared to 2804 grams in those who did develop NAS. The difference was not statistically significant (p=0.41). Mode of delivery was most commonly by normal vaginal birth. It occurred in 61% of those babies who did not develop severe NAS, and
61.2% who did. 22.4% required an emergency Caesarean section in the NAS group, compared with 15% in the no NAS group. The mode of delivery was not significantly different for the babies in either group (p=0.75).

Opiate exposure appears to affect a baby’s ability to establish suck feeds in term babies. In addition we compared the time taken for opiate-exposed babies to regain their birth weight. Because many babies are discharged home or transferred to another hospital before birth weight is regained, this data was available for only 58 of the 149 babies in our study. Of the 58, 43 babies had NAS, and took a mean of 34.2 days to regain their birth weight. This was significantly longer than in the no NAS group (n=15, mean=15.9 days, p<0.0001).

However there was no significant difference in time taken to regain birth weight between the term and preterm opiate-exposed babies. There were 38 term babies, who took a mean of 28.8 days to regain their birth weight. The 20 preterm babies took a mean of 30.8 days to regain their birth weight.

Although one could hypothesise that maternal opiate use in pregnancy may give rise to an increase in neonatal complications, the evidence for this is lacking. In our study we collected data regarding the incidence of common complications, such as congenital abnormalities, neonatal sepsis, respiratory disease, vomiting, diarrhoea, feeding difficulties, abdominal distension, patent ductus arteriosus (PDA), apnoea and jaundice. Congenital anomalies were any abnormalities detected and recorded in the initial examination in the baby medical record. They included abnormalities such as talipes and tracheo-oesophageal fistula. There was no significant association between the maternal opiate used and the risk of congenital anomaly. When comparing the incidence of these in babies who developed NAS to those who did not, the only complication, which occurred with increased frequency, was that of sepsis. For the purpose of this study, sepsis was defined as an episode for which the baby had clinical or laboratory evidence of infection for which antibiotics were commenced, even though blood cultures may have had no growth. There were significantly more episodes of sepsis amongst those babies who developed NAS (25 of 49 babies with NAS, p=0.001).
Table 5-8 Incidence of common neonatal complications by NAS status

<table>
<thead>
<tr>
<th></th>
<th>NAS</th>
<th>%</th>
<th>No NAS</th>
<th>%</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital abnormality</td>
<td>9/49</td>
<td>18%</td>
<td>11/100</td>
<td>11%</td>
<td>0.22</td>
</tr>
<tr>
<td>Respiratory</td>
<td>15/49</td>
<td>31%</td>
<td>22/99</td>
<td>22%</td>
<td>0.32</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>6/44</td>
<td>14%</td>
<td>16/90</td>
<td>18%</td>
<td>0.81</td>
</tr>
<tr>
<td>Apnoea</td>
<td>5/95</td>
<td>5%</td>
<td>2/46</td>
<td>4%</td>
<td>0.83</td>
</tr>
<tr>
<td>Feeding problems</td>
<td>24/48</td>
<td>50%</td>
<td>39/96</td>
<td>41%</td>
<td>0.53</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8/46</td>
<td>17%</td>
<td>12/96</td>
<td>13%</td>
<td>0.49</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>4/46</td>
<td>9%</td>
<td>3/96</td>
<td>3%</td>
<td>0.24</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>0/46</td>
<td>0%</td>
<td>1/96</td>
<td>1%</td>
<td>0.46</td>
</tr>
<tr>
<td>Jaundice</td>
<td>5/47</td>
<td>11%</td>
<td>18/97</td>
<td>19%</td>
<td>0.37</td>
</tr>
<tr>
<td>PDA</td>
<td>2/49</td>
<td>4%</td>
<td>4/99</td>
<td>4%</td>
<td>0.99</td>
</tr>
<tr>
<td>Sepsis</td>
<td>25/49</td>
<td>51%</td>
<td>23/99</td>
<td>23%</td>
<td>P=0.001</td>
</tr>
</tbody>
</table>

