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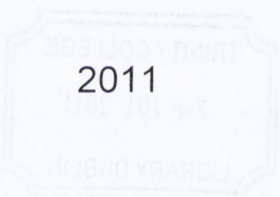
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Methadone Use in Pregnancy: Prevalence and Pregnancy Outcomes in an Irish Obstetric Cohort

A thesis submitted to the University of Dublin, Trinity College for the
degree of Doctor of Philosophy in the Department of Obstetrics and
Gynaecology, School of Medicine.



2011

Brian James Cleary

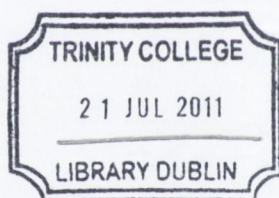
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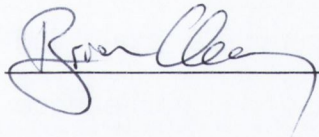


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DECLARATION

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SUMMARY

Background

This thesis aimed to address current knowledge deficits relating to the issues of medication use in early pregnancy in an Irish healthcare setting and adverse perinatal outcomes in opioid-dependent pregnant women on methadone maintenance treatment.

Methods

An initial descriptive study aimed to establish population estimates of the prevalence and determinants of medication use in early pregnancy. As this study identified methadone as one of the most commonly used medications with potential for fetal harm, subsequent studies examined perinatal outcomes after the use of methadone in pregnancy. Initially, a systematic review and meta-analysis examined the impact of maternal methadone dose on neonatal abstinence syndrome (NAS). Study limitations identified in the systematic review informed the design of two cohort studies, one retrospective and one prospective, examining perinatal outcomes in opioid-dependent women on methadone maintenance treatment.

Results

The descriptive study found that four in ten women used a medication besides folic acid before booking for antenatal care and that potentially harmful medications were used by approximately 3% of women. Women were more likely to report using medications with potential for fetal harm if they had an unplanned or multiple pregnancy, or if they were unemployed, smokers, single or booked for antenatal care prior to 12 weeks gestation. Methadone was the most commonly reported medication with potential for fetal harm.

The systematic review and meta-analysis found small differences in the incidence of NAS in infants of women on higher compared with lower methadone doses which were statistically non-significant in analyses restricted to prospective studies or to those using an objective scoring system to diagnose NAS. Maternal methadone dose did not have a consistent statistically significant effect on the incidence of medically treated NAS.

The retrospective cohort study found that methadone exposure was associated with an increased risk of adverse perinatal outcomes even when known adverse socio-demographic factors had been accounted for. Methadone exposure was associated with an increased risk of very preterm birth (<32 weeks), being small for gestational age (birth weight <10th centile), admission to the neonatal unit and diagnosis of a major congenital anomaly. There was a significant dose-response relationship between methadone and diagnosis of NAS.

The prospective cohort study found that adverse perinatal outcomes including being small for gestational age (birth weight <10th centile) and admission to the neonatal unit were common after methadone maintenance treatment in pregnancy. The duration of hospitalisation for the neonate was affected by concomitant use of opiates, benzodiazepines and cocaine. The incidence and duration of NAS were not affected by methadone dose, though the severity of NAS, as indicated by the cumulative dose of morphine treatment for NAS, was increased with methadone doses $\geq 80\text{mg}$.

Conclusion

Medication use in early pregnancy was common. Methadone use was associated with a range of adverse perinatal outcomes. Methadone dose did not have a consistent statistically significant effect on the incidence of NAS. Further work is required to facilitate optimal use of medicines in pregnancy and help improve outcomes for opioid-dependent pregnant women and their children.

ACKNOWLEDGEMENTS

I gratefully acknowledge the extensive help and input from my supervisors. Prof. Deirdre Murphy was generous with her time and knowledge, providing the initial encouragement to begin this research and an optimistic outlook that helped me complete it. Prof. Tom Fahey gave excellent methodological advice and added great clarity to each of the studies. Prof. Paul Gallagher and Judith Strawbridge provided invaluable mentoring, support and feedback throughout. I am also indebted to Prof. Bengt Källén of the Tornblad Institute, Lund University, for providing an inspirational training placement.

This project would not have been possible without the support of the Friends of the Coombe charity and the School of Pharmacy, RCSI. I am extremely appreciative of their help. The Health Research Board PhD Scholars' Programme in Health Services Research provided an essential, structured learning environment and, most importantly, my fellow Scholars: Caitriona Cahir, Deirdre Holly, Maria Kelly, Sheena McHugh, Dr. Gerald McKenna, Catriona Murphy, Dr. Michael Power and Aisling Sheehan. I would like to thank Prof. Hannah McGee, Prof. Charles Normand and Prof. Ivan Perry; other academic and administrative staff, particularly Shani Rushin; and library staff in RCSI and TCD, especially Paul Murphy and Jane Moriarty.

I would also like to thank everyone who helped within the Coombe Women and Infants University Hospital. The Master, Dr. Chris Fitzpatrick, provided the necessary encouragement and support to get the project off the ground. My colleagues Mairead McGuire, Peter Duddy and other Pharmacy staff provided continuous support, a listening ear and proofreading services. Emma Mc Namee and Tadhg O'Sullivan extracted the raw data and solved numerous IT problems over the years. Nursing, midwifery and other staff spent countless hours conducting booking interviews and recording perinatal outcomes. My fellow PhD candidates, Dr. Sharon Sheehan and Dr. Aoife Mullally, shared in the highs and lows of the PhD process.

I am grateful to everyone who collaborated or helped out with various elements of the project: Marion Brennan, Dr. Hajeera Butt, Deirdre Carmody, Dr. Mike Clarke, Prof. Tom Clarke, Alan Collins, Dr. Gráinne Cousins, Eimear Curran, Dr. Jean Donnelly, Dr. Maeve Eogan, Justin Gleeson, Tracy Gray, Dr. Hans George Koenig, Christine McDermott, Dr. Alan Montgomery, Dr. Aoife Mullally, Orla Nolan, Dr. Michael O'Connell, Niall O'Donoghue, Anne O'Sullivan, Emilie Petit, Dr. Conor Teljeur and Dr. Martin White.

I am indebted to all the study participants who kindly gave of their time to help improve information on methadone use in pregnancy.

Finally, I want to express my deepest thanks to my parents Jimmy and Josephine. Always supportive, you led by example and gave me every opportunity.

I dedicate this thesis to my incredible wife Aideen and my wonderful little girls Shauna and Róisín.

Aideen, for your loving support, which never faltered through long days and late nights. You made this possible.

Shauna, for all the joy and happiness that you bring and your attempts to say: "Pharmacoepidemiologist".

Róisín, for learning to smile and laugh just as the work was at its hardest.

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GLOSSARY

Term	Definition
Apgar score	The Apgar score is a measure of a baby's condition at birth. A midwife or paediatrician assesses the baby at 1 minute and 5 minutes of age. The baby's heart rate, breathing, colour, tone and response to stimuli are considered in generating the score.
CI	Confidence Interval.
Congenital anomaly (major)	Any abnormality present at birth, particularly a structural one, which may be inherited genetically or acquired during gestation, with serious medical or cosmetic consequences for the child.
Congenital anomaly (minor)	Any abnormal anatomic feature that is of lesser medical, functional or cosmetic consequence than a major congenital anomaly.
Drug utilisation research	Examination of the extent, nature and determinants of medication use in a given population, facilitating the rational use of medications.
Elective caesarean section	Planned caesarean section. Usually performed at about 39 weeks' gestation.
Emergency caesarean section	Caesarean section which has not been planned. It may take place before or after the onset of labour.

Term	Definition
Finnegan score	Scoring system which allows semi-objective measurement of the degree to which a neonate is experiencing abstinence symptoms. Central nervous system, respiratory, gastrointestinal and other signs and symptoms are considered in generating the score.
Infant mortality	Death of an infant in the first year of life.
Instrumental delivery	Sometimes called an assisted birth or operative vaginal birth. Uses instruments (either forceps or ventouse) that are attached to the baby's head so that traction can be used to aid delivery.
IQR	Interquartile range.
Methadone maintenance treatment	Treatment for opioid-dependence which involves administration of methadone as a substitute opioid at doses sufficient to relieve withdrawal symptoms and prevent opioid use.
NAS	Neonatal abstinence syndrome. A generalised disorder caused by neonatal withdrawal from opioids or other drugs active in the central nervous system (CNS). NAS is characterised by signs and symptoms of CNS hyperirritability, gastrointestinal dysfunction, respiratory distress and vague autonomic symptoms including yawning, sneezing, mottling and fever.

Term	Definition
Neonate	A baby under four weeks of age.
Opiate	Natural alkaloids and semi-synthetic derivatives such as heroin and oxycodone derived from the opium poppy (<i>Papaver somniferum</i>).
Opioid	Any agent that binds to opioid receptors, found principally in the central nervous system and gastrointestinal tract. There are four broad classes: endogenous opioid peptides, produced in the body; opium alkaloids, such as morphine and codeine; semi-synthetic opioids such as heroin and oxycodone; and fully synthetic opioids such as pethidine and methadone that have structures unrelated to the opium alkaloids. Some authors use the terms opiate and opioid interchangeably.
OR	Odds Ratio.
Parity	The number of babies over 24 weeks' gestation a woman has given birth to. A woman who has never completed a pregnancy beyond 24 weeks is referred to as nulliparous.
Perinatal mortality	Death of a baby of at least 24 weeks' gestation prior to birth, during birth or in the first seven days of life.
Pharmacoepidemiology	The study of the utilization and effects of drugs in large numbers of people.

Term	Definition
Pierre Robin sequence	Congenital facial anomaly consisting of a combination of small lower jaw (micrognathia), displacement of the tongue upwards and towards the back of the oral cavity, and cleft palate.
Preterm birth	The birth of a baby before 37 weeks' gestation
RR	Relative Risk.
SD	Standard deviation.
Small for gestational age	Babies whose birth weight is below the 10 th centile for a specific gestational age.
SSRI	Selective serotonin reuptake inhibitor. A class of antidepressant.
SVD	Spontaneous vertex delivery or spontaneous vaginal delivery. This refers to childbirth with vaginal delivery of the baby without the assistance of instruments such as forceps or ventouse.
Teratogen	An agent which, if administered to a pregnant mother causes, directly or indirectly, structural or functional abnormalities in the fetus, or in the child after birth, which may not be apparent until later life.
Teratology	The science that deals with abnormal prenatal development leading to congenital anomalies.

CHAPTER 1. INTRODUCTION

1.1 Introduction

This thesis documents a programme of work with four distinct but linked elements examining the use of medicines in pregnancy. An initial descriptive study aimed to establish population estimates of the prevalence and determinants of medication use in early pregnancy. This study identified methadone as one of the most commonly reported medications with potential for fetal harm. Further studies examined perinatal outcomes after the use of methadone in pregnancy. Initially a systematic review and meta-analysis examined the impact of maternal methadone dose on neonatal abstinence syndrome (NAS). Studies identified in the systematic review informed the design of retrospective and prospective cohort studies examining perinatal outcomes in opioid-dependent women on methadone maintenance treatment. Routinely collected data for a large cohort of women was used in the retrospective study. The prospective cohort study included more detailed longitudinal data collection on a smaller cohort of women delivering over a one year period.

This chapter provides some background on medication use in pregnancy followed by an overview of the use of methadone in opioid-dependent pregnant women. The aims and objectives of the research programme are then presented, followed by an outline of how these aims and objectives are addressed in the remaining chapters of the thesis.

1.2 Background

1.2.1 Medication use in pregnancy

Any discussion of medication use in pregnancy is coloured by the thalidomide tragedy which came to light in late 1961 when Widukind Lenz, a German Paediatrician and William McBride, an Australian Obstetrician independently noted an association between thalidomide exposure and a range of congenital anomalies including limb reduction defects.^{1 2} Thalidomide was initially marketed as a sedative, but it was also used in the treatment of nausea and vomiting in early pregnancy. UK marketing materials claimed that thalidomide "...can be given with complete safety to pregnant women and nursing mothers, without adverse effects on the mother or child".³ By the time thalidomide had been withdrawn from markets in dozens of countries worldwide an estimated 8,000 to 12,000 infants had been affected by the medicine, with approximately half surviving infancy.³

Despite the commonly held perception that the placenta protected the foetus from toxic insults, the idea that maternal environmental exposures could lead to congenital anomalies was not new in the early 1960s. Pelvic irradiation during pregnancy was identified as the first environmental teratogen in humans by the US Obstetrician Douglas Murphy in 1929.⁴ The link between Vitamin A deficiency in pregnancy and eye anomalies was demonstrated by Hale *et al* in animal studies in 1935.⁵ In 1941 Norman McAlister-Gregg, an Australian Ophthalmologist, noted the link between an outbreak of rubella and congenital cataracts and associated heart conditions.⁶ Exposure to cortisone was demonstrated to cause cleft palate in mice in the early 1950s.⁷ In 1952 an antifolate antineoplastic agent, Aminopterin, became one of the first medicines noted to cause congenital

anomalies in humans after early pregnancy exposure.⁸ All of these discoveries demonstrated the vulnerability of the human embryo, unfortunately this vulnerability was not widely appreciated. The thalidomide disaster strengthened the nascent field of teratology and regulatory overview of the licensing of medicines for use in pregnancy. Safeguards were put in place requiring animal reproductive toxicology studies prior to the licensing of new medicines. Clinicians and researchers became aware of the need for basic science studies examining the process of teratogenesis and epidemiological studies examining the impact of medication exposures on maternal and neonatal outcomes.

Pharmacoepidemiological studies have demonstrated varying rates of medication use in pregnancy. A recent Norwegian study based on prescription records reported that 57% of women received at least one medication during pregnancy,⁹ while Dutch¹⁰ and German¹¹ studies using a similar methodology found that 79% and 96% of pregnant women received at least one prescription. First trimester medication use has been reported to range from 33-43%.^{9 10 12} An international survey of medication use during pregnancy carried out by the World Health Organisation (WHO) concluded that “there can be no doubt that at present some drugs are more widely used in pregnancy than is justified by the knowledge available”.¹³ Few data are available on the extent of medication use in pregnancy in the Irish healthcare setting with the exception of studies of the prevalence of alcohol and illicit drug use¹⁴ and folic acid uptake.¹⁵

It has been estimated that over 90% of medications approved by the Food and Drug Administration (FDA) between 1980 and 2000 have insufficient data available to allow a recommendation on their safety in pregnancy or otherwise to

be made.¹⁶ The majority of currently used medications have not been studied in a way that would reveal moderate teratogenic risks.¹⁷ This is remarkable, considering the fact that the first victims of the thalidomide disaster are already over 50 years old. In light of the dearth of data to inform prescribing decisions in pregnant women, studies assessing the safety of medicines in pregnancy are required.^{16 17} Studies of the prevalence of medication use in pregnancy allow a prioritisation of research, identifying regularly used medications that may have unanswered research questions. Data from such studies could be used to examine the impact of commonly used medications on perinatal outcomes including congenital anomalies. By assembling cohorts with several hundred exposed pregnancies it is possible to determine if a medication is a major teratogen or not. Larger studies are required to test associations with specific birth defects or to detect more subtle rises in the rate of congenital anomalies.

1.2.2 Methadone use in pregnancy

Methadone was discovered in Germany in 1939 but World War II hampered its clinical development and it did not become available for general use until Eli-Lilly began production in the United States (US) in 1947.¹⁸ Isbell and Vogel first described the use of decreasing doses of methadone as a treatment for heroin addiction in 1948.¹⁹ This detoxification protocol called for tapering the methadone dose over a short period of time, usually one to two weeks. High relapse rates with this detoxification approach became apparent over the following years.²⁰ Dole *et al* developed methadone maintenance treatment in response to an epidemic of heroin addiction in New York City in the early 1960's.²¹ This approach used doses of methadone that achieved "narcotic blockade" to relieve opioid withdrawal while

also blocking the effects of concomitant opioids. Patients were then maintained on a constant dose of 60-120mg daily. This treatment was based on the hypothesis that opioid addiction caused permanent physiological changes that could be alleviated by regular administration of methadone. One of the reasons for not including women in the early methadone treatment trials of was the fear of fetal injury.²² These trials took place shortly after the thalidomide disaster had become evident.

The first reports of perinatal outcomes in opioid-dependent women treated with methadone began to emerge in the late 1960's. Prior to this there had been some reports of attempts to use methadone as an obstetric analgesic in the late 1940's ,²³ but methadone was found to have an unacceptably high risk of neonatal respiratory depression when used in opioid-naïve patients in this way. Early reports, which emerged initially out of New York and subsequently from other US cities, indicated that methadone use improved perinatal outcomes compared to continued illicit opioid use.²⁴ Women who were treated with methadone did not have to go through repeated cycles of intoxication and withdrawal associated with continued illicit drug use, facilitating engagement with antenatal care.²⁵ Methadone maintenance treatment, in the context of a multi-disciplinary comprehensive care programme, led to a reduced incidence of low birth weight, preterm birth and infant morbidity and mortality compared to continued illicit drug use.^{26 27}

Before methadone was first used to treat opioid dependence in pregnancy withdrawal effects were known to occur in the neonate after *in utero* exposure to opioids. In 1959 Cobrinik *et al* described withdrawal symptoms in the infants of 20

women addicted to heroin or morphine, along with a review of case reports dating back to 1885.²⁸ It became apparent from the preliminary reports of perinatal outcomes in opioid-dependent women treated with methadone that there was also a risk of withdrawal in the neonate after methadone exposure in utero.²⁹ Manifestations of this withdrawal syndrome included central nervous system, gastrointestinal and respiratory symptoms. Finnegan *et al* described diagnostic criteria and an objective scoring system, the Finnegan Neonatal Abstinence Score, to assess the severity of neonatal abstinence syndrome (NAS) in 1975.³⁰ There have been conflicting findings on the relationship between maternal methadone dose and the incidence of NAS from the early studies in the 1970s^{31 32 33 34} up to the present day.^{35 36} This remains an unanswered research question.