There was also an association between sepsis and prematurity in opiate-exposed babies. 25 of the 48 preterm opiate-exposed babies had an episode of sepsis (presumed or confirmed), p<0.0001, compared to 23 of 107 term opiate-exposed babies. This may be because clinicians will be screening for potential sepsis more keenly in all premature babies, and will have a lower threshold to institute antibiotic therapy. Secondly, being premature makes a baby more susceptible to sepsis. This is where comparison to non-opiate-exposed premature babies is of use. As expected, the common complications of the newborn period occurred with more frequency in the premature group. These included respiratory illness (20 of 41 babies, p<0.0001), apnoea and jaundice. Of note, there was no significant difference in the incidence of feeding difficulties in the term and preterm opiate-exposed groups. There were 6 babies with patent ductus arteriosus, 4 of whom were born at less than 32 weeks. The other two babies were IUGR, and born at 37+3 weeks (birth weight 1712g), and 33+4 weeks (birth weight 1525g).

When only the babies who developed NAS were considered, preterm babies had significantly more respiratory illness when compared to the term babies (p=0.01). However, they were no longer more likely to be treated for sepsis (p=0.06). Again, feeding difficulties, abdominal distension, and vomiting were not significantly different amongst the term and preterm babies who developed NAS.
In summary, there were 149 opiate-exposed babies included in our study. 108 were term and 41 were preterm. All the babies were comparable with regard to maternal age, parity, and antenatal care. Birth weight and mode of delivery were also comparable between those babies who developed NAS and those who did not, perhaps reflecting the quality of antenatal care offered. The overall rate of NAS was 32.9%. The most significant factor in the NAS group was the difficulty experienced in establishing feeding, particularly noticeable in the term group. Comparison of outcome in non-opiate exposed preterm babies will assist in establishing whether this difficulty in feeding is possibly an opiate effect alone.
5.2 Effects of opiates, not identified by the Finneganscoring system, in:

5.2.1 opiate-exposed preterm babies

5.2.2 ‘control’ (non-opiate-exposed) preterm babies

Comparing the neonatal course of opiate-exposed babies across all gestations is hampered by the varying course of neonates born preterm, regardless of opiate exposure. The feeding difficulties seen as a consequence of maternal opiate use in pregnancy are more obvious in term babies as there is an expectation that a full term baby should establish full enteral feeds and full suck feeds shortly after birth. In the case of preterm babies, depending on gestation, there is often a period after birth where feeding is establishing, and the timeframe will vary depending on the gestation of the baby, as well as any illnesses complicating the neonatal course, particularly respiratory distress.

By matching our preterm opiate-exposed babies to a baby matched by gender, socioeconomic status, and gestation, we hoped to examine what effects could be attributed to the effects of maternal opiate ingestion. There were 41 preterm opiate-exposed babies, which included one fetal death in utero (FDIU) at 36 weeks gestation, and one neonatal death at 26 weeks gestation. No control babies were sought for these two. There was one set of dichorionic, diamniotic twins, two girls, born at 34 weeks gestation. It proved difficult to provide a control that matched all criteria. Consequently, a match was found which was a set of twin girls, at 34 weeks whose postcode differed by one quintile from that of the study babies.

There were 39 control babies. Due to some mothers opting for private obstetric care, complete information regarding antenatal care was available for only 25 of their mothers, as this was held in the hospital medical record. In the control group, neither the mean parity at booking (0.97, compared to 1.46 in the opiate group, p=0.14), nor the number of antenatal visits (7.9 visits versus 6.6 visits in the opiate group, p=0.51) was significant. However, the gestation at booking was significantly earlier in the control group (12 weeks versus 19.1 weeks, p<0.0001), and they had significantly less FTAs (failure to attend clinic appointments) than the opiate-exposed group. Maternal age was
also significantly greater in the control group, with a mean of 31.3 years, all perhaps suggesting a more stable background.