There has been controversy in the past surrounding the prescribing of methadone during pregnancy.³⁷ It is evident from the addiction literature in general and from the extant literature on the management of opioid-dependence in pregnancy that there are varying approaches adopted in methadone prescribing. Some authors advocate for detoxification,³⁸ while others have argued that reduction in methadone dose puts the woman and foetus at unacceptable risk of withdrawal, preterm labour and relapse of illicit drug use.³⁹ Varying approaches to prescribing methadone in pregnancy may be influenced by the continuing maintenance versus abstinence debate.^{40 41}

1.3 Aims and objectives

There were two broad aims to this research, initially to examine medication use in pregnancy in the general population and subsequently to examine the impact of a commonly used medication on perinatal outcomes. These aims were addressed through four distinct elements:

- Descriptive study of medication use in early pregnancy
- Systematic review of methadone dose and neonatal abstinence syndrome
- Retrospective cohort study of methadone use and perinatal outcomes
- Prospective cohort study of methadone use and perinatal outcomes

The descriptive study had the following specific objectives:

1. Determine the prevalence of medication use in early pregnancy among a large cohort of women
2. Explore the use of medications with potential for fetal harm and prescribing for women with chronic medical disorders
3. Examine the determinants of medication use in early pregnancy

The systematic review had the following specific objective:

1. Determine if there is a relationship between maternal methadone dose in pregnancy and the diagnosis or medical treatment of neonatal abstinence syndrome

The retrospective cohort study had the following specific objectives:

1. Establish population-based estimates of the risk of adverse perinatal outcomes including preterm birth, intrauterine growth restriction, congenital anomalies, admission to the neonatal unit and perinatal death in methadone-exposed and unexposed pregnancies
2. Explore the determinants of the incidence of NAS in methadone-exposed neonates

The prospective cohort study had the following specific objectives:

1. Describe maternal characteristics, addiction profiles and perinatal outcomes for the cohort
2. Compare perinatal outcomes and NAS for women stabilised on methadone only and those with concomitant exposure to other drugs
3. Compare perinatal outcomes and NAS for women on low and high methadone doses at delivery
4. Examine the influence of clinical characteristics such as preterm birth, being small for gestational age and smoking on the incidence of NAS

1.4 Thesis outline

The first section of chapter 2 reviews international studies examining the prevalence and determinants of medication use in pregnancy. The varying approaches used to examine the safety of medication exposures in pregnancy are then reviewed. The third section reports on studies of methadone maintenance treatment in pregnancy. Perinatal outcomes in general and NAS in particular are addressed along with methodological issues with research in this area.

The descriptive study of the prevalence and determinants of medication use in early pregnancy in a large cohort of pregnant women delivering in the Coombe Women and Infants University Hospital is reported in Chapter 3. Commonly used medications with potential for fetal harm are highlighted. As methadone was one of these medications, subsequent studies examined the use of methadone in pregnancy.

NAS is a common adverse outcome when methadone maintenance treatment is used in pregnancy. As there is no consensus on whether there is a relationship between maternal methadone dose at delivery and the incidence of NAS this question was addressed. The resulting systematic review and meta-analysis is reported in Chapter 4.

The studies identified in the process of carrying out the systematic review and meta-analysis were used to inform the design of the retrospective and prospective cohort studies reported in Chapters 5 and 6. These studies addressed the issue of maternal methadone dose and NAS while also examining other perinatal outcomes.

The thesis is summarised and implications for patient care and future research are highlighted in the concluding chapter.

CHAPTER 2. LITERATURE REVIEW

2.1 Introduction

This chapter summarises existing knowledge providing context for the subsequent chapters in the thesis. The first section gives an overview of drug utilisation research in pregnancy, before examining the extent of medication use in pregnancy internationally. Studies examining the determinants of medication use in pregnancy are then described. The second section reviews epidemiological techniques used to examine the impact of medication exposures on perinatal outcomes. The third section gives an outline of studies reporting on methadone use in pregnancy, focusing on perinatal outcomes in general and NAS in particular.

2.2 Medication use in pregnancy

The use of medications during pregnancy is an important subject. There is a paucity of safety data for many medications commonly used during pregnancy. Women and prescribers often have to make difficult decisions on medication use in pregnancy with little evidence to guide them. In many developed countries the mean maternal age at delivery is increasing.⁴² Consequently, women are more likely to have co-existing medical disorders in pregnancy. This fact, combined with high rates of unplanned pregnancy,⁴³ means that exposure to medications in early pregnancy is often unavoidable and may increase. Epidemiological studies of the safety of medications in pregnancy are required to guide patients and prescribers when making decisions on medication use in pregnancy.

2.2.1 *Drug utilisation research in pregnancy*

Drug utilisation research is important to examine the extent, nature and determinants of medication use in a given population, facilitating the rational use of medications.⁴⁴ It is of particular relevance to the use of medications in pregnancy as it generates an estimate of the numbers of pregnant women exposed to specific medications. Drug utilisation research also facilitates estimation of the extent of potentially inappropriate medication use in pregnancy and comparison of current medication use patterns to prescribing guidelines. The FDA pregnancy labelling categories and similar systems from Sweden and Australia are commonly used in drug utilisation studies in pregnancy to categorise medications according to available safety data and allow an estimation of the prevalence of potentially inappropriate medication use.⁴⁵ Such research facilitates focused investigation of the safety of commonly used medications with potential for fetal harm in future research.⁴⁶ As patterns of medication use change over time, up to date drug utilisation studies are required. Mitchell suggests that prevalence information along with data on the magnitude and severity of a given drug's adverse effects is important to allow an assessment of a given medication's "teratogenic burden" at a population level.¹⁷

A variety of methodologies are used to carry out drug utilisation research in pregnancy. Information on medication use may be derived from different sources including prescription or dispensing records, and patient interviews. Information may be collected specifically for a study of the prevalence of medication use in pregnancy or for other purposes such as routine antenatal care or from control

groups in ongoing case-control surveillance of congenital anomalies.⁴⁷ Each approach has its merits and weaknesses.

Prescription and dispensing records have the advantage of accurate recording of the specific medication and dosage used, but there is no coverage of medications administered in hospitals, over the counter (OTC) medications, herbal/dietary supplements or illicit drugs. With dispensing records an assumption must be made that the patient actually took the dispensed medication. For prescription records there is the extra assumption that the prescription was actually dispensed. Estimates of the rate of patient compliance with prescribed medication after a prescription has been dispensed during pregnancy range from 43-95%.^{48 49} A Dutch validation study of medication exposure data found that pharmacy records and maternal interviews provided complementary information on medication use during pregnancy.⁴⁹ This study reported that 43% of drugs used during pregnancy were not recorded in pharmacy records. The most commonly missed medications were OTC products such as analgesics and multivitamins, and medications used during hospital admission. This reinforces the importance of validation studies when routinely collected electronic records are used for ascertainment of exposures and outcomes in epidemiological research.

Studies which use direct patient interviews have better coverage of a wide range of medication exposures including OTC medications or herbal and dietary supplements. However, this comes at the expense of incomplete or biased recall, along with difficulty in identifying the specific medication and dosage used. These varying approaches to recording medication exposures for drug utilisation research may lead to over or underestimation of the prevalence of medication use

in pregnancy. Apart from data on medication exposures prescription register studies are sometimes limited by lack of information on date of last menstrual period or gestational age based on ultrasonography. These studies must then rely on other methods to determine the timing of medication use during pregnancy e.g. assumed duration of gestation⁵⁰ or first record of a pregnancy related consultation.⁵¹

2.2.2 Prevalence of medication use during pregnancy

Studies that reported on the prevalence of medication use during pregnancy are summarised in Table 2-1. These studies were identified by searches of MEDLINE (1966–September 2010) using Pubmed, and EMBASE (1974–September 2010). Combinations of the following search terms were used: “medication”, “medicines”, “drug utilization research”, “pharmacoepidemiology”, “prevalence”, “prescribing”, “pregnancy”, “pregnant”, “gestation” and “trimester”. Reference lists of relevant studies and review articles were reviewed to identify further articles.

International comparisons and analysis for temporal trends in medication use in pregnancy are complicated by methodological and reporting differences between studies. Differing methods for ascertainment of medication exposures were used. There were also varying definitions of what constituted an exposure, with some studies excluding over the counter medications and varying reporting of the use of vitamin and iron supplements. Despite these difficulties it is evident that in most studies the majority of women used at least one medication during pregnancy. Studies from France,⁵²⁻⁵⁴ Germany,¹¹ the United Kingdom (UK),⁵⁵ Pakistan⁵⁶ and the United States (US)⁵⁷ reported that over 90% of pregnant women had been prescribed a medication or reported taking a medication during pregnancy.

More moderate estimates were obtained from prescription register studies carried out in Canada (56%),⁵⁸ Norway (57%),⁹ the UK (65%)⁵¹ and Finland (46%).⁵⁹ Among studies that reported the prevalence of medication use excluding vitamin and iron supplements there were still high rates of medication use with estimates above 80% in France,⁵² the UK⁵⁵ and Germany.¹¹ It is interesting to note that two studies carried out in overlapping time periods in the UK reported differing rates of medication use.^{51 55} The prescription register study of Hardy *et al.* reported that 65% of women were prescribed at least one medication in the periconceptional period or during early pregnancy.⁵¹ Headley *et al.*'s maternal questionnaire-based study reported that 92% of women reported use of at least one medication during pregnancy.⁵⁵ This may be explained differing windows of exposure or by more complete reporting of medication exposures in the Avon Longitudinal Study of Parents and Children questionnaires than in the primary care records from the General Practice Research Database used by Hardy *et al.* Across these studies, apart from vitamin and iron supplements, commonly reported medications included analgesics and antipyretics, antimicrobials, gastrointestinal medications, respiratory medications and sex hormones.

Table 2-1 Prevalence of Medication Use in Pregnancy

Study	Data Source	Time Period	Number of Pregnancies	% of Women using at least one Medication (% excl. Folic Acid, Vitamins & Minerals)
Lacroix ⁵² 2009, France	Dispensed prescription register	2004-2005	10008	95 (93)
Kulaga ⁵⁸ 2009, Canada	Dispensed prescription register	1998-2002	109344	56
Gagne ¹² 2008, Italy	Dispensed prescription register	2004	33343	70 (48)
Rohra ⁵⁶ 2008, Pakistan	Prescription register	2007	3679	100 (20)
Engeland ⁹ 2008, Norway	Dispensed prescription register	2004-2006	106329	57
Hardy ⁵¹ 2006, UK	Prescription register	1991-1999	81975	65
Bakker ¹⁰ 2006, Netherlands	Dispensed prescription register	1994-2004	5412	79
Al-Humayyd ⁶⁰ 2006, Saudi Arabia	Prescription register	2004-2005	727	69
Checa ⁶¹ 2005, Spain	Maternal Interview	2002	1103	75
Riley ⁶² 2005, US	Hospital Medical Records	2001-2002	1626	(56)
Schirm ⁶³ 2004, Netherlands	Dispensed prescription register	1995-2001	7500	86 (69)
Headley ⁵⁵ 2004, UK	Self-completion Questionnaire	1991-1992	11545	92 (83)
Egen-Lappe ¹¹ 2004, Germany	Dispensed prescription register	2000-2001	41293	96 (85)
Andrade ⁶⁴ 2004, US	Dispensed prescription register	1996-2000	152531	82 (64)

Study	Data Source	Time Period	Number of Pregnancies	% of Women using at least one Medication (% excl. Folic Acid, Vitamins & Minerals)
Malm ⁵⁹ 2003, Finland	Dispensed prescription register	1999	43470	46
Glover ⁵⁷ 2003, US	Maternal Interview	1999-2001	578	95 (60)
Beyens ⁵³ 2003, France	Dispensed prescription register	-	911	93
Lacroix ⁵⁴ 2000, France	Prescription register	1996	1945	99
Donati ⁶⁵ 2000, Italy	Maternal Interview	1995-1996	9004	75
Olesen ⁶⁶ 1999, Denmark	Dispensed prescription register	1991-1996	16001	(44)
Irl ⁶⁷ 1997, Germany	Self-completion Questionnaire	1995	453	85
Bonassi ⁶⁸ 1994, Italy	Maternal Interview	1989-1990	3268	83
Rubin ⁶⁹ 1993, US	Maternal Interview	-	2752	68
CGDUP ¹³ 1992, International	Maternal Interview	-	14778	86
De Jong-van den Berg ⁷⁰ 1991, Netherlands	Dispensed prescription register	-	1948	86
Buitendijk ⁷¹ 1991, US	Maternal Interview	1980-1982	4186	66
Rubin ⁷² 1986, UK	Self-completion Questionnaire	1982-1984	2765	(35)
Bracken ⁷³ 1981, US	Maternal Interview	-	4428	44

CGDUP- Collaborative Group on Drug Use in Pregnancy

Some studies reported on the prevalence of medication use in early pregnancy, the critical period for organogenesis, when most teratogenic medications exert their adverse effects. A recent Chinese study examined medication exposure in the first trimester as reported in self-completed questionnaires or health records.⁷⁴ At least one medication was used by 75.9% of women. Excluding vitamin and iron supplements, 24% of women reported first trimester use. A Norwegian study reported that 33% of pregnant women were dispensed a medication in the first trimester.⁹ The equivalent figure for a similar Danish study was 22% excluding vitamin and iron supplements.⁶⁶ Similar rates of 29% and 31% were reported in Scandinavian⁷⁵ and Italian⁶⁵ studies where mothers were interviewed regarding first trimester medication use. Slightly higher rates of 44% and 41% were reported in Danish¹⁰ and Italian¹² studies, however these figures include the use of iron supplements.

Various studies reported on, or focused specifically on the use of potentially harmful medications during pregnancy. A variety of systems for categorizing medications according to their potential for fetal harm are available. The most commonly used is the FDA pregnancy labelling categories for pharmaceuticals.⁷⁶ This system, which was introduced in 1979, has five categories designed to standardise the presentation of information from human and animal studies and provide risk-benefit information to prescribers. Table 2-2 provides a description of each of the categories. This system has been criticised for some time due to inflexibility, a tendency to create prescriber and patient anxiety and the common misunderstanding that the categories represent a simple, convenient measure of risk with a graduated increase from one category to the next.^{76 77} New FDA

requirements for pregnancy labelling have been proposed to address these shortcomings.⁷⁸ The European Medicines Agency has also introduced new labelling guidelines to improve communication of potential or identified risk from medications in pregnancy.⁷⁹

Table 2-2 FDA Pregnancy Labelling Categories

Category	Description ⁷⁸
A	Adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters)
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women <u>or</u> Animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to confirm this risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters)
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans <u>or</u> There are no animal reproduction studies and no adequate and well controlled studies in humans The benefits from the use of the drug in pregnant women may be acceptable despite its potential risks
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans The potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks
X	Studies in animals or humans have demonstrated fetal abnormalities <u>or</u> There is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both Risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit

2.2.3 *Determinants of medication use in early pregnancy*

Several studies have examined maternal characteristics that predispose women to using medications during pregnancy. Interpretation of such studies is complicated by the heterogeneity of the exposure indication - women use medications during pregnancy for a wide range of reasons. Some relate to the inadvertent use of medications in early pregnancy, others to the treatment of a pre-existing, long-term health condition. Some studies have focused on the determinants of exposure to potentially harmful medications in early pregnancy.

A Canadian population-based dispensed prescription register study found that women with chronic health conditions, younger age, increased parity and without private health insurance were more likely to have an FDA category C, D or X medication dispensed during pregnancy.⁸⁰ In contrast to this a US cross-sectional survey of ambulatory care consultations by pregnant women found that women with private health insurance and older age were more likely to receive a prescription for an FDA category D or X medication.⁸¹ This study also found that living in a metropolitan area, having pregnancy complications and being prescribed more than one medication were associated with being prescribed a category D or X medication. Another US maternal interview-based study found that category D or X exposure was associated with higher parity, single marital status and history of a chronic health condition or infertility.⁶² A similar Italian study based on maternal interviews also found that co-existing illness was a determinant of medication use during pregnancy, along with longer duration of education and smoking.⁶⁸ The finding relating to the association between educational status and medication use was not discussed by the authors. The

association was explained by a greater use of dietary supplements and other medicines generally in more educated women. These differences may be explained by age differences or by women with more education having better engagement with antenatal care and consequently being more likely to be prescribed a medicine or dietary supplement. A further US study examining risk factors for harmful medication use among pregnant women enrolled in Medicare found that women above the age of 35 and women who were insured as a result of a disability were more likely to use a category X medication.⁸²

2.3 Studying the safety of medication use in pregnancy

This section outlines the varying approaches to examining the safety of medication use during pregnancy. Animal studies, the “alert clinician” approach and epidemiological studies are described along with an overview of strengths and limitations of research in this area.

Studying the safety of medication use during pregnancy involves assessing effects on perinatal outcomes such as preterm birth, size for gestational age, neonatal condition at birth and also the medication’s teratogenic potential. Sufficient follow-up is also required to assess effects on long-term neurodevelopmental outcomes. An agent is considered a teratogen if its administration to the pregnant mother causes, directly or indirectly, structural or functional abnormalities in the fetus or child after birth, which may not become apparent until later in life.⁸³ Teratogens can be further classified according to their teratogenic risk. High-risk teratogens are those that dramatically increase the rate of congenital anomalies, typically affecting in the order of one in four exposed pregnancies e.g. thalidomide or isotretinoin.¹⁷ Moderate-risk teratogens might not have such a significant effect on the overall rate of congenital anomalies but can increase the rate of specific anomalies by two to tenfold or higher e.g. among other problems, the antiepileptic agent valproic acid increases the incidence of spina bifida approximately twelve to sixteen-fold from the background incidence of approximately 0.5 per 1000 in Europe.⁸⁴ Studying the safety of medication use during pregnancy is essential to guide medication use in pregnant women or women who may become pregnant. In the absence of adequate safety data women may be exposed to potentially

harmful medications during pregnancy or be unnecessarily deprived of essential medical treatment.

2.3.1 *Animal studies*

When a medication is initially marketed there is usually very little information available on pregnancy outcomes after human use as pregnant women or women who may become pregnant are invariably excluded from pre-marketing trials. Pharmaceutical companies seeking marketing authorisation for a new medication use animal studies as a preliminary indication of potential teratogenic risk. In the 1940's Warkany *et al*, while studying iodine deficiency, demonstrated that dietary deprivation of the B vitamin riboflavin in pregnant rats could cause congenital anomalies in the offspring.⁸⁵ After the thalidomide disaster animal studies of reproductive toxicology, usually in rats and rabbits, were required by regulatory authorities for the licensing of new medications.

Animal studies have the potential to systematically examine congenital anomalies, growth, and functional, neurodevelopmental and reproductive outcomes in offspring. Animal studies identified the teratogenic potential of the acne treatment isotretinoin (Roaccutane®) before it was marketed allowing for warnings against its use in pregnancy.⁸⁶ Pregnancy prevention programmes were subsequently developed; unfortunately these programmes have met with varying degrees of success.⁸⁷ All known human teratogens have also caused congenital anomalies when used in sufficient doses in animal studies using susceptible species.⁸⁸ Notwithstanding this, teratogenicity may not always occur in routinely tested species or at tested doses. After the human teratogenicity of thalidomide became apparent initial tests in a variety of species including mice, rats, hamsters, pigs,

cats, dogs, ferrets, armadillos and chickens failed to produce comparable malformations.⁴ Teratogenesis similar to that observed in humans was demonstrated eventually in primates and in a specific species of rabbit at doses 150 times above human dosage levels.³ Some teratologists concede that thalidomide would pass through the currently mandated reproductive toxicology testing procedures “with flying colours”.⁴

When adverse outcomes are identified in animal studies they do not necessarily predict occurrence with human exposure at clinically relevant doses. Inter-species differences in pharmacokinetics and teratogenic susceptibility also complicate interpretation of animal studies. As the utility of animal studies to prospectively identify human teratogens is limited, post-marketing assessment of the safety of medication use in human pregnancy is required.