**Table 5-9 Preterm opiate exposed versus control babies**

<table>
<thead>
<tr>
<th></th>
<th>Opiate-exposed</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>28.7yrs (mean +/- 5.1yrs)</td>
<td>31.3yrs (mean +/- 5.8yrs)</td>
<td>0.03</td>
</tr>
<tr>
<td>Gestation at booking</td>
<td>19.0 wks (mean +/- 7.1 wks)</td>
<td>12.1 wks (mean +/- 4.6 wks)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of “Failure to Attend Booked Appointment” (mean)</td>
<td>2.72 appointments (mean +/- 2.6)</td>
<td>0.29 appointments (mean +/- 0.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Birth weight (median)</td>
<td>2300gm (IQR 1510 to 2598gm)</td>
<td>2290gm (IQR 1985 to 2590gm)</td>
<td>0.63</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td>NVD 23/41 (56%)</td>
<td>NVD 18/39 (46%)</td>
<td></td>
</tr>
<tr>
<td>Length of stay (mean)</td>
<td>25.4 days (mean +/- 24.5 days)</td>
<td>20.6 days (mean +/- 31.9 days)</td>
<td>0.01</td>
</tr>
<tr>
<td>Time to enteral feeds</td>
<td>2.43 days (mean +/- 3.4 days)</td>
<td>3.82 days (mean +/- 7.1 days)</td>
<td>0.85</td>
</tr>
<tr>
<td>Time to suck feeds</td>
<td>12.2 days (mean +/- 17.3 days)</td>
<td>11.4 days (mean +/- 23.0 days)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Despite this, the median birth weights between the two groups were similar, and a normal vaginal delivery was the commonest mode of delivery for both groups. Preterm opiate-exposed babies had a longer admission to hospital than their controls. This is despite the fact that the time taken, to establish full enteral feeds and full suck feeds were not significantly different. On further examination, 13 of the 39 preterm opiate-exposed babies developed NAS requiring treatment. Their length of stay was significantly longer (median 30 days, compared to 12 days for the ‘no NAS’ group, p=0.01), and there was no significant difference in their gestations at birth. Therefore it is likely that the increased duration of admission in the preterm opiate-exposed group is due to NAS requiring treatment, rather than prematurity or feeding difficulties.

Information regarding the incidence of common neonatal complications was sought from the medical records of the control babies. There was no significant difference in the
incidence of congenital abnormalities, respiratory disease at birth, apnoea, feeding
difficulties, jaundice, or patent ductus arteriosus. Of note, there was no significant
difference in the incidence of sepsis between the opiate-exposed and non-opiate-
exposed preterm baby groups.

Table 5-10 Rate of neonatal complications in preterm babies by opiate exposure

<table>
<thead>
<tr>
<th></th>
<th>Preterm opiate group</th>
<th>%</th>
<th>Control group</th>
<th>%</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>6/41</td>
<td>15</td>
<td>1/39</td>
<td>3</td>
<td>0.06</td>
</tr>
<tr>
<td>Congenital</td>
<td>7/41</td>
<td>17</td>
<td>7/39</td>
<td>18</td>
<td>0.92</td>
</tr>
<tr>
<td>Respiratory</td>
<td>20/41</td>
<td>49</td>
<td>16/39</td>
<td>41</td>
<td>0.51</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>9/35</td>
<td>26</td>
<td>6/39</td>
<td>15</td>
<td>0.03</td>
</tr>
<tr>
<td>Apnoea</td>
<td>5/38</td>
<td>13</td>
<td>7/39</td>
<td>18</td>
<td>0.19</td>
</tr>
<tr>
<td>Feeding problems</td>
<td>16/39</td>
<td>41</td>
<td>10/39</td>
<td>26</td>
<td>0.13</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6/38</td>
<td>16</td>
<td>5/39</td>
<td>13</td>
<td>0.21</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2/38</td>
<td>5</td>
<td>0/39</td>
<td>0</td>
<td>0.79</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>1/38</td>
<td>3</td>
<td>5/39</td>
<td>13</td>
<td>0.06</td>
</tr>
<tr>
<td>Jaundice</td>
<td>13/38</td>
<td>34</td>
<td>15/39</td>
<td>38</td>
<td>0.21</td>
</tr>
<tr>
<td>PDA</td>
<td>5/41</td>
<td>12</td>
<td>8/39</td>
<td>21</td>
<td>0.31</td>
</tr>
<tr>
<td>Sepsis</td>
<td>25/41</td>
<td>61</td>
<td>20/39</td>
<td>51</td>
<td>0.38</td>
</tr>
</tbody>
</table>