2.3.2 *The “alert clinician”*

Early reports on the teratogenicity of medications and other exposures in human pregnancy involved case series or case reports by the “alert clinician”.⁸⁹ McAllister-Gregg noted the association between a rubella outbreak in Australia in the early 1940s and congenital cataracts, deafness and associated cardiovascular anomalies in affected infants.⁶ Lenz and McBride independently spotted a sudden increase in otherwise rare limb anomalies including phocomelia and linked this to thalidomide exposure in early pregnancy.^{1 2} As medication exposures and adverse perinatal outcomes may co-occur by chance, this approach may lead to spurious associations. Also, as specific exposure-anomaly combinations will usually occur rarely, observation of an association is unlikely. Observations of potential associations can act as signals to be tested in future epidemiological

studies. National regulatory authorities have systems in place for the spontaneous reporting of potential associations. These reports are then systematically examined to detect “signals” of any association between a medication and adverse perinatal outcomes which may require further testing in epidemiological studies.

Relying solely on case reports or case series by alert clinicians would also cause considerable time delays before any associations are noted. In the case of thalidomide it took nearly five years from the birth of the first affected child, a baby girl born without ears on Christmas Day 1956, until the initial reports of Lenz and McBride were published in November and December 1961.³ Valproic acid had been marketed for 15 years before unusual patterns of use among women who had infants with spina bifida were noted by French researchers.⁹⁰ The thalidomide disaster and subsequent discovery of other teratogens highlighted the need for systematic assessment of the safety of medication use in pregnancy.

2.3.3 Epidemiological studies of the safety of medication use in pregnancy

Epidemiological studies are required to provide information which will guide prescribers and patients when making prescribing decisions in pregnancy or before pregnancy. Pharmacoepidemiology is a term that is used to describe some of these studies, which examine the effects of medication exposures in large numbers of people. Studies of the safety of medications in pregnancy tend to be predominantly observational due to obvious ethical constraints of carrying out randomised studies in this population. A notable exception is the testing of potentially beneficial exposures such as folic acid.⁹¹ The two predominant study designs in this context are case-control studies and cohort studies.

Case-control methodology may be used to examine the association between an exposure and a specific congenital anomaly or range of anomalies. These studies are commonly carried out within an ongoing multicentre case-control study infrastructure where a common, continually growing dataset of cases and controls is used for multiple studies. Examples include the US-based Slone Epidemiology Center Birth Defects Study and the Centers for Disease-control and Prevention National Birth Defects Prevention Study.⁹² A collaborative European Register of Congenital Anomalies (EUROCAT) is also used to conduct case-control research.⁹³ These ongoing case-control studies involve registration of all congenital anomalies in defined geographical areas along with information on medication and other exposures during the critical period of organogenesis in the first trimester. Cases with the congenital anomalies under study are selected and the rate of exposure to the medication of interest is compared for the cases and appropriate controls.

Case-control studies have the advantage of good statistical power to study rare outcomes, such as specific congenital anomalies. There is potential for detailed data collection on outcomes and potential confounders. Case-control studies can be used to quickly and cheaply assess associations suggested by other epidemiological studies. These studies can identify exposures that cause moderate increases in risk, provided that the use of the exposure is not very rare among cases. If the exposure is rare, confidence intervals for the odds ratio estimate may be too wide to be clinically useful.

Validity of case-control studies may be threatened by information bias associated with ascertainment of exposures and selection of an appropriate control group.

Many studies identify exposures by maternal interview after delivery of a neonate with a congenital anomaly. Recall may be limited as the woman is asked about medication use at least six months previously. There may be maternal recall bias with better recall of exposures in cases than in controls⁹⁴ and interviewer bias if the interviewer is aware of the case or control status of the infant.⁸⁹ It has been suggested that there may be poorer recall among cases for illegal exposures such as illicit drugs.⁹⁵ There is debate on the selection of appropriate controls for case-control studies in this context.⁹⁶ Some studies attempt to overcome these limitations by using controls with a congenital anomaly other than that which is under study, as mothers of “sick controls” should have similar recall to mothers of cases.⁹² A complementary approach involves the use of multiple data sources such as dispensed prescription registers or hospital records to improve ascertainment of medication exposures.⁴⁹

Cohort studies can be used to examine congenital anomalies and a range of other adverse perinatal outcomes after exposure to a specific medication or group of medicines. Perinatal outcomes for a group exposed to the medication of interest are compared to outcomes for an unexposed comparison group, or perinatal outcomes may be compared for women with varying levels of an exposure. Varying methods are used to identify cohorts. Data may be collected specifically for the purposes of the study or there may be secondary use of data routinely collected for another purpose. Some birth cohort studies have collected detailed information on medication and other exposures in the periconceptional period and throughout pregnancy for large cohorts of women e.g. the Danish National Birth Cohort⁹⁷ and US Collaborative Perinatal Project.⁸⁹ Such studies have the

advantage of detailed information on exposures, potential confounders and outcomes for a large cohort of pregnant women. This must be balanced against the considerable costs of collecting this information. Despite collecting information on 60,000 to 100,000 pregnancies these cohort studies are limited by the fact that there may still be few pregnancies exposed to a specific medication of interest. On a smaller scale Teratogen Information Services conduct international collaborative studies assembling cohorts of women exposed to a medication of interest and following up perinatal outcomes with a standardised protocol.⁹⁸ Perinatal outcomes are then compared to a comparison group with exposure to no medications or a non-teratogen.

Cohorts of exposed pregnancies may also be assembled in pregnancy registries, usually run by the pharmaceutical industry, to collect standardised information on exposure and subsequently, perinatal outcomes.⁹⁹ Prospective ascertainment of exposure information before pregnancy outcomes are known is important as reliance on retrospective identification of exposures after adverse outcomes have occurred will lead to biased risk estimates, as adverse outcomes are more likely to be reported to manufacturers or regulatory authorities than normal outcomes. An example is one of the early reports on perinatal outcome after exposure to the antidepressant fluoxetine.¹⁰⁰ The congenital anomaly rate among live births, where fluoxetine exposures was ascertained prospectively in relation to pregnancy outcome, was 4.1%, compared to over 20% among cases with retrospective ascertainment of fluoxetine exposure after pregnancy outcome was known.

Routinely collected information from hospitals, health insurers and linked national registries of perinatal outcomes, prescription records and congenital anomalies

can also be used to identify exposed and unexposed pregnancies. These approaches have the advantages of large sample size, good ascertainment of exposure information and the ability to study a broad range of perinatal outcomes rather than a limited range of congenital anomalies. Research using electronic records of routinely collected data may be limited by incomplete ascertainment of exposures and outcomes and also by the limited availability of information on potential confounders. Some electronic recording systems may constrain the level of detail that can be recorded due to restrictive categorisation systems or drop-down menus. For these reasons validation studies are important to compare recorded information against a gold standard. In the context of recording medication exposures in pregnancy this may involve comparing self-reported medication use with dispensing and medical records or a further, more detailed maternal interview.⁴⁹

Cohort studies lack the statistical power of case-control studies to examine associations with specific congenital anomalies unless they have a large exposed cohort. Initial cohort studies of the safety of selective serotonin reuptake inhibitor (SSRI) antidepressants in pregnancy did not detect any increase in the rate of congenital anomalies.¹⁰¹ Larger studies with datasets such as the Swedish Medical Birth Register were better powered to examine associations between specific SSRIs and specific congenital anomalies, allowing the detection of an association between paroxetine exposure and cardiac septal defects.¹⁰² This association, which leads to a small increase in the absolute risk of cardiac septal defects, has been confirmed in other studies¹⁰³ and for other SSRIs.¹⁰⁴

Sample size is a common limitation when examining teratogenicity with a cohort study as congenital anomalies occur relatively infrequently. Individual anomalies are rarer still e.g. neural tube defects occur in approximately 1 in 1000 pregnancies in Dublin.¹⁰⁵ This, combined with infrequent use of individual medications, means that statistically significant associations are only likely to be found in very large studies. To have 80% power to detect a five-fold increase in the incidence of neural tube defects, with an α of 0.05, a cohort study would have to include nearly 3000 exposed pregnancies and a similar number of unexposed. Cohort studies with sample sizes of several hundred exposed pregnancies would not be powered to identify a moderate risk teratogen as an increase in the incidence of a rare outcome may still not increase the overall congenital anomaly rate significantly. This does not mean that smaller cohort studies are not useful. Information on several hundred exposed pregnancies from a cohort study is sufficient to rule out major increases in the rate of congenital anomalies and provides useful information for counselling women who require a medication during pregnancy or those with inadvertent exposure during early pregnancy.

There may be maternal characteristics that covary with exposure and outcome. If adequate data are not available on potential confounders any detected associations may not be caused by the exposure being tested. It can be difficult in these studies to disentangle the effects of the maternal illness from the effects of the treatment on perinatal outcomes. Even after controlling for known or suspected confounders there may be residual confounding from unmeasured or unknown confounders that could explain some or all of an observed association.

Congenital anomalies may be recorded with varying degrees of accuracy depending on the data source used and length of follow up. Ascertainment is likely to be incomplete if follow-up is short e.g. only covering the perinatal period. Varying levels of treatment in the neonatal period may also lead to varying degrees of ascertainment. For example, admission to a neonatal unit may lead to increased use of diagnostic procedures and increased likelihood of detection of a congenital anomaly that may have gone undetected if the neonate had not been admitted. Ideally multiple sources of ascertainment and active case finding should be used, along with detailed recording and validation of diagnoses of congenital anomalies using a standardised protocol.¹⁰⁶

Cohort studies in this context may involve retrospective analysis of data already collected for another reason e.g. electronic health records, such retrospective cohort studies are also termed historical cohort studies. Alternatively, a prospective cohort study may be carried out. This involves the recruitment and prospective follow up of a cohort and comparison of outcomes for groups with and without exposure to a risk factor of interest.

Retrospective cohort studies have the advantages of the ability to assemble a large cohort relatively quickly with minimal costs. This comes at the expense of incomplete information on exposures and outcomes and greater risk of error due to confounding and bias. There may be insufficient recording of information to allow adjustment for characteristics that differ between the exposed and unexposed groups, this could lead to the detection of associations between the exposure and outcome of interest that are due to residual confounding. There is also an increased risk of bias in outcome ascertainment.

Prospective cohort studies have the advantages of the ability to collect detailed data on exposures and outcomes in an objective manner, allowing adjustment for potential confounders and reducing the potential for bias. More time and resources are required to conduct prospective cohort studies given the need to recruit and follow up patients specifically for the study. There may be ethical considerations around the inclusion of subjects in prospective cohort studies and the potential for patients to refuse participation may lead to a selection bias with participants differing from non-participants.

Results from individual studies should be interpreted with caution due to the limitations of research methodologies in this context. Independent estimates of the effect of an exposure on perinatal outcomes from different studies are required. With regard to the effect of medication exposures on rates of congenital anomalies, it is important to use proper epidemiological techniques and apply the basic principles of teratology when assessing any potential associations.¹⁰⁷ The limitations of the various methodologies described here mean that individual studies are not usually sufficient to allow firm conclusions relating to the safety of medications in pregnancy to be drawn. Meta-analysis has been used to pool results of individual studies to examine the impact of a range of medication exposures or other interventions on congenital anomalies, e.g. antidepressants,¹⁰⁸ antiepileptics¹⁰⁹ and preconception care.¹¹⁰ No published meta-analysis has assessed the risk of congenital anomalies after methadone exposure in early pregnancy.

2.4 Methadone use in pregnancy

2.4.1 *Prevalence of opioid use in pregnancy*

There are an estimated 1.5 million problem opioid users in the European Union and Norway.¹¹¹ The prevalence of opioid use in Europe is rising. This is reflected by increasing drug-induced deaths, heroin seizures and new treatment episodes.

¹¹¹ In some European hospitals up to 3% of infants are born to drug-misusing mothers.³⁶ It has been estimated that there may be over 30,000 pregnant women using opioids each year in Europe.¹¹²

A capture-recapture study carried out in 2001 estimated the prevalence of opioid use in Dublin to be 16 per 1000 in the overall population.¹¹³ The estimated prevalence for women between the ages of 25 to 34 was approximately 16 per 1000. In an updated study performed in 2006, these estimates were increased to 17.6 per 1000 and approximately 22 per 1000, respectively. There was a drop in the prevalence in the 15-24 age group between 2001 and 2006. There were 11,538 people treated for problem opioid use in Ireland in 2007.¹¹⁴ An estimated 25-30% of opioid users in treatment are women, with the vast majority of childbearing age.

2.4.2 *Methadone pharmacology*

Methadone is a long-acting opioid analgesic that acts as an agonist at the μ -opioid receptor producing morphine-like effects.¹¹⁵ Methadone is well absorbed after oral administration. Peak plasma concentrations occur approximately four hours after an oral dose. The half life of methadone is approximately 15-40 hours, facilitating once daily dosing. Methadone's long half-life and similar pharmacological activity to heroin make it a suitable agent to alleviate opioid withdrawal symptoms in

dependent patients. Competitive binding of methadone to μ -opioid receptors also has the advantage of attenuating the activity of any concomitantly used heroin. Plasma methadone concentrations have been shown to be lower during pregnancy than in the post-partum period.¹¹⁶ Plasma concentrations have also been shown to decrease as pregnancy progresses.¹¹⁷ These changes may be due to physiological changes during pregnancy such as increased total body water, a larger tissue reservoir, enhanced clearance of methadone during pregnancy or a reduction in the absorption of methadone after oral administration.^{117 118} Placental tissue has the capacity to metabolise methadone, converting it to an inactive metabolite.¹¹⁹ This metabolic capacity, however, shows strong inter-patient variability.¹²⁰

As methadone leads to a withdrawal syndrome in a proportion of exposed neonates and also causes neonatal respiratory depression if used for obstetric analgesia in opioid-naïve patients, it is clinically evident that methadone crosses the placenta. Passage of methadone across the placenta has been demonstrated in studies of cord blood³¹ and *ex-vivo* experiments using dually-perfused human placenta lobules.¹²¹ Methadone transfer occurs at a higher rate in the fetal to maternal direction than in the maternal to fetal direction,¹²² possibly due to the activity of the p-glycoprotein efflux transporter which actively removes methadone from the fetal circulation.¹²³ Polymorphisms in the gene encoding p-glycoprotein have been shown to influence methadone dosing requirements in a non-pregnant population.¹²⁴ All of these pharmacological and physiological characteristics may have a role to play in the manifestation of NAS.

2.4.3 *Benefits and risks of methadone use in pregnancy*

In developed countries methadone maintenance is the most commonly used treatment for opioid-dependent pregnant women. In the non-pregnant opioid-dependent population, there is evidence that methadone maintenance treatment improves retention in treatment and leads to reductions in HIV risk behaviours, consumption of illicit opioids, criminal activity and mortality.¹²⁵ These benefits are also likely to apply in the context of opioid-dependence in pregnancy. Methadone maintenance treatment provides stability for the woman during pregnancy, avoiding repeated cycles of intoxication and withdrawal that may adversely affect the foetus.¹²⁶ Women are also freed from the constraints of drug-seeking behaviour and are not forced to engage in illicit activities such as prostitution and crime to fund their addiction. This allows the woman to engage with antenatal care leading to reduced risk of adverse perinatal outcomes.

Continued illicit opioid use in pregnancy can lead to a range of perinatal problems. An early case series from a New York hospital described outcomes for 384 infants born to 382 heroin-addicted mothers during the 1960s.¹²⁷ Nearly half of the infants were below 2500g, compared to 15% in the total population delivered in the same time period at the study centre. The perinatal mortality rate was 3.6%, with most deaths related to prematurity. In a further study by the same authors, which described outcomes for 45 women who used heroin throughout pregnancy, 53% of mothers were seen for the first time when admitted in labour and 35% of infants were “low weight for dates”.¹²⁸ A study from another New York hospital reported a perinatal mortality rate of 10%.¹²⁹ Heroin-exposed infants were also more likely to be small for gestational age than a non-exposed comparison group in this study.

This effect seemed to be independent of maternal nutritional status. In 1976 Kandall *et al* confirmed heroin's effect on birth weight, demonstrating that exposed infants were significantly lighter than controls and infants exposed to methadone.¹³⁰ Ostrea *et al* reported increased mortality, prematurity, low birth weight, small size for gestational age and meconium staining of the amniotic fluid with subsequent aspiration pneumonia among heroin-exposed infants.¹³¹ The pattern of a high rate of premature birth and high incidence of intrauterine growth restriction was confirmed in a more recent study of narcotic addicts from Hong Kong.¹³² Opioid-dependent pregnant women, especially those who continue intravenous abuse, are at risk of nutritional, medical and infectious complications.¹³³ As these women engage poorly with antenatal care, there may be no opportunity to manage obstetric complications or prevent vertical transmission of HIV or Hepatitis B infection. Heroin use in pregnancy is also associated with the risk of maternal mortality.¹³⁴ ¹³⁵ An enquiry in the UK found that among 295 maternal deaths identified during the 3 year period from 2003-2005 there were 52 (18%) cases of maternal death in women who were dependent on illicit drugs.¹³⁶

Since the early 1970s the benefits of methadone maintenance treatment in pregnancy have been demonstrated in observational studies. One of the earliest large studies of a multidisciplinary care concept that combined management of the woman's opioid-dependence with antenatal care and psychological and social support was carried out by Finnegan *et al* in Philadelphia.²⁶ This study demonstrated that in the context of a multi-disciplinary, comprehensive care programme, methadone maintenance treatment reduced the risks of continued illicit drug use, facilitating engagement with healthcare services. Compared to

women who continued to use illicit opioids, methadone-maintained women had more antenatal care visits, decreased incidence of low birth weight and obstetric complications, increased average birth weight and gestational age and an overall reduction in neonatal morbidity. This study also highlighted differences within the methadone-maintained group. The incidence of low birth weight, prematurity and neonatal morbidity was greater in those who had poor compliance with antenatal care. Similar findings relating to the effect of methadone maintenance treatment on fetal growth were reported by Kandall *et al*¹³⁰ and Ostrea *et al*³⁴ Both studies reported that mean birth weights were higher in infants of women treated with methadone than those of women who continued to use heroin in pregnancy, this finding was confirmed in a 1997 meta-analysis.¹³⁷

Subsequent studies produced similar results showing improved maternal and infant outcomes compared to historical rates of adverse outcomes for women who continued to use illicit opioids.²⁷ It became apparent that although perinatal outcomes were improved compared to ongoing heroin use, methadone-maintained women were still at an increased risk of adverse outcomes such as low birth weight, being small for gestational age and preterm labour compared to background population rates.¹³⁸⁻¹⁴⁰ More recent studies reflect a similar pattern of adverse outcomes for this group of women.^{36 141} Methadone maintenance treatment has been shown to lead to improved antenatal care in a variety of studies. Jones *et al* demonstrated a significantly higher number of obstetric visits in methadone-maintained women compared to women who were withdrawn from methadone during pregnancy.¹⁴² This presents an opportunity to deal with other medical disorders such as psychiatric comorbidities that are prevalent in this

group.¹⁴³ The stability conferred by methadone treatment affords the woman an opportunity to address social issues and prepare to care for her child. Stability in a maintenance opioid treatment programme has been shown to be predictive of retention of custody of the infant.¹⁴⁴ Increased contact with maternity services also affords the opportunity to address obstetric and medical problems and reduce the potentially high risk of vertical transmission of HIV and Hepatitis B.