To assess weight gain, we looked at the time taken to return to birth weight.
Unfortunately due to transfer of babies to other hospitals, this information was only
available in 35 babies (15 control babies and 20 opiate-exposed babies). In this small
sample there was significantly less time required for the control babies to regain birth
weight (median 8.0 days, compared to 15.0 days in the opiate-exposed group,
p<0.0001). This is interesting as the birth weights between the two groups did not differ
significantly, and similarly the amount of weight lost was also not significantly different.
Further examination with a larger sample size is warranted in order to draw any further
conclusions. Of note, the mean rate of weight gain, in grams per day, was 22.5 in the
opiate-exposed group and 25.4 in the control group (p=0.88).

In summary preterm opiate-exposed babies had a similar postnatal course to a control
group made up of preterm babies with no known opiate exposure, matched for gender,
gestation, and socioeconomic status based on postcode. They did not have an increased
rate of common neonatal complications and their length of stay in hospital was increased, if neonatal abstinence syndrome was diagnosed. They took significantly longer to regain their birth weight.
6 Discussion

Neonatal abstinence syndrome is a global problem, causing considerable morbidity to newborns, and cost to the community. At a time where obstetric and neonatal care has come far in improving birth outcome generally, there remains many unanswered questions regarding how and why only some babies are affected by in utero opiate exposure. As clinicians, we can expect to care for opiate-exposed babies across Australia. They will be represented across all gestations and with the full range of manifestations of opiate withdrawal.

This study set out to explore how neonatal abstinence syndrome manifests in term and preterm babies, and to challenge the long-held belief that premature babies did not experience opiate withdrawal to the same extent and with the same severity as term babies. The modified Finnegan NAS scoring system is the standard clinical tool by which we diagnose, assess and manage NAS across all gestations in Australia. Using this system, term and preterm opiate-exposed babies in this study were assessed over a period of at least seven days in hospital.

Ethics approval was sought and obtained from the Mercy Hospital for Women Human Research and Ethics Committee, with the stipulation that an attempt at obtaining verbal consent be made prior to the medical record being accessed. Our concern was that our sample could be skewed if only those women who were both contactable and who consented were included in the study. Whilst no one refused consent there were only four women who were actually contactable. However it is perhaps a marker of the chaotic life this group lead that this was the case in so many. Telephones were often disconnected, unanswered on more than one occasion, or were numbers for drug rehabilitation clinics or agencies. In addition it proved relatively hazardous to attempt to contact these women on the telephone numbers recorded in the case notes, as there were some women who had listed family members’ homes for contact, but these family members were unaware of the woman’s history of drug use. We were permitted to access the record if the woman was not contactable.
In our study design we required 82 mothers and babies in each of the study groups: term opiate-exposed babies and preterm opiate-exposed babies. We recognised that having adequate numbers in the preterm group would always be a challenge so our retrospective medical record review spanned a five-year period. Even so, numbers in our preterm opiate-exposed group fell short of the number required. To have extended the study period to encompass the necessary sample would have potentially created problems with alterations in clinical practice amongst the clinical staff caring for the baby. The rate of preterm birth amongst the opiate-dependent women in our cohort was 27.5% (41/149), which was actually higher than that in Doberczak's cohort (34/212, 16%)\(^1\). We had 41 preterm babies, a number comparable to the numbers used in Doberczak's study of 34 preterm babies, and therefore valuable inferences may still be made. Liu et al\(^4\) had 66 preterm babies in their cohort of 232 methadone-exposed babies (28%).

We estimated the incidence of NAS to be 30% in the term group and 10% in the preterm opiate-exposed group, based on the figures quoted by Kuschel\(^2\) who quoted the rate of NAS to be 30 to 80%, depending on the data used. Our estimate was conservative given that many studies had a much higher rate of NAS\(^3\). However, these studies were often based in the United States of America, where social and demographic details differ markedly from Australia. With 149 opiate-exposed babies in our study, the overall rate of NAS was 32.9%. 36 of 108 term babies (33.3%), and 13 of 41 preterm babies (31.7%) developed NAS. We found no significant difference in the incidence of NAS between the two groups (p=0.85).

It is unclear why the proportion of babies overall developing severe NAS requiring treatment in our study remained relatively low. We know that the rate of NAS worldwide varies from population to population depending on social factors, such as poverty and the nature of the health care provided, the size of the drug problem in the area, and the rate of polydrug use. Doberczak's study had a greater proportion of term babies with a history of maternal polydrug use, which may have been a contributing factor.

However, an incidence of NAS of over 80% amongst the term babies, exposed to
methadone in utero, seen in Doberczak’s study, would be considered unacceptable in our current climate. Although a multidisciplinary approach was employed, one wonders whether the antenatal care provided addressed all the issues concerning the overall health and wellbeing of the women in their care. We know nothing of their health and nutrition, or whether there was concomitant cigarette and alcohol use, as well as drugs such as cannabis, and benzodiazepines. Although the methadone dose prior to delivery is documented, the philosophy behind the prescription of methadone is not clearly evident. Were doses prescribed with caution, with the risk of neonatal abstinence in mind, or were the women maintained on high doses to ensure that drug cravings did not result in illicit drug use?

The criteria for diagnosing and treating NAS were more conservative in our study population, requiring three consecutive scores greater than eight, and an element of clinician’s judgement as to when therapy should be instituted. Perera et al \(^{36}\) analysed the scores of 10 randomly selected opiate-exposed babies and found that there were babies scoring high but were thought not to require treatment, or another medical cause was found. Regardless the rate of NAS varies amongst study populations. Liu \(^{46}\) in his retrospective study based in western Sydney, spanning the years from 2000 to 2006 had a rate of NAS of 74%. Burns \(^{43}\) in a linkage study using data from 1992 to 2002 in New South Wales found a rate of NAS of 27%. It may be that the treating staff of the time may have had less awareness of the manifestations of neonatal abstinence syndrome, and so any neonatal morbidity may have been given another diagnosis. In the United Kingdom, Dryden \(^{22}\) had 45.5% of their opiate-exposed babies requiring treatment for neonatal abstinence syndrome.

The obvious factors under scrutiny when investigating the incidence of neonatal abstinence syndrome in babies exposed to opiates in utero is the nature of the opiate and the amount of opiate used. It seems likely from our study that heroin use in pregnancy places the baby at more risk of neonatal abstinence syndrome than either methadone or buprenorphine. For the study timeframe (2003 to 2007) and in our study hospital, buprenorphine was only just being introduced to manage opiate dependence in pregnant women. Our figures and that of Kakko \(^{19}\) suggest that buprenorphine is less likely to produce NAS than methadone.
Because there are limited legal ramifications for a woman to confide to her healthcare workers her illicit drug use, than that seen in the United States or Sweden for instance, one could hypothesise that polydrug use was less of a confounding factor in our study. Finally, the median methadone dose for those women whose babies developed NAS in our study was 62.5mg, and 65mg for the 79 methadone-exposed babies who did not develop NAS. These doses are modest, but greater than those used by Doberczak, and less than the doses used by Dryden.

The current approach to managing pregnant women on opiate maintenance therapy (methadone or buprenorphine) utilised by the study hospital over the study period has resulted in a low rate of NAS, by international standards. Although we attempted to investigate maternal demographic and lifestyle factors, which may have contributed to, or been protective over the development of NAS, many of these details were not documented in adequate detail in the medical record. This is a major limitation of the retrospective study. However it seems likely that the provision of free accessible medical and midwifery care, and social and emotional support has contributed to our population staying engaged with services, seeking and receiving help in times of crisis and perhaps being less likely to use illicit drugs.