The definite benefits of methadone maintenance treatment in pregnancy need to be balanced against the potential risks, the most prominent of which is NAS. Estimates of the incidence of NAS after exposure to methadone *in utero* vary between 13% and 94%.^{142 145-149} Prior to the earliest reports of methadone use in pregnancy, it was known that opioids could lead to a withdrawal syndrome in the neonate after regular use during pregnancy.²⁸ This was subsequently confirmed with methadone. The occurrence of neonatal abstinence syndrome sparked debate on appropriate dosing of methadone during pregnancy. From the early years of methadone maintenance until the late 1970s, most pregnant women were treated with high “blockade” doses of methadone in the range of 60 to 120mg that had been found to be effective in the original work by Dole *et al.*¹⁵⁰ In 1972 Finnegan *et al* reported that 82% of infants born to methadone treated mothers in a Philadelphia hospital manifested symptoms of withdrawal compared to 93% of infants born to a heroin-using control group.¹⁵¹ Rajegowda *et al* found a greater incidence of narcotic withdrawal in methadone-exposed than among heroin-exposed infants.¹⁵² Women in this study used between 80 to 160mg of methadone daily. Ostrea *et al* reported on factors that influenced the severity of neonatal narcotic withdrawal in a prospective cohort of 95 infants delivered at a

Chicago hospital.¹⁵³ This study found that the maternal methadone dose was correlated with the severity of withdrawal. Infants exposed to doses above 20mg a day were more likely to exhibit moderate to severe withdrawal. Ostrea *et al* subsequently suggested that women should be maintained on a low-dose regimen beginning at least a month before delivery to prevent serious withdrawal in the infant.³⁴ Similar findings of a relationship between methadone dose and the severity, or the need for medical treatment of NAS were reported by Harper *et al*³³ and Madden *et al*,¹⁴⁸ respectively. These data led to further suggestions of reducing women's doses to less than 20mg as soon as possible.¹⁴⁸ Other studies carried out in the US during the same time period did not find evidence of a dose-response relationship.^{31 32 154} In 1977 the FDA recommended that the methadone dosage should be maintained as low as possible if continued treatment was deemed necessary during pregnancy.²² Over the years there were continued conflicting findings, with more recent studies finding evidence for^{36 155 156} and against^{141 157 158} a dose-response relationship.

Potential limitations common to many of the studies examining the relationship between maternal methadone dose and NAS include small sample sizes and lack of control for factors which could potentially confound the relationship such as concomitant illicit and licit drug use, smoking and gestational age. Many studies in this setting use a retrospective study design, with the inherent limitations of incomplete and possibly biased recording of information. Despite the use of an objective scoring system to assess NAS, decisions to initiate treatment may still be subjective and influenced by clinicians' awareness of maternal methadone dose and concomitant drug use. This potential for observer bias could be minimised by

blinded assessment and treatment of NAS. Few studies in this setting had diagnosis and treatment of NAS blinded to maternal methadone dose and concomitant drug use.^{172 173} Varying approaches to the pharmacological treatment of NAS in different settings also complicate comparisons between studies.

Further evidence which would shape the debate about appropriate methadone dosing in pregnancy emerged subsequently. Various authors have demonstrated that methadone's pharmacokinetic properties are altered in pregnancy.^{116-118 159} These studies suggested that higher methadone doses may be required as pregnancy progresses to get an equivalent plasma concentration. Results of studies in non-pregnant populations have shown that higher doses of methadone were associated with better retention in treatment.¹⁶⁰ Other authors have suggested that opioid withdrawal or attempting to minimise methadone doses during pregnancy may predispose patients to relapse or continued illicit drug use and also uncontrolled *in utero* withdrawal, leading to preterm delivery or fetal death.³⁹

Methadone exposure *in utero* has been reported to be associated with adverse neurodevelopmental outcomes in a range of studies. However, it is difficult to separate the effects of methadone from the confounding effects of concomitant medication and illicit drug exposures, and low socioeconomic status.^{161 162} A recent review summarised emerging reports of an increased incidence of visual abnormalities including strabismus, nystagmus, failed vision tests and abnormal visual evoked potentials, a measure of abnormalities of the visual system, after methadone exposure *in utero*.¹⁶³ Early reports suggested an increased incidence

of sudden infant death syndrome after methadone exposure in pregnancy.¹⁶⁴ This association was confirmed in a US case-control study which controlled for ethnicity, maternal age, parity, smoking status, low birth weight and year of birth.¹⁶⁵ A recent population-based Australian study demonstrated significantly higher rates of infant mortality in methadone exposed infants compared with a non-exposed comparison group.¹⁶⁶ The increased risk of infant death in methadone-exposed infants remained statistically significant after controlling for maternal smoking, Apgar score at five minutes, size for gestational age, type of delivery and attendance at antenatal care.

As a result of the potential for adverse effects from methadone use in pregnancy, some investigators have examined the efficacy of other treatment modalities such as abstinence-oriented approaches or buprenorphine treatment. Abstinence throughout the course of pregnancy would be an ideal outcome, but over emphasis on achieving abstinence could have detrimental effects, placing the mother under considerable stress and potentially driving the woman away from appropriate care. There is evidence of high rates of relapse into opioid use with abstinence-oriented approaches, resulting in a cycle of intoxication and withdrawal which can lead to fetal compromise.^{142 167} It is possible to achieve abstinence in highly motivated stable women under close medical supervision with slow reduction of methadone doses, however this approach is controversial due to the associated risks of preterm delivery and relapse of illicit drug use.¹⁶⁸

Buprenorphine is a partial μ -opioid receptor agonist. Uncontrolled studies suggested that buprenorphine treatment provides comparable maternal benefits to methadone in pregnancy.¹⁶⁹⁻¹⁷¹ The incidence of NAS seems to be similar in

methadone and buprenorphine exposed infants.¹⁷⁰ Two pilot, double-blind, double-dummy, randomised controlled trials comparing methadone and buprenorphine for the management of opioid-dependent women have been reported to date.^{172 173} These studies, though small, demonstrated similar perinatal outcomes for women treated with methadone and buprenorphine. A larger multicentre randomised controlled trial is currently being completed.¹⁷⁴

Methadone has become accepted as the treatment of choice for the management of opioid-dependent pregnant women. National guidelines which address the treatment of opioid-dependent women in pregnancy have been developed in the US,¹⁷⁵ the UK,¹⁷⁶ and Australia.¹⁷⁷ These guidelines provide in-depth recommendations for management of the woman's addiction, antenatal care and care of the neonate. The US guidelines discourage reducing methadone dosage in pregnancy, highlighting that there is no compelling evidence to support methadone dose reduction in pregnancy to attenuate NAS. Based on the evidence assessed, the consensus panel recommended that methadone dosages for pregnant women should be determined individually to achieve an effective therapeutic level. The authors also advise against the medically supervised withdrawal of methadone during pregnancy. The UK guidelines are similar with respect to methadone dosing, recommending maintenance prescribing at a dose that stops or minimises illicit use. This guideline does acknowledge that many women will request detoxification and provides recommendations on the optimal approach. Other UK guidelines have been developed to address service delivery for women with substance misuse disorders.¹⁷⁸ The Australian guidelines take a similar approach

to methadone dosing during pregnancy, specifically warning against using low doses in an attempt to reduce neonatal abstinence syndrome.

2.4.4 Methadone use in pregnancy in Ireland

There are currently no Irish guidelines for the care of opioid-dependent pregnant women. Women using heroin during pregnancy are offered prioritised access to a methadone maintenance programme. The woman's engagement with antenatal care is facilitated by Drug Liaison Midwives who work between the Addiction Service and the Dublin Maternity Hospitals.¹⁷⁹ The differing rates of opioid dependence between Dublin, other Irish cities and rural areas indicate that the rates of methadone use in pregnancy are likely to be much higher in Dublin than in the rest of Ireland. A recently published review of the management of opioid dependence in Ireland, "The Introduction of the Opioid Treatment Protocol", indicates that the prevalence estimate of opiate users aged 15-64 years was 14,904 for Dublin and 5,886 for the rest of Ireland.¹⁸⁰ This equates to rates of 17.6 and 2.9 per 1000 for Dublin and the rest of Ireland, respectively. Though fewer women will be treated with methadone outside of Dublin, they are likely to have similar characteristics to opioid-dependent women treated in Dublin.

Early reports of the management of opioid-addicted pregnant women in the Dublin Addiction Services were published in the 1980s.^{181 182} At this time low dose methadone maintenance of approximately 20mg daily was prescribed during pregnancy. Follow up studies of one of these cohorts have been performed at six¹⁸³ and 20 years.¹⁸⁴ At 20-year follow up 53% of the women were deceased, mainly as a consequence of HIV infection. Approximately half of the women interviewed had urinalysis positive for opiates in the previous two months. Follow-

up for the infants was limited to forensic history and substance misuse as reported by the women at the follow-up interview. Of the 19 offspring 37% had served a custodial sentence and 42% had a documented history of substance misuse. A 1990 report describes perinatal outcomes for 29 opioid-dependent women delivering 42 infants in a Dublin maternity hospital between 1982 and 1985.¹⁸⁵ Like international studies, the infants had significantly lower mean gestational age and mean birth weight than a comparison group. Withdrawal symptoms were present in 84% of infants. More recently, perinatal outcomes were described for women who delivered in the first year after the Drug Liaison Midwife post was introduced in one of the Dublin maternity hospitals.¹⁸⁶ There was a lower mean birth weight and increased rate of preterm delivery compared to the background population. Maternal methadone dose at delivery was found to be a significant predictor of the occurrence of NAS.

2.4.5 Studying Methadone use and Perinatal Outcomes: Methodological Issues

Studies examining maternal and neonatal outcomes after methadone use in pregnancy are usually observational. As with studies of the use of other medications in pregnancy, randomised controlled trials of methadone use in pregnancy are rare. Methadone maintenance treatment frequently co-occurs with other maternal exposures or characteristics that may affect perinatal outcomes. Adequate adjustment for and reporting of potential confounders or effect modifiers is important. Kaltenbach and Finnegan highlighted the need to consider the “continuum of risk factors” before the aetiology of perinatal effects of methadone exposure can be fully understood.¹²⁶ LaGasse *et al* outline three classes of confounding factors in research relating to prenatal exposure to substances of

abuse: polydrug use, social and demographic factors, and medical and health status.¹⁸⁷ It is important to consider the effect of polydrug use incorporating concomitant illicit drug use, smoking, alcohol consumption and medication use; social factors such as poverty and chaotic lifestyle; and maternal health status including co-morbidities, obstetric risk factors and poor nutritional status. Historically few studies take these myriad factors into account. Inconsistent or inadequate reporting of these factors in the extant literature on methadone use in pregnancy makes interpretation and comparison of previous studies difficult.

LaGasse *et al* also emphasise issues relating to sample size with research in this area. Although control for confounding variables is important in this context, sample size limitations constrain the ability to control for multiple covariates. There may also be other problems relating to violation of statistical assumptions of the models used and reduction of power to detect significant associations with inclusion of multiple covariates in statistical models.

Many studies in this context have been based on retrospective review of medical records as recruitment of participants for prospective cohort studies in this area presents several difficulties. Recruitment of patients must take account of the sensitive nature of the exposures and outcomes under study and the fact that opioid-dependent pregnant women and their children are a vulnerable group. It is important that women do not feel any degree of coercion to participate. There is a risk of sampling bias as a result of non-participation of unstable women who are difficult to recruit because of poor compliance with care. After women have been recruited to participate accurate ascertainment of exposures may be difficult due to the illicit nature of concomitant drug use. Ideally objective measures of illicit drug

use should be used. It is important that the study methodology does not require significant deviation from routine care in order to ensure adequate participation rates and minimise loss to follow up. With regard to outcome assessment, few studies in this context have had assessment of NAS by observers blinded to maternal methadone dose and concomitant drug use.^{172 173 188}

The difficulties in studying perinatal outcomes after prenatal exposure to methadone and concomitant drugs have been recognised for some time. Conducting research on this topic has been described as “fraught with methodological difficulties”.¹⁸⁹ However, if these difficulties are recognised and taken into consideration when interpreting study findings, such research has the potential to help ensure optimal care of opioid-dependent pregnant women and their children.

2.5 Summary

Medication use in pregnancy is common and up to date studies to assess its prevalence in geographically diverse locations are necessary to inform future research on the safety of specific medications in pregnancy. A sizeable minority of women take medications with potential for fetal harm during pregnancy. No studies of the overall prevalence of medication use in pregnancy in an Irish healthcare setting have been reported.

Opioid dependence in pregnancy can seriously affect maternal and infant outcomes. Methadone maintenance treatment, delivered in the context of a multidisciplinary service incorporating antenatal care, improves outcomes for mother and child. Even with multidisciplinary care and methadone maintenance treatment these women and infants still appear to be at increased risk of adverse perinatal outcomes. One of the most commonly occurring adverse outcomes after methadone use in pregnancy is NAS. The determinants of NAS are not completely understood and conflicting reports on the existence of a dose-response relationship continue to be published. Pregnant women who are dependent on opioids are often concerned about the occurrence of NAS. Conflicting findings relating to NAS in the literature can make optimal prescribing of methadone during pregnancy difficult.

This thesis aims to address current knowledge deficits relating to the issues of medication use in early pregnancy in an Irish healthcare setting and adverse outcomes after methadone use in pregnancy.

CHAPTER 3. PREVALENCE AND DETERMINANTS OF MEDICATION USE IN EARLY PREGNANCY

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3.1 Introduction

Despite the thalidomide disaster, the safety of many medications that are commonly used during pregnancy has yet to be confirmed.¹⁶ Even though medications are thought to account for a small percentage of congenital anomalies, the inappropriate use of medications during pregnancy is a potentially preventable cause of what can be a major burden to affected infants and their families. Discontinuation of necessary medications during pregnancy, however, can put both mother and baby at risk of the complications of untreated chronic medical disorders.^{136 190} In Ireland and other developed countries women are having children at a later age when chronic conditions are more prevalent.¹⁹¹⁻¹⁹³ In addition, a considerable proportion of pregnancies are unplanned.⁴³ This can result in inadvertent exposure to prescription, OTC, illicit and herbal medicines or supplements during organogenesis. The issue of safe prescribing of medications during pregnancy has been highlighted by proposals to amend the Food and Drug Administration pregnancy labelling categories (FDA categories) to make it easier for clinicians to provide appropriate information on the safety of medications during pregnancy.⁷⁸ The proposed changes come as a result of criticism of the current system, highlighting the fact that it is inflexible and prone to misinterpretation and creating patient and clinician anxiety.⁷⁶

The reported prevalence of medication use in pregnancy varies with the setting and research methodology used. Studies in the United Kingdom have shown that 83% of pregnant women reported medication use at some time in pregnancy, while 65% of women were prescribed a medication in the periconceptual period.

^{51 55} French and US studies found that 99% and 64% of pregnant women received

a prescription during pregnancy respectively.^{54 64} A Norwegian study found that 33% of women were dispensed a medication during their first trimester, with 57% dispensed a medication at some stage during their pregnancy.⁹

While this topic has been explored previously, up to date drug utilization studies from geographically diverse locations are important to establish research priorities in this area.⁴⁶ As previous studies have often used prescription or dispensing records, there are few data available on the full extent of medication use including prescription, OTC, illicit and herbal medicines or supplements. Few studies have examined the determinants of the use of medications with potential for fetal harm. This study aimed to determine the prevalence of medication use in early pregnancy among a large cohort of women giving birth in a maternity hospital over an eight year period, exploring the use of medications with potential for fetal harm, prescribing for women with chronic medical disorders and the determinants of medication use.

3.2 Methods

The study population comprised women with booking and delivery records in the Coombe Women and Infants University Hospital (CWIUH) between 2000 and 2007. CWIUH is a tertiary care maternity hospital serving a diverse catchment area with over 8,000 births annually (approximately 12% of all Irish births). Women were excluded from the study if they did not book for antenatal care or if they did not deliver in the hospital, as the dataset was established to examine perinatal outcomes. Delivery records were not routinely available for women who deliver at less than 24 weeks gestation or 500g weight.

Ascertainment of antenatal medication exposure was by maternal self-report, recorded as part of a computer-guided booking interview carried out by a midwife. This usually occurs at the end of the first trimester. Patients were asked: 'Have you taken any tablets, medicines or had any injections this pregnancy?' Specific medication exposures were recorded with free text entry by a midwife. A pharmacist analysed free text medication entries to extract the approved non-proprietary names. A medication dictionary was assembled which linked approved non-proprietary names to World Health Organisation Anatomical Therapeutic Chemical (ATC) codes, FDA categories and OTC status. The ATC classification system (2008 version) was chosen, as this is a widely used, internationally accepted classification system for medications. Of the internationally available systems, the FDA pregnancy categorization system was selected as an indicator of potential for fetal harm. Although this system has been criticised,¹⁹⁴ it is widely used in drug utilization research in pregnancy and classifications are readily accessible for most medications. FDA categories were obtained from a standard reference text¹⁹⁵ or the manufacturer's product information as necessary.

Medications were classified as over the counter according to their marketing authorisation status in Ireland, and included non-prescription products available from pharmacies and non-pharmacy outlets. Multiple ingredient products were classified according to Anatomical Therapeutic Chemical methodology and the most stringent FDA category of the ingredients was used. Where there was ambiguity regarding the reported medication name the Anatomical Therapeutic Chemical 1st level (anatomical group) and 2nd level (therapeutic subgroup) codes were assigned if possible.