Fundamental to answering the question whether preterm babies undergo opiate withdrawal is to also pose the question why only some opiate-exposed babies, be they term or preterm, undergo withdrawal. In our study the rate of neonatal abstinence syndrome in term and preterm babies was not statistically different. With a rate of NAS overall at 32.9% there remain almost 70% of opiate-exposed babies who did not withdraw. Further in the methadone group (which had the largest numbers and who were the easiest to follow), the dose of methadone at the time of delivery was not statistically different, between those babies that withdrew and those who did not.

This raises the interesting concept that, in addition to the necessary exposure to opiate, there is perhaps a necessity for the individual, mother and/or baby, to possess a vulnerability to opiate effects. When one examines the literature over the
last forty years, many authors have sought to find a link between the baby with NAS and intrauterine or maternal factors. Jansson\textsuperscript{52,53} proposed altered vagal tone in some mothers on methadone which possibly affected the development of normal autonomic responses in the growing fetus. Genetic factors such as the 393T>C polymorphism of the GNAS1 gene are thought to affect the degree of withdrawal experienced by adult opiate addicts. Those TT homozygous demonstrated a significantly higher heart rate than comparable C-allele carriers also undergoing withdrawal\textsuperscript{180}. However, the most obvious factor is the extent of opiate exposure, or in simpler terms, the dose of opiate prescribed. The literature here is divided, with some authors reporting a link between high prescribed doses of methadone in pregnancy and an increased rate of NAS\textsuperscript{20,24,46}. Other authors have found no such link\textsuperscript{21,24}.

Even in those studies which do find a relationship between NAS and methadone dose, they vary at what dose is required to increase the baby’s risk of withdrawal. Dashe et al\textsuperscript{20} found a rate of NAS to be 90% in 18 mothers who were prescribed a minimum of 40mg per day of methadone. Wouldes and Woodward\textsuperscript{27} had 16 women in their “high” dose group, which was 59mg or greater of methadone per day, and the rate of NAS in their babies was 50%. The rate of NAS in their “low dose” group was 19%. In contrast McCarthy\textsuperscript{24} in his study had a “high dose” group, prescribed a minimum of 100mg methadone per day (mean 132mg) compared to a “low dose” group prescribed less than 100mg of methadone per day (mean 62mg). The rate of NAS in the babies of these two groups was not significantly different: 49% in the “high dose” group and 51% in the “low dose” group.

We can answer the question as to whether “preterm” babies withdraw from opiates. Our data suggest that they do. If one asks if being preterm is protective for developing NAS then the numbers in our preterm group are insufficient to answer this conclusively. However, if one were to use “gestational age”, then there is acknowledgement of the developmental spectrum present across the range of gestations between 26 and 37 weeks. Using our current methods of assessing and diagnosing NAS, we found that preterm babies over 34 weeks gestation were more likely to withdraw than those born less than 34 weeks gestation. However the numbers of opiate-exposed babies born less than 34 weeks are small.
In recent times there has been an acknowledgement that preterm babies born been 34 and 36+6 weeks are not the same physiologically as term babies\textsuperscript{81,82}. It is possible that there is a "late preterm" group from 34 to 37 weeks that manifest NAS in a similar way to "term" babies, though at least in some studies\textsuperscript{12,13,46}, their susceptibility is relatively less. Although an analysis of the modified Finnegan NAS scoring system was beyond the scope of this study, it should be noted that the preterm babies diagnosed with NAS severe enough to require treatment came to the clinician’s notice because they were behaving in a similar fashion to a term opiate-exposed baby undergoing withdrawal. A baby who is not exhibiting the most obvious clinical signs such as tremors and irritability may quite easily be missed. This is particularly so if the baby, regardless of their gestation fails to suck, for example. A term baby still requiring nasogastric feeds at one week of life is alarming, even though "poor feeding" is only scored a maximum of "2".

For the second part of the study the clinical course of preterm opiate-exposed babies and drug-free controls were compared. Controls were matched for gender, gestation and socioeconomic status. Socioeconomic status was assessed using postcode of residence at time of booking, and then assigning a socioeconomic quintile based on Australian Bureau of Statistics data involving such criteria as household income, education, home and car ownership\textsuperscript{68}. The highest quintile was "1", and each postcode in Victoria was grouped in the appropriate quintile. Therefore control babies were matched for an opiate-exposed baby who had a postcode of residence in the same quintile. However, actual socioeconomic status was not always represented when for instance one mother was residing temporarily in a refuge, which was located in a suburb assigned a high quintile.

Finding appropriate controls based on all three criteria (gender, gestation, and postcode) was challenging. Hunt et al\textsuperscript{83} also looked at long-term outcome of opiate-exposed babies, and used suburb of residence, as well as employment status, and years of maternal education. Unfortunately, our study was retrospective, and education level and employment status were not often available from the medical record. Typically, controls were significantly older women, who missed fewer antenatal appointments, and started their antenatal care earlier. This would suggest
a more stable mother. Even though mothers in the control group were living in a comparable postcode, they were fundamentally different. Indeed, many were privately insured. Postcodes with this mix of people from potentially different socioeconomic backgrounds perhaps also reflects the changing neighbourhoods in Melbourne where inner city areas and areas near public housing are being repopulated by more affluent people. It seems that even though mothers in our control and study groups were living in similar areas, drug use itself could change the outcome for both mother and baby. This is suggested in the work published by Sharpe\textsuperscript{44}, when he compared babies born to women on methadone, prescribed for opiate dependence versus chronic pain.

We postulated that the length of stay, and number of neonatal complications would be increased in the preterm opiate-exposed group, as a consequence of maternal opiate dependence. However, this was not the case. Length of stay was only increased significantly if NAS requiring treatment was diagnosed. Neonatal complications did not occur with increased frequency either in this group. Again this result is consistent with that of Sharpe\textsuperscript{44}, who also found that babies born to opiate-dependent mothers stabilised on methadone were at risk of opiate withdrawal but generally did not have any other immediate perinatal complications. In contrast Abdel-Latif\textsuperscript{57} found babies of substance–abusing mothers were over-represented in NICUs in New South Wales. Because this was a population study, details regarding the antenatal care provided and polydrug use are not available.

Feeding itself was not affected to a greater degree than one would expect with prematurity alone. The two groups took similar time to reach full enteral and suck feeds. However, the opiate-exposed preterm babies took significantly longer to regain their birth weight, and had a lower mean rate of weight gain, though this did not reach significance. This would suggest that preterm babies with opiate exposure had increased caloric requirements, when compared to preterm babies with no in utero opiate exposure. One could also postulate that perhaps the increased caloric intake reflected ongoing withdrawal.

Overall the most prominent factors noted in the study in the babies were the difficulties in feeding and weight gain that opiate exposure seemed to produce. This
has been well documented in previous studies\(^ {84,85}\). Observation of how well normal and opiate-exposed babies suck formed the foundation for Finnegan’s further work in designing the NAS scoring system. It is then interesting that “poor feeding” is not allocated a high score in the assessment, particularly as her own study suggested that sucking improved once treatment with opiate for NAS was commenced\(^ {2,34}\). The inability to suck effectively is an important sign in the opiate-exposed newborn.

LaGasse et al\(^ {79}\) added that feeding a baby is an important and fundamental part of the mother’s role. It is an important interaction between mother and baby in early infancy. As part of the Maternal Lifestyle Study, 76 opiate-exposed babies who were still with their biological mother and were bottle-fed were videotaped feeding by day 3 of life. Factors observed were sucking pattern, infant behaviour (positing, crying), and maternal behaviour (offering the bottle, interacting with the baby whilst feeding). Opiate-exposed babies showed prolonged sucking with fewer pauses, and more feeding problems such as spitting up and refusal to feed. Since excessive suck is a sign of withdrawal, these features were thought to represent part of the withdrawal process.