Data on patient demographics and medical, obstetric and social history as reported at the booking interview were extracted from the hospital's electronic medical records database. Patients' responses to questions on their medical history were analysed by an obstetrician and International Statistical Classification of Diseases (ICD) 10th revision, version for 2007 codes were assigned.

Descriptive statistics were used to characterise the reported medication exposures, calculating the prevalence of any medication use in pregnancy among all deliveries with an antenatal booking interview. Women were classified as taking any medication during pregnancy if they reported any prescription, OTC, illicit or herbal medicine or supplement (excluding folic acid). The proportion of women who reported OTC medications, illicit drugs or methadone and herbal medicines or supplements were also determined. Medication use was categorised in terms of ATC groups to describe the nature of medication use in early pregnancy. The proportion of exposures to each FDA pregnancy category was determined as an indicator of potentially harmful medication use.

Asthma, depression and hypertension were selected in order to characterise prescribing for common chronic medical disorders during pregnancy within the cohort. Prescribing for chronic medical disorders in pregnancy was cross-referenced with UK and US clinical guidelines on the management of asthma, antenatal mental health, and hypertension.¹⁹⁶⁻¹⁹⁹ The proportion of women reporting a history of these medical disorders and the most frequently reported medication groups and individual medications were determined.

FDA category D (evidence of fetal risk, benefits may outweigh risks) and category X (evidence of fetal risk, benefits clearly outweighed by risks) medications were considered potentially harmful. Oral contraceptives, fertility treatments and progestogens were excluded from this group. Although they are commonly reported category D/X medications, they do not carry the same level of risk as other medications in these categories.²⁰⁰⁻²⁰²

To examine maternal characteristics associated with medication use, logistic regression analyses were used to calculate crude and adjusted odds ratios and 95% confidence intervals for the association between any medication use or potentially harmful medication use and potential associated maternal characteristics including: age at delivery, booking gestation, nulliparity, planning of pregnancy, occupational group, nationality, region, marital status, multiple pregnancy, smoking status, periconceptional alcohol consumption and receipt of private obstetric care. Analysis was restricted to individuals with complete data for the relevant variables. Analysis including only one pregnancy for each woman in the dataset yielded odds ratios that were only marginally different from those calculated for the entire cohort (results not shown). Therefore, each pregnancy was treated as an independent event in the logistic regression model, with no adjustment for the lack of independence between pregnancies of women with more than one delivery during the study period. SPSS 14.0 (SPSS Inc., Chicago, IL) was used for all analysis. The study was approved by the CWIUH Research Ethics Committee. Electronic data were stored on a networked, password-protected computer with daily data backups. Personally identifiable information such as name, address, medical card number and maternal date of birth were not

included in the dataset. A mathematical derivation of the woman's hospital number was included to allow linkage between maternal and infant records and to facilitate validation of records.

3.3 Results

There were 62,063 pregnancies with delivery records during the study period (66,272 pregnancies were booked for antenatal care during the same period). Of the women with delivery records, 811 (1.3%) were excluded, as there was no record of a complete antenatal booking interview. The median gestation at the antenatal booking interview was 14.3 weeks (interquartile range 12.3-17.1). Use of folic acid for any duration was reported in 52,078 (85%) pregnancies. Excluding folic acid, at least one medication was reported in 23,989 (39.2%) pregnancies, with 11,970 (19.5%) women reporting taking an OTC medication, 545 (0.9%) an illicit drug or methadone, and 352 (0.58%) a herbal medicine or supplement. Of the women who reported taking medication, 16,890 (70.4%), 4,737 (19.7%) and 2,318 (9.7%) reported taking one, two and three or more medications respectively. The most commonly reported medications were analgesics (e.g. paracetamol, ibuprofen, aspirin), antibacterials, antianaemics and medications for obstructive airways disease (Figure 3-1). The five most commonly reported OTC medications are outlined in Figure 3-2.

FDA category D and X medications were reported by 1,532 (2.5%) and 1,987 (3.2%) women respectively (Figure 3-3). Excluding oral contraceptives, fertility treatments and progestogens, 1,478 (2.4%) and 90 (0.1%) pregnancies were exposed to FDA category D and X medications. Table 3-1 outlines the 10 most frequently reported FDA category D/X medications. Among the women that reported an FDA category D/X medication, 107 (3.1%) reported a combination of

two or more. The most common combination was methadone and benzodiazepines.

Asthma, depression and hypertension were among the most commonly reported chronic medical disorders under the medical history question; 5,692 (9.3%), 5,641 (9.2%) and 1,408 (2.3%) respectively. Of the women with a history of asthma, 3,583 (62.9%) reported using a medication for the condition; the corresponding figures for women with a history of depression and hypertension were 548 (9.5%) and 329 (23.3%). Table 3-2 describes the prevalence of self-reported medical disorders along with the most frequently reported medication groups and the five most common individual medications for each condition.

The determinants of the use of any medication are shown in Table 3-3. Data were missing for some variables used in the logistic regression model (range 0-11.8%, see Table 3-3 and Table 3-4). Women were more likely to report any medication use if they had an unplanned pregnancy (aOR 1.44, 95% CI 1.37-1.50) or a multiple pregnancy (aOR 1.28, 95% CI 1.11-1.48). Relative to those in the 25 to 29 year age group, medication use was less likely in women in the <20 years age group (aOR 0.77, 95% CI 0.69-0.85). Women receiving publicly-funded maternity care were less likely to report any medication use than those receiving private care (aOR 0.57, 95% CI 0.55-0.60). Women who booked after 20 weeks gestation were more likely to use medication than women booking between 12 and 20 weeks (aOR 1.53, 95% CI 1.45-1.62). There were international variations in the likelihood of reporting any medication use. Compared to women from Western Europe, the odds ratio for reporting any medication use was lower for women from Eastern Europe (aOR 0.75, 95% CI 0.66-0.85), and Asia/Middle East (aOR 0.74, 95% CI

0.65-0.84), and higher for women from North America (aOR 1.46, 95% CI 1.16-1.84). Women who reported drinking alcohol prior to pregnancy were more likely to take medications than women who reported never drinking alcohol.

Table 3-4 shows the determinants of the use of FDA D/X medications (excluding oral contraceptives, fertility treatments and progestogens). Women were more likely to take FDA category D/X medications if they had an unplanned pregnancy (aOR 1.31, 95% CI 1.12-1.52) or multiple pregnancy (aOR 2.15, 95% CI 1.46-3.17), or if they were a smoker (aOR 1.96, 95% CI 1.67-2.28) or single (aOR 1.28, 95% CI 1.06-1.54). Women who booked for antenatal care prior to 12 weeks gestation were also more likely to take FDA category D/X medications than women booking between 12 and 20 weeks (aOR 1.83, 95% CI 1.58-2.13). Women who were unemployed were more likely to use potentially harmful medications than women in the professional/manager/employer socioeconomic group (aOR 2.58, 95% CI 2.03-3.29). Compared to women who never used alcohol prior to pregnancy, light to moderate drinkers (less than 14 units per week) were less like to report potentially harmful FDA D/X medications.

3.4 Discussion

Four in ten women reported using a medication before booking for antenatal care, while one in five used an OTC medication. Medications classified as category D/X in the FDA pregnancy labelling system were reported in 3,412 (5.6%) pregnancies. Medications known to cause fetal harm were reported by 86 (15.7%) women treated for depression (paroxetine) and 68 (20%) women treated for hypertension (atenolol and agents acting on the renin angiotensin system). FDA category D/X medications (excluding oral contraceptives, fertility treatments and progestogens)

were reported more often among women over 25 years of age, those with unplanned pregnancies, the unemployed, single women, smokers and nulliparous women.

This study describes early pregnancy medication use in a large cohort of women who delivered in a tertiary care maternity hospital in Dublin, Ireland. The hospital serves a diverse population, delivering approximately one in every eight babies in Ireland. Data were available on a variety of social, demographic and medical factors allowing a detailed profile of maternal factors contributing to medication exposure and specifically, to potentially harmful medication exposure during pregnancy. Ascertainment of medication exposures was unbiased by perinatal outcome, having occurred prior to delivery. Maternal recall bias, with perinatal outcome affecting recall of medication exposure has been highlighted as a potential problem with retrospective ascertainment of medication exposures after pregnancy outcome is known.⁹⁴ As medication exposures were ascertained by computer-guided patient interview carried out by an experienced midwife, there was recording of the full range of medications beyond that which is available in prescription registries (OTC and inpatient medications, illicit drugs and herbal medicines or supplements). This revealed that the level of self medication in early pregnancy was high among these women. It is likely that maternal self-reports reflect actual medication use in pregnancy.

This study design has the potential weakness of under-reporting of medication exposures due to poor recall, language difficulties or a decision by the woman not to disclose medication use. Poor recall is unlikely to have a major impact on prevalence estimates as the recall interval was short. The fact that women from

non-English speaking regions were less likely to report any medication use may reflect language difficulties in the antenatal booking interview. The relatively low prevalence of reported illicit drug use is indicative of many women failing to disclose use,^{14 203} suggesting a need for validation studies of exposure to medications and illicit drugs. As a result of these limitations, the prevalence of medication exposures during pregnancy may have been underestimated. This study is limited by the fact that medication use was not evaluated at a consistent time point in pregnancy, e.g. first trimester use exclusively, due to the inherent variability in gestational age at the time of the booking interview. This may result in the recording of some medication exposures that do not reflect early pregnancy use. It is problematic that some women did not know the precise names of the medications that they took. It is also unfortunate that there is no information on medication use during early pregnancy for women who do not book for antenatal care as these women are a particularly vulnerable group. As methadone and illicit drugs were the most predominantly reported FDA category D/X medications, determinants of FDA category D/X exposures were influenced mainly by this group.

Other studies have reported higher prevalences of medication use during pregnancy (44-99%).^{11 54 59 64} This may be explained by the fact that the current study concerned early pregnancy medication use rather than exposures throughout pregnancy and also by geographical and temporal variations in the prevalence of medication use in women of childbearing potential. Among those studies that reported on the prevalence for the first trimester specifically, the rates were similar to this study (33-43%).^{9 10 12} The prevalence of early pregnancy FDA

category D/X medication use was also comparable with other studies.^{50 80} A US study found that 1.2% of women were dispensed an antihypertensive medication during the first trimester.²⁰⁴ In this study 371 (0.6%) women reported taking an antihypertensive agent. A recent Dutch study examined trends in the use of SSRIs during pregnancy, reporting that 2.1% of women were dispensed an SSRI in the first trimester.²⁰⁵ In comparison, 390 (0.6%) women in the cohort reported using an SSRI, although a further 160 women (0.2%) reported using an unknown antidepressant. Discrepancies between studies that use different sources to ascertain medication exposures may be partially explained by women not taking prescribed medication during pregnancy, possibly due to fears of fetal harm.⁴⁸ This will lead to higher prevalence estimates from studies using prescription records. Perhaps more relevant is the finding that less than one in 10 of those with a history of depression took antidepressant medications during early pregnancy. This may reflect concerns about fetal exposure or a preference for non-pharmacological therapeutic approaches in women of reproductive age. Similarly, less than a quarter of women reporting a history of hypertension reported current use of an antihypertensive agent at the booking visit. The overall number of women with a history of hypertension may include women reporting previous high blood pressure measurements which did not warrant pharmacological treatment because of low absolute risk of cardiovascular disease due to gender, younger age and absence of additional risk factors, as well as women with a history of hypertension exclusively in pregnancy or women who have discontinued antihypertensive medication early in pregnancy following the physiological fall in blood pressure seen in the first trimester.

Some groups within the cohort were found to report sub-optimal medications during pregnancy. Of the women on antihypertensives, the majority were treated with agents of choice,¹⁹⁹ although 68 (20%) were on either atenolol or agents acting on the renin-angiotensin system, medications known to cause adverse perinatal outcomes.²⁰⁶⁻²⁰⁸ Similarly, paroxetine was the most commonly prescribed SSRI during the study period. The majority of paroxetine exposures were reported before evidence of the adverse effects of early pregnancy paroxetine use began to emerge in 2005.^{102 209} Use of paroxetine was less common after 2005, though it was still reported by between 8 to 14 patients a year.

This study also examines the factors associated with potentially harmful medication use. Previous smaller studies found that FDA category D/X exposures were associated with ethnicity, multiparity, single marital status, history of chronic illness, lower age groups and receipt of social welfare assistance.^{80 81} The current study lends support to some of these findings in a European setting. Some new associations with category D/X exposures were found. Women who booked before 12 weeks gestation were more likely to report these medications, as chronic medical disorders were more common in these women, which may explain the increased category D/X medication use. Women with multiple pregnancies were also more likely to report category D/X exposures, as prednisolone is commonly prescribed as part of local in vitro fertilisation protocols in some assisted conception units. This is also reflected in the increased likelihood of nulliparous women reporting category D/X exposures. Perhaps the most worrying group are women with unplanned pregnancies who may have taken category D/X

medications before they realised they were pregnant. Women who smoked during pregnancy and those above 25 years of age were also more likely to report use of a potentially harmful medication. Private patients were more likely to report the use of any medication than public patients. This may relate to greater compliance with antenatal care and consequently more frequent use, or possibly more complete reporting of medication use. As private patients were older than public patients, medication use for chronic diseases may have been more prevalent, however after controlling for maternal age, the association between private obstetric care and medication use persisted.

It is evident that a significant number of women take medications in early pregnancy before booking for antenatal care. With regard to the safe use of medications in early pregnancy, it is reassuring that excluding contraceptives, fertility treatments and progestogens only 2.4% and 0.1% of patients reported potentially harmful FDA category D and X medication use respectively. Of these exposures some may have been unavoidable, where use of the medication was deemed appropriate given the benefits and risks of its use in early pregnancy. It is likely however that there is some potentially avoidable use of inappropriate medications during pregnancy. While it is over-simplistic to advise avoidance of all medications during the first trimester, it is important that prescribers and women themselves are aware of the lack of pregnancy safety data for the majority of medications. It is equally important, however, that necessary medications are not inappropriately discontinued during pregnancy. Women should be made aware of the need for pre-conception counselling to ensure optimal treatment for chronic medical disorders. In light of the high rate of unplanned pregnancies, all

prescribers should be aware of the danger of prescribing medications with known harmful effects during pregnancy to women of childbearing potential. There is a need for a co-ordinated effort to routinely capture information on medication exposures and perinatal outcomes in order to improve the evidence base for using medications during pregnancy.

Table 3-1 Most Frequently Reported FDA Category D/X Exposures

Category D	Number (%)	Category X	Number (%)
Methadone	496 (0.81)	Oral Contraceptive	1614 (2.64)
Diazepam	188 (0.31)	Emergency Contraceptive	159 (0.26)
Paroxetine	125 (0.20)	Estradiol	80 (0.13)
Prednisolone	123 (0.20)	Flurazepam	26 (0.04)
Quinine	101 (0.16)	Clomifene	22 (0.04)
Valproate	82 (0.13)	Contraceptive Patch	21 (0.03)
Carbamazepine	77 (0.13)	Cannabis	18 (0.03)
Propylthiouracil	52 (0.08)	Cocaine	12 (0.02)
Atenolol	49 (0.08)	Medroxyprogesterone	11 (0.02)
Alprazolam	39 (0.06)	Atorvastatin	10 (0.02)

Table 3-2 Reported Medical Disorders and Most Frequently Used Medications for Each Disorder.

N=61252		Asthma		Depression [†]		Hypertension	
No. of patients (% of cohort)		5692 (9.3%)		5641 (9.2%)		1408 (2.3%)	
No. of patients reporting a medication for medical disorder (% of patients with history of medical disorder)		3583 (62.9%)		548 (9.5%)		329 (23.3%)	
Most frequently reported medication groups (% of treated patients)	Selective β2 receptor agonists	3422 (95.5%)	Selective serotonin reuptake inhibitors	306 (55.8%)	β blocking agents	115 (34.9%)	
	Glucocorticoids	1309 (36.5%)	Unknown	141 (25.7%)	Antiadrenergic agent, centrally acting	92 (30.0%)	
	Unknown	325 (9.1%)	Other antidepressants *	59 (10.8%)	Unknown	56 (17.0%)	
	Anticholinergics	44 (1.2%)	Non-selective monoamine reuptake inhibitors	55 (10.0%)	Agents acting on renin angiotensin system	25 (7.6%)	
	Xanthines	36 (1.0%)			Calcium channel blockers	22 (6.6%)	
	Leukotriene receptor antagonists	14 (0.39%)			Diuretics	22 (6.6%)	
Top 5 individual medications (% of treated patients)	Salbutamol	2932 (81.8%)	Unknown Antidepressant	141 (25.7%)	Methyldopa	92 (30.0%)	
	Beclometasone [‡]	833 (23.2%)	Paroxetine [‡]	86 (15.7%)	Labetalol	58 (17.6%)	
	Unknown	325 (9.1%)	Fluoxetine	85 (15.5%)	Unknown	56 (17.0%)	
	Fluticasone	285 (7.9%)	Citalopram	61 (11.1%)	Antihypertensive		
	Salmeterol	253 (7.1%)	Venlafaxine	47 (8.6%)	Atenolol [†]	43 (13.1%)	
					Amlodipine	17 (5.2%)	

* includes venlafaxine, mirtazepine, duloxetine, nefazodone, trazodone [†] includes postnatal depression

[‡] UK asthma guidelines recommend use of inhaled beta 2 agonists and steroids as normal during pregnancy, ¹⁹⁶ US guidelines select budesonide as the inhaled steroid of choice. ¹⁹⁷; [‡] UK guidelines for the management of depression in pregnancy warn against the use of paroxetine and cite fluoxetine as the antidepressant with 'lowest known risk' in pregnancy. ¹⁹⁸; * UK guidelines for the management of hypertension cite a lack of evidence on which to make firm recommendations, but identify methyldopa as the antihypertensive of choice in pregnancy, with prolonged release nifedipine, hydralazine and labetalol being second line agents. ¹⁹⁹

Table 3-3 Maternal Factors Associated with the Use of Any Medication among all Women

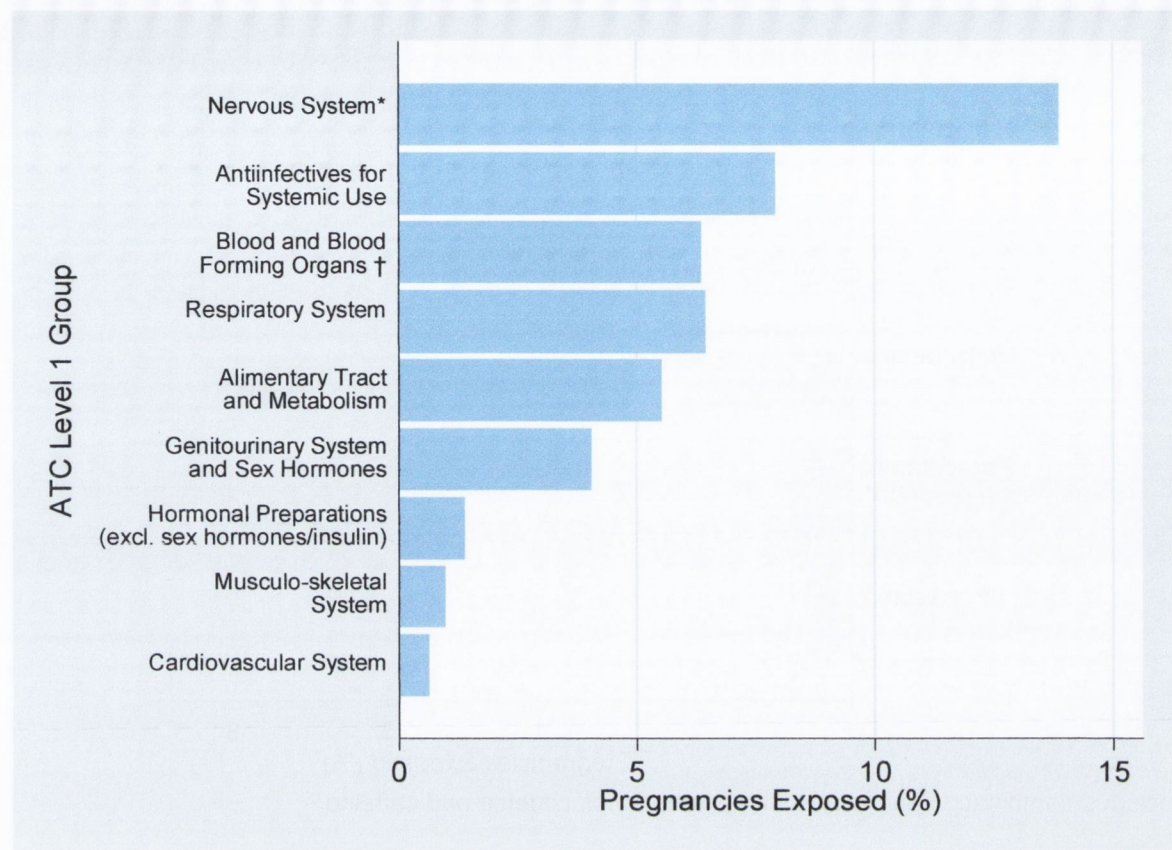
	N=61203	No Medication Reported n=37214 (60.8%)	Medication Reported n=23989 (39.2%)	Odds Ratio	95% CI	Adj. * Odds Ratio	95% CI
Age at delivery (years)- mean (standard deviation)	61203	29.88 (5.77)	30.11 (5.90)				
Age at delivery	61203						
<20 years		1903 (62.6%)	1136 (37.4%)	0.96	0.89-1.04	0.77	0.70-0.85
20-24 years		5282 (60.3%)	3479 (39.7%)	1.06	1.00-1.12	0.92	0.86-0.98
25-29 years		9048 (61.6%)	5630 (38.4%)	1.00	-	1.00	-
30-34 years		12701 (61.9%)	7818 (38.1%)	0.99	0.95-1.03	0.97	0.92-1.01
35-39 years		7056 (58.8%)	4940 (41.2%)	1.13	1.07-1.18	1.04	0.98-1.10
>40 years		1224 (55.4%)	986 (44.6%)	1.30	1.18-1.42	1.11	1.00-1.23
Gestation at delivery (weeks)- mean (standard deviation)		39.56 (2.31)	39.79 (4.51)				
Booking gestation (weeks)	53982						
< 12 weeks		6622 (61.7%)	4103 (38.3%)	1.05	1.01-1.10	0.96	0.92-1.01
12 - 20 weeks		22541 (62.9%)	13269 (37.1%)	1.00	-	1.00	-
> 20 weeks		4021 (54.0%)	3426 (46.0%)	1.45	1.38-1.52	1.53	1.45-1.62
Nulliparous	61203						
No		21885 (60.7%)	14153 (39.3%)	1.00	-	-	-
Yes		15329 (60.9%)	9836 (39.1%)	0.99	0.96-1.03	-	-
Planned pregnancy	61013						
Planned		25067 (63.4%)	14463 (36.6%)	1.00	-	1.00	-
Unplanned		11894 (55.7%)	9452 (44.3%)	1.38	1.33-1.42	1.44	1.37-1.50
Socioeconomic group	61190						
Prof./Manager/ Employer		8545 (59.6%)	5794 (40.4%)	1.00	-	1.00	-
Home duties		7848 (61.7%)	4877 (38.3%)	0.92	0.87-0.96	1.04	0.98-1.10
Non-Manual		12025 (62.1%)	7347 (37.9%)	0.90	0.86-0.94	0.98	0.93-1.03
Manual		1629 (62.4%)	980 (37.6%)	0.89	0.81-0.97	0.95	0.86-1.05
Unemployed		5321 (59.1%)	3676 (40.9%)	1.02	0.97-1.08	1.04	0.96-1.11
Non-classifiable		1840 (58.4%)	1308 (41.6%)	1.05	0.97-1.13	1.11	1.01-1.22
Nationality	60219						
Irish		28865 (60.3%)	19033 (39.7%)	1.00	-	1.00	-
Non-Irish		7740 (62.8%)	4581 (37.2%)	0.90	0.86-0.94	1.07	0.99-1.16
Region	60219						
Western Europe		30883 (60.2%)	20428 (39.8%)	1.00	-	1.00	-
Asia/Middle East		1536 (69.0%)	690 (31.0%)	0.68	0.62-0.74	0.74	0.65-0.84
Eastern Europe		1629 (68.0%)	766 (32.0%)	0.71	0.65-0.78	0.75	0.66-0.85
Africa		2202 (60.6%)	1429 (39.4%)	0.98	0.92-1.05	0.99	0.88-1.11
South America		93 (67.9%)	44 (32.1%)	0.72	0.50-1.02	0.63	0.42-0.94
North America		181 (49.9%)	182 (50.1%)	1.52	1.24-1.87	1.46	1.16-1.84
Australia & New Zealand		81 (51.9%)	75 (48.1%)	1.40	1.02-1.92	1.37	0.97-1.93
Marital Status	61083						
Married		24573 (62.0%)	15053 (38.0%)	1.00	-	1.00	-
Single		11994 (58.7%)	8431 (41.3%)	1.15	1.11-1.19	1.12	1.06-1.18
Multiple Pregnancy	61203						
No		36688 (60.9%)	23539 (39.1%)	1.00	-	1.00	-
Yes		526 (53.8%)	450 (46.1%)	1.33	1.17-1.51	1.28	1.11-1.48
Smoked During Pregnancy	61144						
No		29179 (61.7%)	18108 (38.3%)	1.00	-	1.00	-
Yes		7976 (57.6%)	5881 (42.4%)	1.19	1.14-1.24	1.11	1.06-1.17
Periconceptional Alcohol Use (units per week)	61099						
Never		7222 (62.7%)	4298 (37.3%)	1.00	-	1.00	-
Occasional		16389 (63.0%)	9597 (36.9%)	0.98	0.94-1.03	0.93	0.88-0.99
1 – 5		10096 (57.9%)	7328 (42.1%)	1.22	1.16-1.28	1.06	0.99-1.13
6 – 9		2683 (56.7%)	2050 (43.3%)	1.28	1.20-1.38	1.07	0.98-1.16
10 - 14		529 (51.1%)	506 (48.9%)	1.61	1.42-1.83	1.38	1.19-1.59
15 - 20		148 (51.4%)	140 (48.6%)	1.59	1.26-2.01	1.41	1.07-1.85
>20		51 (45.1%)	62 (54.9%)	2.04	1.41-2.97	1.60	1.04-2.45
Public Patient	61013						
No		8424 (53.9%)	7201 (46.1%)	1.00	-	1.00	-
Yes		28618 (63.1%)	16770 (36.9%)	0.69	0.66-0.71	0.57	0.55-0.60

* Adjusted for age at delivery, booking gestation, planning of pregnancy, occupational group, nationality, region, marital status, multiple pregnancy, smoking status, peri-conceptional alcohol consumption and receipt of private obstetric care

Table 3-4 Maternal Factors Associated with the Use of FDA Category D/X Medications (excluding oral contraceptives, infertility treatments and progestogens) among Women Reporting any Medication Use.

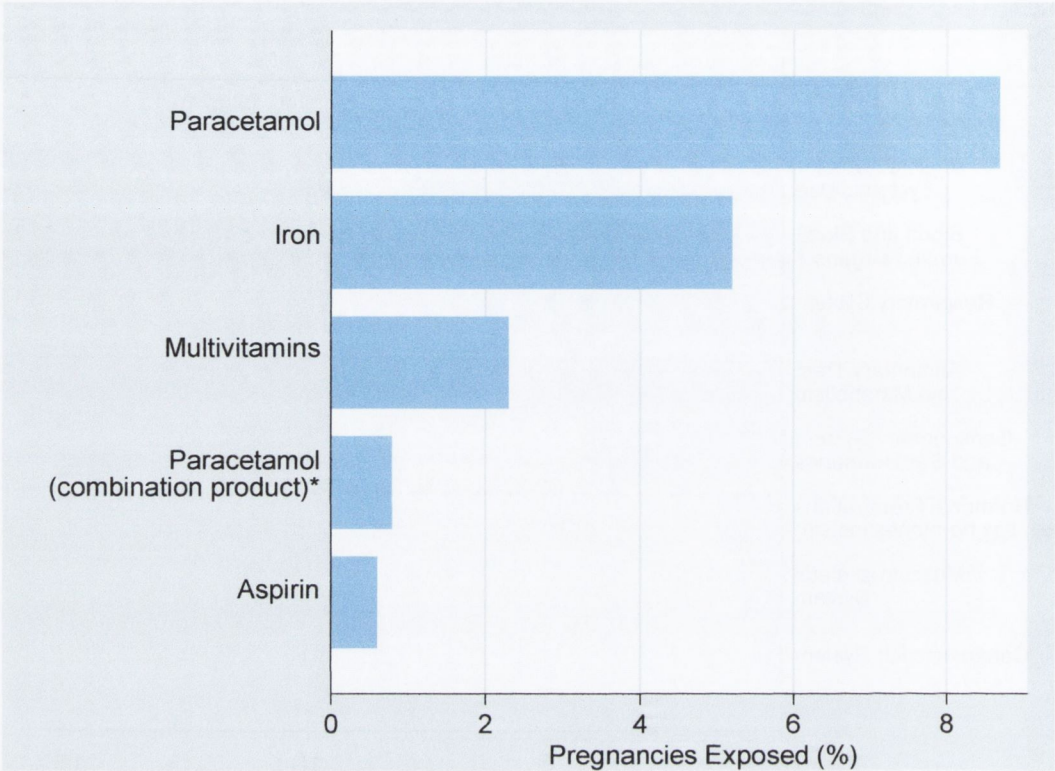
		No FDA D/X Medication Reported n=22466 (93.7%)	FDA D/X Medication Reported n=1523 (6.3%)	Odds Ratio	95% CI	Adj.* Odds Ratio	95% CI
n=23989							
Age at delivery (years)- mean (standard deviation)	23989	30.15 (5.90)	29.56 (5.87)				
Age at delivery	23989						
<20 years		1078 (94.9%)	58 (5.1%)	0.63	0.48-0.84	0.32	0.22-0.48
20-24 years		3206 (92.2%)	273 (7.8%)	1.00	0.86-1.17	0.66	0.53-0.82
25-29 years		5189 (92.2%)	441 (7.8%)	1.00	-	1.00	-
30-34 years		7397 (94.4%)	421 (5.4%)	0.67	0.58-0.77	0.95	0.80-1.13
35-39 years		4676 (94.7%)	264 (5.3%)	0.66	0.56-0.78	0.94	0.77-1.16
>40 years		920 (93.7%)	66 (6.7%)	0.84	0.65-1.10	1.13	0.82-1.57
Gestation at delivery (weeks)- mean (standard deviation)	20807	39.47 (2.43)	39.27 (3.07)				
Booking gestation (weeks)	20798						
< 12 weeks		3777 (92.1%)	326 (7.9%)	1.74	1.52-2.00	1.83	1.58-2.13
12 - 20 weeks		12642 (95.3%)	627 (4.7%)	1.00	-	1.00	-
> 20 weeks		3273 (95.5%)	153 (4.5%)	0.94	0.79-1.13	0.83	0.68-1.00
Nulliparous	23989						
No		13241 (93.6%)	912 (6.4%)	1.00	-	-	-
Yes		9225 (93.8%)	611 (6.2%)	0.96	0.87-1.07	-	-
Planned pregnancy	23915						
Planned		13734 (95.0%)	729 (5.0%)	1.00	-	1.00	-
Unplanned		8664 (91.7%)	788 (8.3%)	1.71	1.54-1.90	1.29	1.11-1.50
Socioeconomic group	23982						
Professional, Manager,							
Employer		5555 (95.9%)	239 (4.1%)	1.00	-	1.00	-
Home duties		4621 (94.8%)	256 (5.2%)	1.29	1.07-1.54	1.29	1.04-1.59
Non-Manual		6996 (95.2%)	351 (4.8%)	1.16	0.99-1.38	1.05	0.86-1.27
Manual		921 (94.0%)	59 (6.0%)	1.49	1.11-1.99	1.22	0.87-1.72
Unemployed		3160 (86.0%)	516 (14.0%)	3.79	3.23-4.45	2.35	1.85-2.98
Non-classifiable		1206 (92.2%)	102 (7.8%)	1.97	1.55-2.50	1.65	1.20-2.27
Nationality	23614						
Irish		17707 (93.0%)	1326 (7.0%)	1.00	-	1.00	-
Non-Irish		4423 (96.6%)	158 (3.4%)	0.48	0.40-0.56	0.79	0.56-1.06
Region	23614						
Western Europe		19018 (93.1%)	1410 (6.9%)	1.00	-	1.00	-
Asia/Middle East		676 (98.0%)	14 (2.0%)	0.28	0.16-0.47	0.38	0.20-0.72
Eastern Europe		747 (97.5%)	19 (2.5%)	0.34	0.22-0.54	0.40	0.22-0.74
Africa		1403 (98.2%)	26 (1.8%)	0.25	0.17-0.37	0.25	0.14-0.43
South America		42 (95.5%)	2 (4.5%)	0.64	0.16-2.66	0.54	0.07-4.09
North America		173 (95.1%)	9 (4.9%)	0.70	0.36-1.37	1.23	0.57-2.66
Australia & New Zealand		71 (94.7%)	4 (5.3%)	0.76	0.28-2.08	1.53	0.52-4.45
Marital Status	23936						
Married		14395 (95.6%)	658 (4.4%)	1.00	-	1.00	-
Single		7611 (90.3%)	820 (9.7%)	2.36	2.11-2.62	1.31	1.09-1.59
Multiple Pregnancy	23989						
No		22060 (93.7%)	1479 (6.3%)	1.00	-	1.00	-
Yes		406 (90.2%)	44 (9.8%)	1.62	1.18-2.22	2.17	1.47-3.20
Smoked During Pregnancy	23989						
No		17353 (95.8%)	755 (4.2%)	1.00	-	1.00	-
Yes		5113 (86.9%)	768 (13.1%)	3.45	3.11-3.84	1.89	1.62-2.21
Periconceptional Alcohol Use (units per week)	23981						
Never		3946 (91.8%)	352 (8.2%)	1.00	-	1.00	-
Occasional		8986 (93.6%)	611 (6.4%)	0.76	0.66-0.87	0.58	0.48-0.70
1 - 5		6948 (94.8%)	380 (5.2%)	0.61	0.53-0.71	0.49	0.40-0.59
6 - 9		1922 (93.8%)	128 (6.2%)	0.75	0.61-0.92	0.52	0.40-0.68
10 - 14		478 (94.5%)	28 (5.5%)	0.66	0.44-0.98	0.43	0.27-0.70
15 - 20		128 (91.4%)	12 (8.6%)	1.05	0.58-1.92	0.63	0.31-1.29
>20		50 (80.6%)	12 (19.4%)	2.69	1.42-5.09	1.10	0.47-2.57
Public Patient	23971						
No		6865 (95.3%)	336 (4.7%)	1.00	-	1.00	-
Yes		15583 (92.9%)	1187 (7.1%)	1.56	1.37-1.76	0.90	0.76-1.08

*Adjusted for age at delivery, booking gestation, planning of pregnancy, occupational group, nationality, region, marital status, multiple pregnancy, smoking status, peri-conceptional alcohol consumption and receipt of private obstetric care



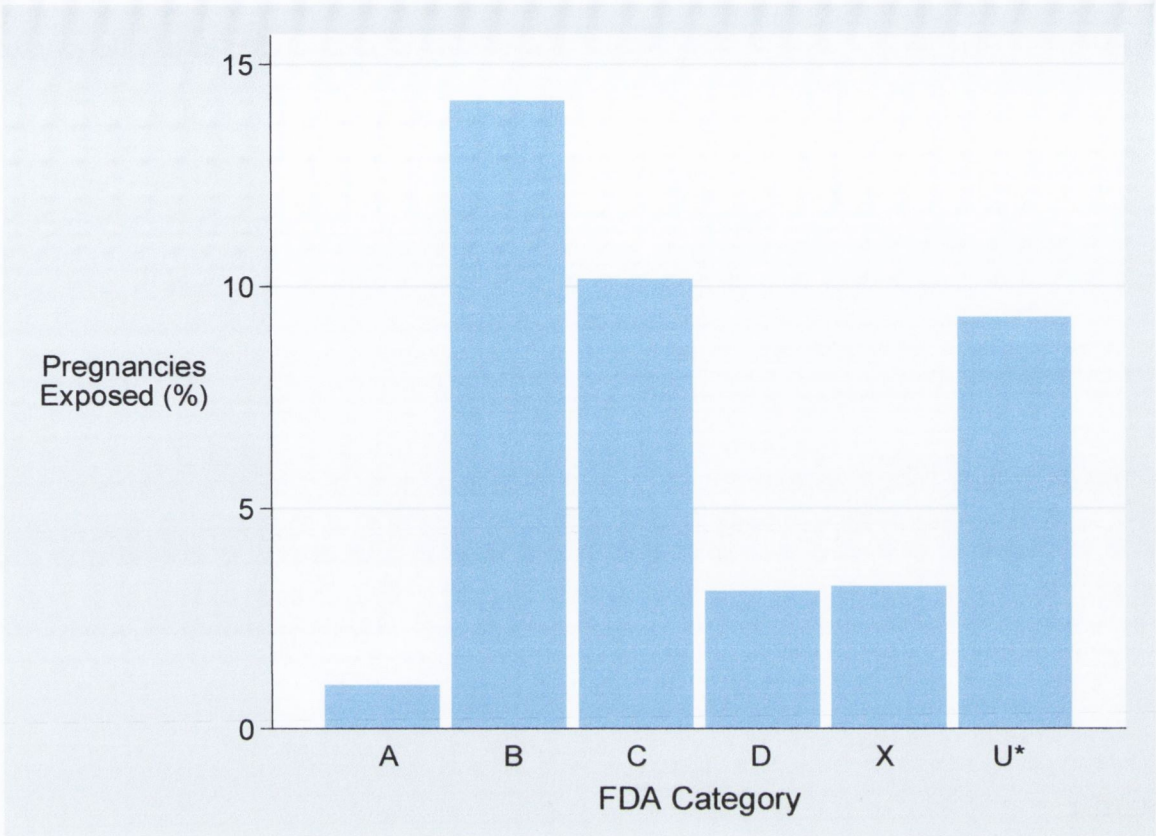
* Includes analgesics, psychotropics and antiepileptics
† Includes antianemic and antithrombotic agents

Figure 3-1 Most Commonly Reported Medications by WHO Anatomic Therapeutic Chemical Classification Level 1 Groups



*Includes combination analgesics with paracetamol, codeine and caffeine.