Another study examining feeding, weight gain and opiate exposure was by Martinez et al\(^ {86}\). They studied 44 babies born to mothers on methadone who remained in hospital for the treatment of NAS, and measured their oral intake and weight gain. They defined hyperphagia as an oral intake of greater than 190ml/kg/day, and found that 26% of their cohort by day 8 of life, and 56% by day 16, were hyperphagic. They ascribed this as part of the withdrawal process, and found the presence of this sign was independent of maternal methadone dose (mean dose 50mg per day, range 15-95mg). Despite the increased caloric intake, these babies lost significantly more weight during the first week of life than non-hyperphagic babies also undergoing withdrawal. Interestingly they found that actually sucking was not problematic for their cohort and none required nasogastric feeds. However these babies were all treated with morphine for their withdrawal at the time, which may explain this.

In summary whilst we had adequate numbers in the term group, numbers of preterm babies included in the study fell short of the required figure. Consequently
our study was inadequately powered to detect a difference in incidence of NAS in the two groups. Nevertheless, our preterm group had a higher incidence of NAS than the 10% we had expected. The diagnosis of severe NAS was based on the modified Finnegan NAS scoring system, the current “gold standard” which was largely designed for the assessment of term babies. The term babies who went on to require treatment scored higher in their NAS scores than their preterm counterparts. This may reflect the fact that term babies have the neurodevelopmental capacity to exhibit the signs we associate with opiate withdrawal such as increased tone.

Brown et al\textsuperscript{87} compared the effects of maternal drug use in pregnancy (cocaine, alcohol, or both) on their babies born at different gestations. Whilst the drug exposure is different to our study, they closely examined physiological signs such as respiratory rate to find subtle differences in baseline between their cocaine only group, their alcohol only group, and their polydrug group. With the addition of a gestation-matched control, perhaps collecting data regarding baseline heart rate, and respiratory rate, as well as caloric intake and weight gain, would be useful in our opiate-exposed cohort to detect more subtle evidence of autonomic dysfunction associated with withdrawal. Our data collection centred more on growth and weight gain, as well as documenting neonatal complications, in addition to recording the NAS scores.

Length of stay in hospital was markedly increased in term and preterm babies once severe NAS was diagnosed and treatment with morphine commenced. This adds greatly to the difficulties faced by the mother who will generally be discharged home before the baby. It also adds to the healthcare costs associated with managing an opiate-dependent mother and her baby through pregnancy. Oei et al\textsuperscript{88} describe a practice of continuing morphine treatment at home with regular follow-up, which would certainly reduce length of stay. However, to do this, full suck feeds must be established and this can also take days if not weeks. In Oei’s study there were not the same issues with establishing feeding seen in our study. We can only postulate the reason for this. There may have been more polydrug use in our population, or potentially suboptimally treated NAS. Outpatient treatment of NAS is not however an option at the study hospital.
From our work we have identified that opiate-exposed babies experience withdrawal across gestations, if the standard tool for diagnosing severe NAS is used. We have shown that preterm opiate-exposed babies take significantly longer to return to their birth weight than their non-opiate-exposed counterparts, of similar gestation. Further work is required to identifying why this is so. It may be that these babies experience stress, which manifests as poor weight gain despite adequate or even increased caloric intake. Identifying a physiological marker for this “stress”, by using salivary cortisol for example or observing the baby using an actigraph to monitor motion or agitation, or even EEG monitoring, are paths for future investigation.

Finally, we know that babies born to opiate-dependent mothers represent a vulnerable population. The second part of our study compared preterm babies with and without opiate exposure in utero. Although in our cohort the babies in both groups had a comparable neonatal course, in terms of birth weight and complications, the outlook of the opiate-exposed babies even if they did not experience withdrawal is different. Their mothers, despite matching for socioeconomic status, had a different pregnancy, in terms of antenatal care, and often had been flagged as requiring extra support by virtue of their contact with social services. Beyond the neonatal period these babies are at risk both socially, in terms of neglect and abuse, and developmentally particularly in the first 3 years of life. Further research into the nature of their prenatal insult and its manifestations is necessary, and these children will benefit from long-term follow-up.
7 Bibliography


14 Mercy Hospital for Women Management of NAS Clinical Pathway, Neonatal Unit


73 Australian Bureau of Statistics Household data, according to Victorian Postcode


95


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