Figure 3-2 Most Commonly Reported Over the Counter Medications



*Medications not categorised under FDA system

Figure 3-3 Early Pregnancy Medication Use by FDA Pregnancy Category (excluding folic acid, vitamins and minerals)



Figure 3-3 Early Pregnancy Medication Use by FDA Pregnancy Category (excluding folic acid, vitamins and minerals)

CHAPTER 4. SYSTEMATIC REVIEW AND META- ANALYSIS: METHADONE DOSE AND NEONATAL ABSTINENCE SYNDROME

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4.1 Introduction

Methadone is a long-acting opioid which is the standard treatment for the management of opioid-dependent pregnant women.¹⁷⁵⁻¹⁷⁷ Compared with continued illicit drug use, methadone maintenance therapy during pregnancy has been associated with improved attendance at antenatal care, reduced maternal morbidity, and improved neonatal outcomes including higher birth weight.^{22 26 137}²¹⁰ Neonatal abstinence syndrome (NAS) is a potential consequence of maternal methadone maintenance therapy during pregnancy. NAS is characterised by central nervous system hyperirritability, respiratory distress, gastrointestinal dysfunction and autonomic symptoms.^{30 211} Although NAS is a treatable condition that can be managed with decreasing doses of oral morphine, it can lead to prolonged hospital stays for the infant and impaired maternal-infant bonding. Estimates of the incidence of NAS after exposure to methadone *in utero* vary between 13% and 94%.^{142 145-149}

There is a lack of clarity on the relationship between maternal methadone dose and NAS. Individual studies examining the impact of methadone dosage on NAS have had conflicting results. Some studies have reported a relationship between maternal methadone dose and the incidence, severity or duration of NAS^{27 33 34 36}^{140 148 155 156 186 212-222} and others have not.^{31 32 154 157 158 170 223-233} Few studies have examined the relationship between duration of methadone use and NAS,¹⁴⁹ though some examine cumulative methadone doses during pregnancy²³⁰ while others looked at mean methadone doses over the last trimester.^{234 158} Women and their physicians require information on the relationship between methadone dose and NAS to facilitate decision making about methadone dosage during

pregnancy. It should be noted that NAS is only one of many factors patients and their physicians need to consider when deciding on appropriate methadone doses. From a public health perspective, it is important to determine if there is a relationship between methadone dose and NAS. Some addiction services reduce methadone doses or detoxify women during pregnancy in the hope of preventing NAS. This could put the mother at risk of relapse of illicit drug use and its consequences. The alternative approach of increasing methadone doses to counteract alterations in methadone's pharmacokinetics in pregnancy may exacerbate the risk and severity of NAS. Clinical decisions regarding the need to increase or decrease methadone dosages during pregnancy are hampered by a lack of good quality data from randomised trials, due to the ethical challenges and practical constraints of conducting such research in this population. There are considerable difficulties in conducting randomised trials of different dosing strategies in this group of women. As a result, this systematic review primarily examined the evidence from observational studies which reported on cohorts of women who used methadone during pregnancy. Previous systematic reviews and meta-analyses in this setting have examined outcomes such as neonatal mortality²³⁵ and birth weight;¹³⁷ none have addressed the issue of methadone dose and NAS.

This systematic review and meta-analysis of the evidence available to 2009 aims to examine the impact of maternal methadone dose on the incidence of NAS in neonates of opioid-dependent pregnant women.

4.2 Methods

The review was carried out with a pre-specified protocol developed in accordance with guidelines for reviews of observational studies.^{236 237} Cohort studies and randomised controlled trials that reported on methadone use in opioid-dependent pregnant women and neonatal abstinence syndrome were included in the review. Studies were included in the systematic review if there was a description of maternal methadone dose during pregnancy along with the incidence of NAS. To be included in the meta-analyses, a study had to report the incidence of NAS for infants born to mothers in different methadone dosage bands. Studies using any scoring system or description of NAS were included. Studies were excluded if there was insufficient reporting of methadone dosages or outcomes related to NAS. Studies that focused solely on the management of a group of neonates diagnosed with NAS were excluded, as were reviews and studies that only reported on the use of agents other than methadone during pregnancy e.g. buprenorphine, slow release morphine and levomethadone. Case-control studies and case reports were also excluded, as lack of a denominator would not allow estimation of the incidence of NAS, a key outcome of the systematic review..

4.2.1 Search strategy

The following databases were searched: MEDLINE (1966 to August 2009) using Pubmed, the Cochrane Library (2009, Issue 1), EMBASE (1974 to January 2009) and PsychINFO (1967 to January 2009). The MEDLINE and EMBASE search strategies are included in Appendix I. These were developed by an iterative process with advice from a medical librarian. There was no systematic search of the grey literature, however reference lists of relevant studies and review articles

were reviewed by one author (BC) to locate further eligible studies. Articles published in languages other than English were reviewed for relevance by their English titles or abstracts, and translations were sought where necessary.

Title and abstracts were independently screened by two reviewers (BC, JD). Full text versions of all potentially relevant studies and those that could not be excluded on the basis of title or abstract were retrieved to determine final inclusion in the review. Two reviewers (BC, JD) independently assessed full text versions of the studies to decide whether the studies met the inclusion criteria. After application of the inclusion criteria and removal of duplicate studies, there were disagreements on inclusion or exclusion for four out of 98 studies (4%). Disagreements were resolved by discussion.

4.2.2 Data extraction and quality assessment

A data extraction form was piloted on five randomly selected studies. One author (BC) used this form to extract data and conduct a quality assessment of all included studies. Data extraction sought information on study location, when published, participants, design, aims, inclusion and exclusion criteria, setting, methadone dose, illicit drug use, NAS outcomes (incidence, severity and duration) and key conclusions. In the absence of a single, accepted tool for assessing the quality of observational epidemiological studies,²³⁸ the degree of compliance with a modified version of the US Agency for Healthcare Research and Quality's 'Systems to Rate the Strength of Scientific Evidence' was used.²³⁹ This checklist was selected as it complied with the broad recommendations made by Sanderson *et al*: it focused on a small number of key domains, it was as specific as possible for observational studies (which constitute the vast majority of studies in this topic

area), it was a simple checklist rather than a scale, and it was carefully developed by a respected agency.²³⁸ This checklist had seven questions to assess whether there was a clearly focused research question; if study populations, exposures and outcomes were clearly defined; if confounding was assessed; if outcomes were measured appropriately; and if the conclusions of the study were supported by the results. Quality assessment was not possible for translated studies due to time constraints. A second author (JD) extracted data required for the meta-analysis in duplicate, this included study design, methadone doses and NAS outcomes.

The authors of 17 studies published in the last 10 years were contacted by email to seek the additional information on methadone dosage and medically treated NAS, which was needed for the meta-analysis. Six authors responded, providing data on nine studies.

4.2.3 Data synthesis and analysis

NAS outcomes selected *a priori* for analysis in the review included the incidence, severity and duration of NAS. Studies that reported the number of cases of diagnosed/medically treated NAS for different maternal methadone dosage bands were included in the meta-analyses, which were done using The Cochrane Collaboration's RevMan 5 software.²⁴⁰ Comparisons of the incidence of diagnosed/medically treated NAS in infants of women on methadone doses above and below a range of cut-off doses were carried out. Initially, a single comparison of the incidence of NAS above and below just one commonly reported cut-off dose was planned. However, methadone doses varied considerably among included studies and in order to compare the incidence of NAS across a wide range of methadone doses, comparisons of the incidence of NAS above and below the

following commonly reported dosages were carried out: 20mg, 30mg, 40mg, 50mg, 80mg, and 110mg. Some studies provided data for more than one comparison. Data are reported as relative risks for the dichotomous outcome of diagnosed/medically treated NAS with 95% confidence intervals. Data were pooled using a random effects model in RevMan 5. A random effects model was chosen to allow for variability of results between studies given the anticipated heterogeneity of research in this context.

The I^2 statistic was used to describe the percentage of variability in the effect estimates that can be attributed to heterogeneity rather than chance.²⁴¹ Heterogeneity refers to variation in effect estimates arising from methodological or clinical differences between studies. Pre-planned sensitivity analyses included examining the effects of methadone dose on the incidence of NAS in prospective studies only and in those studies that used an objective scoring system for the diagnosis of NAS. These features were used as proxy indicators of study quality and risk of bias. Sensitivity analyses give an indication of the way in which certain types of study affect the results of the meta-analysis by repeating the analysis including only a specific category of study.²³⁷ A sensitivity analysis was also carried out to examine the effect of including each study in only one comparison, which was chosen as the one in which approximately half the neonates were exposed to lower and higher dosages e.g. a study which was included in both the $\leq 20\text{mg}$ versus $>20\text{mg}$ and $\leq 40\text{mg}$ versus $>40\text{mg}$ comparisons, would only be included in the comparison where approximately half the study population were in the lower dose group and half in the higher dose group. Funnel plots were assessed visually to explore the possibility of publication bias or other biases

related to study size. Stata IC (StataCorp. 2001. Statistical Software: Release 10.1. College Station, TX: Stata Corporation) was used to carry out independent samples t-tests or Mann-Whitney U tests comparing mean methadone dosage and the median number of neonates in studies reporting and not reporting a relationship between methadone dose and NAS. The Stata *metareg* function was used to carry out random effects metaregression examining the relationship between mean study methadone dose and incidence of diagnosed/treated NAS.

4.3 Results

4.3.1 Study characteristics and quality

The flow of information through the phases of the review is described in Figure 4-1. Of the 67 studies that met the inclusion criteria for the systematic review, 28 were retrospective cohort studies, 37 were prospective cohort studies and two were randomised trials. Twenty seven studies were from Europe, 37 from the US and three from New Zealand or Australia.

The most consistently reported outcome was the incidence of NAS, most commonly reported as the proportion of exposed neonates who were medically treated for NAS. Comparison of the severity of NAS between studies was complicated by inconsistent measurement and reporting of NAS across the included studies. Similarly, comparison of the duration of NAS was not attempted due to varied approaches to measurement including: duration in NICU, duration in hospital, duration of treatment and duration of NAS score above a cut-off value. Differing local treatment protocols, policies for retaining neonates in hospital to monitor for NAS and varying approaches to discharging neonates on treatment further complicated interpretation and comparison of results. As a result of these

difficulties, qualitative and quantitative analysis was restricted to the incidence of NAS in the included studies. Table 4-1 describes the incidence of NAS and provides an overview of included studies.

The studies varied in their reporting of NAS. Some reported the number of neonates diagnosed with NAS, while others reported the number medically treated for NAS. Diagnostic criteria for NAS varied over time and geographically, with some version of the Finnegan Neonatal Abstinence Score being the most commonly used objective scoring system. Thresholds for the medical treatment of NAS varied between studies, as did NAS treatment protocols.

Most studies reported a clearly focused objective (40/62, 64.5%) and adequately described the study population (45/62, 72.6%), and exposure to methadone and other substances (42/62, 67.7%). Some studies did not clearly define NAS (27/62, 43.5%). It was rare for the study analysis to include an assessment of the effect of potentially confounding factors on NAS, with few studies attempting to adjust for the effect of concomitant illicit drug use, smoking, use of prescribed medication or gestation at delivery.^{36 225 227 228 230 242} Diagnosis of NAS was potentially biased by knowledge of the maternal methadone dose and drug use history in the majority of studies, as only three reported blinded assessment of NAS.^{172 173 188} The findings of the quality assessment of the included studies are summarised in Appendix II.

4.3.2 *Methadone dose and relationship with NAS*

Sixty seven studies including 5139 neonates exposed to methadone in pregnancy reported on the incidence of NAS. The results of these studies are summarised in Table 4-1. Most studies reported the number of infants treated, but some reported

the number diagnosed with NAS, without mentioning whether pharmacological treatment was used. Based on the overall incidence in studies which used an objective scoring system, the incidence of medically treated NAS varied from approximately 45% to 97%.^{173 213} Diagnostic criteria for NAS were not clearly reported in 24 studies. The remainder used a modified form of the Finnegan scoring system,²⁴³ the Lipsitz tool,²⁴⁴ the Rivers score²⁴⁵ or the Neonatal Narcotic Withdrawal Index.²⁴⁶

Of the 67 studies included in the systematic review, 19 found that there was a relationship between the methadone dose and the incidence, severity or duration of NAS^{27 33 34 36 140 148 155 156 186 212-219 221 222} and 18 did not find such a relationship.

^{31 32 141 154 157 158 170 223-233} The remaining 30 studies did not report on the relationship between methadone dose and NAS, but did provide information on mean methadone dose and overall incidence of NAS. The size of the study did not seem to affect the results. There was no statistically significant difference in the median number of methadone-exposed neonates in studies that found no relationship (70, IQR 40-92) and those that reported a relationship (66.5, IQR 26-100), $p=0.60$. The mean methadone dose was reported for eight of the studies that found a relationship and 13 of the studies that did not. The mean methadone dose across these studies appeared higher in those that did not report a relationship (64.6mg, SD 30.1) compared with studies that did (39.4mg, SD 25.2), $p=0.06$.

The meta-analysis included data from 20 studies which provided information on the incidence of NAS (diagnosed/treated) in different dosage bands.^{25 36 148 155 156}

^{158 186 188 214-216 218 222 231-233 247-251} Nine further studies could be included in the meta-analysis after study authors responded to a request for information on the

incidence of NAS in the relevant dosage bands.^{142 157 170 173 223-225 242 252} In total, 29 studies were included in the meta-analysis. The remaining studies reported the overall incidence of NAS and mean methadone dose rather than the incidence in different dosage bands (see Table 4-1). Comparisons of the incidence of NAS in neonates of women in lower and higher methadone dosage groups using a range of cut-off points showed that there was no statistically significant difference in the incidence of NAS between lower and higher dosage groups with the exception of the comparisons of $\leq 20\text{mg}$ versus $>20\text{mg}$ and $\leq 40\text{mg}$ versus $>40\text{mg}$, when all studies were included in the comparison: relative risk (RR) 0.52 (95% confidence interval (CI) 0.33 to 0.81) from 10 studies with 558 neonates, and RR 0.69 (95% CI 0.51 to 0.94) from 9 studies with 773 neonates, respectively. These relative risks correspond to a 48% relative risk reduction with doses at or below 20mg compared doses above 20 mg (risk reduced from 0.56 to 0.27), and a 31% relative risk reduction with doses at or below 40mg compared to doses above 40 mg (risk reduced from 0.73 to 0.43). Figure 4-2 summarises the relative risk of NAS in lower versus higher methadone dosage groups using the range of cutoff points. For illustrative purposes Figure 4-3 is a Forest plot displaying the results of one of the comparisons of the incidence of NAS in neonates exposed to doses above and below 50mg. The individual point estimates indicate the relative risk of NAS in the low dose group compared to the high dose group in each of the included studies. The diamond represents the final pooled estimate indicating that there is no significant difference in the incidence of NAS in neonates exposed to doses of 50mg or less compared to those exposed to greater than 50mg. The Forest plot displays the results for one of the *a priori* sensitivity analyses of prospective

studies only. The results for all comparisons and the sensitivity analyses are shown in Appendix III.

Pre-specified sensitivity analyses examined the RR of NAS when limited to prospective studies only and studies which reported using an objective scoring system to diagnose NAS. When only prospective studies were included in the analyses, there was no statistically significant difference in the incidence of NAS between lower and higher methadone dosage groups. By limiting to studies using an objective scoring system for the diagnosis of NAS, there was also no statistically significant difference in the incidence of NAS in neonates of women in any of the lower versus higher methadone dosage comparisons. Studies could be included in more than one comparison where they reported the incidence of NAS for multiple relevant dose bands. When individual studies were included in one comparison only (i.e. the one which split their data into roughly equal numbers of neonates in the lower and higher dosage groups), the RRs were only marginally different from those in the reported analyses (data not shown). The graphs produced by three metaregression analyses examining the relationship between mean study methadone dose and incidence of diagnosed/treated NAS in all studies, prospective studies only and studies using an objective scoring system for the diagnosis of NAS are included in Appendix IV.

There was substantial heterogeneity for most of the comparisons when all of the studies were included in the meta-analysis with many comparisons having I^2 scores above 60%. The preplanned sensitivity analyses reduced this in some cases, but substantial heterogeneity still remained in most of the comparisons.

There was no marked evidence of publication, or small study bias in funnel plots for any of the comparisons.

4.4 Discussion

This systematic review and meta-analysis does not demonstrate a consistent, statistically significant difference in the incidence of NAS among neonates of women maintained on low versus high methadone doses at delivery. There was a statistically significant difference in the incidence of NAS in neonates born to women on methadone doses above and below 20mg and 40mg, but these differences lose statistical significance when the analyses are restricted to prospective studies only or to studies using an objective scoring system to diagnose NAS.

There have been conflicting findings on the relationship between the maternal methadone dose and the development of an abstinence syndrome in the neonate since the beginnings of methadone use in pregnancy in the late 1960s and early 1970s.^{24 253} As early as 1973, there were reports of differing approaches to the prescribing of methadone during pregnancy. Some centres used high dose maintenance of up to 160mg and others reduced the methadone dose in late pregnancy, in an attempt to moderate withdrawal signs in the neonate.²⁵⁴ Since then, many studies have reported on the relationship between methadone use in pregnancy and NAS. Some have suggested that the incidence of NAS was related to the maternal methadone dose^{27 33 34 36 140 148 155 156 186 212-222} while others found no such relationship.^{31 32 141 154 157 158 170 223-233} As a result, differing approaches to the management of opioid-dependent pregnant women persist, with some authors advocating increasing methadone dosages to counter the changes in methadone's

pharmacokinetics in pregnancy^{118 255} and minimise the risk of relapse into illicit drug use. Others call for methadone doses to be kept low (for example, below 20mg^{34 188}) or detoxification³⁸ in order to decrease the risk of NAS. There have also been proposals to use the lowest dose of methadone compatible with stability³⁶ or lowering doses from any level in motivated patients, to reduce the incidence and duration of NAS.¹⁵⁶ Australian guidelines recommend dose titration to a level that relieves withdrawal symptoms and blocks heroin use, specifically warning against the practise of using lower doses in order to reduce the risk of NAS.¹⁷⁷ UK guidelines also recommend a maintenance dose that stops or minimises illicit drug use, with dose increases if necessary to achieve this, while acknowledging that many women may request detoxification during pregnancy and providing guidance on dose reduction.¹⁷⁶

Three Cochrane Reviews relate to opioid use in pregnant women, two focus on pharmacological interventions for NAS and one examines the use of pharmacological interventions for opioid-dependent pregnant women.²⁵⁶⁻²⁵⁸ There are also several narrative reviews which address the management of opioid-dependent pregnant women.²⁵⁹⁻²⁶¹ Two meta-analyses have been carried out to examine the relationship between opioid use during pregnancy and birth weight/neonatal death.^{137 235} However, this appears to be the first systematic review or meta-analysis to address the dose-response relationship between methadone and NAS. Whether or not this relationship exists and the strength of the relationship is important to opioid-dependent pregnant women and their clinicians, as it offers an opportunity to decrease the incidence of this condition in motivated, stable patients. If there is no such relationship, then efforts to reduce

the incidence of NAS by decreasing methadone doses or attempting to detoxify opioid-dependent women may be ineffective or counterproductive, if the woman relapses to illicit drug use. Continued illicit drug use in pregnancy can increase the risk of preterm birth and growth restriction, both of which are associated with long-term irreversible adverse effects. NAS is a short-term condition which can be effectively managed with oral morphine. It is important not to consider NAS as the only factor influencing methadone dosage decisions during pregnancy. Relief of maternal withdrawal symptoms and blockage of further opioid use are of primary importance. NAS is only one of many factors patients and their clinicians need to consider when making decisions on methadone maintenance treatment during pregnancy.

The significant heterogeneity evident across the studies included in the systematic review and meta-analysis is an indication of the varying approaches to the management of opioid-dependent pregnant women and their infants, and the assessment of NAS. The heterogeneity may also be explained by significant differences in the populations of pregnant women in the included studies, with geographical diversity, varying addiction histories, rates of concomitant illicit drug use, cigarette smoking, prescribed medication use and delivery gestations. It was deemed reasonable to carry out a meta-analysis despite the substantial degree of heterogeneity in the included studies in order to give some quantitative indication of whether methadone dose affected the incidence of NAS. The metaregression graphs (see Appendix IV) demonstrate the wide variability in the results of the included studies. This heterogeneity meant that any attempt to generate a regression line from the data would be imprudent. Variable reporting of factors that

may be important confounders of the relationship between methadone dose and NAS made it difficult to account for these factors in meta-analyses. The meta-analysis has been hampered by the varying definitions of NAS used in different studies. It is also possible that biases inherent in observational research with unblinded assessment of outcomes, may have affected the overall conclusions. For these reasons, the results of the meta-analysis should be regarded as hypothesis generating, requiring further testing in adequately designed future studies. Although a randomised controlled trial could be used to assess the relationship between methadone dose and NAS minimising the risk of bias, there would be ethical and practical difficulties in randomising women to low or high dose methadone maintenance. An alternative approach could be a large prospective cohort study with careful, objective measurement of all potential confounders and blinded assessment of outcomes related to NAS to determine if methadone dose is an independent predictor of the occurrence of NAS.

A true dose-response effect of methadone on the incidence of NAS may have been missed in the meta-analyses as many of the included studies were inadequately powered to detect clinically significant differences in the incidence of NAS between infants of women in different methadone dosage groups. If more data were available for a planned future update of this review, it may be possible to determine if there is no association between methadone dose and NAS or if a true association was missed in this meta-analysis due to insufficient data. The power of studies included in the meta-analysis to detect a clinically significant increase in the risk of NAS in higher compared with lower dose groups can be estimated by making assumptions about what would constitute a clinically

significant increase in the risk and what the baseline risk of NAS would be in the low dose group. Of the 29 included studies, only 7 had at least 80% power to detect an increased incidence of NAS with a RR of 1.75, assuming an incidence of 40% in the low dose group, an α of 0.05 and equal distribution of women between the low and high dosage groups. The RR of 1.75 was selected, as it constitutes an increased risk of NAS that is large enough to be clinically relevant, but that is not so small that it would be undetectable in all but the largest of studies. An incidence of NAS of 40% in a low dose group was selected as it is in line with studies in this review that reported the incidence for women on methadone doses under 40mg.³⁶

155 186 214

Among large studies with sufficient power to detect differences in the incidence of NAS there were also conflicting findings.^{36 225} Studies which did not demonstrate a dose-response relationship between methadone and NAS appeared to have higher mean methadone doses than those that did. This may be suggestive of a ceiling effect, with studies that have high mean doses less likely to detect an effect of methadone dose on NAS than low dose studies which appeared more likely to show a dose-response effect. Comparisons of methadone doses across these studies were restricted by limited reporting of mean methadone doses.

4.5 Conclusions

This systematic review and meta-analysis has not found a consistent statistically significant difference in the incidence of NAS in infants of opioid-dependent pregnant women maintained on differing doses of methadone. There did appear to be some differences in the incidence of NAS between infants exposed to lower and higher methadone doses; however these differences became statistically non-

significant in analyses restricted to prospective studies or studies using an objective scoring system. Methadone dose is but one factor in a complex array that may affect the incidence of NAS. Further adequately designed studies are required to investigate all the potential determinants of NAS. If methadone dose is confirmed to be an important determinant of NAS in adequately designed future research, there may be a role for targeted careful reduction of methadone dose in motivated, stable women with adequate monitoring of maternal and fetal wellbeing. Risk of NAS is not the only factor to consider in clinical decisions regarding methadone dosage during pregnancy, control of maternal withdrawal symptoms and maintenance of stability should take precedence. The injudicious lowering of methadone doses in the hope that this will decrease the risk of NAS could be counterproductive.

Table 4-1 Summary of Included Studies and Incidence of NAS

Study	Study design	No. neonates	Methadone dose at delivery/last trimester (mean/categories)	Diagnostic criteria	NAS treated
Arlettaz ¹⁵⁵ 2005, Switzerland, Zurich	Prospective Cohort	86	<30mg 51.9% 30-80mg 29.9% >80mg 18.2% Overall 40.9 ± 32.7mg	Finnegan score	<30mg 42.5% 30-80mg 65.2% >80mg 100% Overall 62%
Bakstad ²²⁴ 2009, Norway, Multicentre	Prospective Cohort	26	90 ± 58.6mg	Finnegan score	≤80mg 58.3% >80mg 61.5% Overall 57.7%
Berghella ¹⁵⁸ 2003, US, Philadelphia	Retrospective Cohort	100	<80mg 39% (mean 52.7 ± 14.7mg) ≥80mg 61% (mean 101.6 ± 28.5mg) Overall 95.8 ± 36.7mg	Finnegan score	<80mg 74.3% ≥80mg 62.3% Overall 67%
Blaser ²⁴⁷ 2008, Germany, Leipzig	Retrospective Cohort	28	21.5mg (median) ≤20mg 42.8% >20mg 57.2%	Finnegan score	≤20mg 75% >20mg 87.5% Overall 82.1%
Blinick ²⁶² 1975, US, New York	Prospective Cohort	10	67 ± 29.8mg (10-100)	Other Scoring System	100% some withdrawal signs
Brown ²⁴⁸ 1998, US, Indianapolis	Retrospective Cohort	32	<50mg 40.6% ≥50mg 59.4%	Not Clearly Defined	<50mg 61.5%* ≥50mg 79%*
Brulet ²⁶³ 2007, France, Montpellier	Prospective Cohort	26	99.4mg (15-500)	Not Clearly Defined	80.8%
Chasnoff ²⁶⁴ 1984, US, Chicago	Retrospective Cohort	51	15.9 ± 10.4mg (5-140)	Not Clearly Defined	23.5%
Choo ²⁴² 2004, US, Baltimore	Prospective Cohort	29	Light smokers 75.6 ± 22.9mg Heavy smokers 78.8 ± 14.9mg	Finnegan score	Light smokers 12.5% Heavy smokers 23%
Dashe ²¹⁴ 2002, US, Dallas	Retrospective Cohort	70	<20mg 35.7% 20-39mg 35.7% ≥40mg/d 28.5%	Finnegan score	<20mg 12% 20-39mg 44% ≥40mg/d 90%
Davis ²⁹ 1973, US, Washington	Retrospective Cohort	49	≤50mg 63.3% ≥60mg 36.7%	Other Scoring System	≤50mg 41.9% ≥60mg 55.6%

Study	Study design	No. neonates	Methadone dose at delivery/last trimester (mean/categories)	Diagnostic criteria	NAS treated
Davis ²²² 1975, US, Chicago	Retrospective Cohort	82	<20mg 21.2% 21-40mg 41.2% >40mg 37.6% Overall 35.7mg	Not Clearly Defined	≤20mg 22.2% 21-40mg 57.1% >40mg 62.5% Overall 53.7%
Dawe ¹⁴⁰ 1992, UK, London	Retrospective Cohort	34	22 ± 17mg	Not Clearly Defined	43%
Doberczak ¹⁴⁵ 1991, US, New York	Prospective Cohort	212	Term 49.7 ± 23.3mg Preterm 50.1 ± 18.3mg	Lipsitz score	Term 81% Preterm 58%
Doberczak ²³⁴ 1993, US, New York	Prospective Cohort	21	47 ± 16mg	Lipsitz score	80.9%
Dryden ³⁶ 2009, Scotland, Glasgow	Retrospective Cohort	444	1-29mg 22% 30-59mg 37.6% 60-89mg 30.6% ≥90mg 9.8% Overall median 50mg (5-150mg)	Lipsitz score	1-29mg 33% 30-59mg 45.2% 60-89mg 46.7% ≥90mg 74.4% Overall 45.8%
Ebner ²²⁸ 2007, Austria, Vienna	Prospective Cohort	22	NR	Finnegan score	68.2%
Fajemirokun ²⁶⁵ 2006, UK, Hull	Retrospective Cohort	54	32 ± 20.2mg	Rivers score	63%
Finnegan ²⁶ 1978, US, Philadelphia	Retrospective Cohort	243	Poor ANC 26.7mg Good ANC 29.8mg	Finnegan score	Poor ANC 53.7% Good ANC 60.5%
Fischer ¹⁷² 2006, Austria, Vienna	Randomised Trial	6	52.5mg	Finnegan score	50%
Fundaro ²¹⁹ 1994, Italy, Rome	Retrospective Cohort	162	Methadone 25mg (3-80) Methadone & Heroin 35mg (5-150)	Finnegan score	Methadone 33%* Methadone & Heroin 83.9%*
Geistlich ²²⁹ 1999, Switzerland, Zurich	Retrospective Cohort	26	41.2mg (8-120)	Not Clearly Defined	31%
Green ²⁶⁶ 1979, US, New York	Retrospective Cohort	87	<20mg 59.8% 25-40mg 34.3% >45mg 5.9%	Green Neonatal Narcotic Withdrawal Index	73% diagnosed/18.4% treated

Study	Study design	No. neonates	Methadone dose at delivery/last trimester (mean/categories)	Diagnostic criteria	NAS treated
Hagopian ²³⁰ 1996, US, Detroit	Retrospective Cohort	172	30.7mg ± 10.6	Other Scoring System	98.3% diagnosed with withdrawal Mild 11.6% Moderate 57.6% Severe 29.1%
Harper ²⁶⁷ 1974, US, New York	Prospective Cohort	48	≤30mg 8.8% 31-60mg 62.2% 61-90mg 24.4% 91-120mg 4.4%	Other Scoring System	No withdrawal 6.2% Mild 22.9% Moderate 33.3% Serious 31.2% Severe 6.2%
Harper ³³ 1977, US, New York	Prospective Cohort	22	27mg ± 15.9	Not Clearly Defined	100% treated Mild 18.2% Moderate 50% Serious 22.7% Severe 4.5%
Heiman ²¹³ 2006, Germany, Aachen	Retrospective Cohort	34	40mg (10-50)	Finnegan score	97%
Jansson ¹⁵⁷ 2007, US, Baltimore	Prospective Cohort	50	79.1 ± 17.1mg	Finnegan score	≤80mg 60.7% >80mg 31.8% Overall 48%
Jansson ²⁵⁰ 2008, US, Baltimore	Prospective Cohort	16	71.9 ± 15.3mg	Not Clearly Defined	Overall 31.2%
Jansson ²⁵² 2009, US, Baltimore	Prospective Cohort	40	72.9 ± 19.6mg	Finnegan score	≤80mg 76% >80mg 57.1% 67.5%
Johnson ²⁶⁸ 2003, UK, London	Retrospective Cohort	31	NR	Rivers score	93.5%
Jones ¹⁷³ 2005, Baltimore	Randomised Trial	11	79.1 ± 20.3mg	Finnegan score	≤80mg 33.3% >80mg 60.0% Overall 45.4%

Study	Study design	No. neonates	Methadone dose at delivery/last trimester (mean/categories)	Diagnostic criteria	NAS treated
Jones ¹⁴² 2008, US, Baltimore	Retrospective Cohort	80	3 day MAW & maintenance 10% (mean 58.1mg) 7 day MAW & maintenance 25% (mean 54.8mg) Maintenance only 65% (mean 61.9mg)	Not Clearly Defined	Maintenance only: ≤60mg 31.0% >60mg 21.7% Overall 26.9%
Kakko ²⁶⁹ 2008, Sweden, Stockholm	Retrospective Cohort	36	71.3 ± 27.3mg	Finnegan score-most	77.8% diagnosed/52.8% treated
Kandall ³² 1977, US, New York	Retrospective Cohort	145	NR	Not Clearly Defined	Methadone 77% Heroin-methadone 68%
Kandall ²⁷⁰ 1983, US, New York	Prospective Cohort	153	Treated for NAS 49.8 ± 25.3mg Not treated 29.2 ± 22.8mg	Lipsitz score	72.5%
Kuschel ²²³ 2004, New Zealand, Auckland	Prospective Cohort	25	57 ± 28.5mg (15-105)	Finnegan score	≤50mg 63.6% >50mg 35.7% Overall 48%
Lejeune ¹⁷⁰ 2006, France- 35 centers	Prospective Cohort	100	57 ± 30.4mg	Lipsitz score	≤60mg 40.7% >60mg 60.0% Overall 49%
Lim ¹⁵⁶ 2009, US, Ohio	Retrospective Cohort	66	≤70mg 34.8% (Mean 40.7 ± 17.4mg) 71-139mg 39.4% (Mean 106.7 ± 15.2mg) ≥140mg 25.7% (Mean 159.1 ± 25.2mg) Overall 97.2 ± 49.8mg	Finnegan score	≤70mg 65.2% 71-139mg 73.1% ≥ 140mg 100% Overall 77.3%
Llewelyn ²¹⁵ 1997, UK, Swansea	Prospective Cohort	55	≤30mg 50.9% (Mean 27.5mg) 30-60mg 49.1% (Mean 54mg)	Not Clearly Defined	≤30mg 21% 30-60mg 67%
Mack ²³² 1991, Westmead, Australia	Prospective Cohort	20	≤40mg 50% >40mg 50% Overall 42.4 ± 14.1mg (25-60)	Finnegan score	≤40mg 80% >40mg 60% Overall 70%
Madden ¹⁴⁸ 1977, US, Chicago	Retrospective Cohort	92	≤20mg 25.6% >20mg 74.4%	Not Clearly Defined	≤20mg 17.9% >20mg 62.5%

Study	Study design	No. neonates	Methadone dose at delivery/last trimester (mean/categories)	Diagnostic criteria	NAS treated
Malpas ²¹⁸ 1995, New Zealand, Christchurch	Retrospective Cohort	40	≤10mg 37.5% 11-20mg 47.5% ≥21mg 15% Overall mean 15.4mg	Finnegan score	≤10mg 20.0% 11-20mg 52.6% ≥21mg 66.7%
Mayes ²¹⁷ 1996, US, Connecticut	Retrospective Cohort	68	Methadone only 45.3 ± 12.4mg Methadone & cocaine 43.8 ± 14.3mg	Finnegan score	77.9%
Mayet ²²⁶ 2008, UK, London	Retrospective Cohort	54	37.7 ± 20.3mg	Not Clearly Defined	25.9%
McCarthy ¹⁴¹ 2005, US, Sacramento	Retrospective Cohort	81	<100mg 44.4% (Mean 62 ± 24.3mg) ≥ 100mg 55.6% (Mean 132 ± 24.1mg) Overall 101 ± 42.4mg (14-190)	Finnegan score	<100mg 49% ≥100mg 51% Overall 45.7%
Miles ²²⁷ 2007, UK, Manchester	Retrospective Cohort	176	Pre-DLM 21.5mg Post-DLM 40mg	Other Scoring System	Pre-DLM 79.5% Post-DLM 14.3%
Morrison ²⁷¹ 1995, UK, Liverpool	Retrospective Cohort	61	Treated for NAS 42.3 ± 16.9mg Not treated 31.6 ± 13.8mg Overall 34.6 ± 13.6mg (0-70)	Not Clearly Defined	18%
Newman ²⁵ 1975, US, New York	Retrospective Cohort	313	<40mg 14% 40-60mg 40% 70-90mg 23% 100mg 15% >100mg 9%	Not Clear	<40mg 71%* 40-60mg 77%* 70-90mg 81%* 100mg 81%* >100mg 85%*
Offidani ²⁷² 1986, Italy, Rome	Prospective Cohort	9	29.4mg ± 21.8	Not Clearly Defined	100%
Ostrea ³⁴ 1976, US Detroit	Prospective Cohort	95	Mild NAS 11.9 ± 6.94mg Moderate/severe NAS 18.7 ± 11.68mg	Other Scoring System	100%* Mild 67% Moderate 27% Severe 6%
Rohrmeister ²⁷³ 2001, Austria, Vienna	Prospective Cohort	42	45 ± 25mg (5-95)	Finnegan score	76.2%

Study	Study design	No. neonates	Methadone dose at delivery/last trimester (mean/categories)	Diagnostic criteria	NAS treated
Rosen ³¹ 1975, US, New York	Prospective Cohort	29	38.1 ± 3.9mg	Not Clear	86.2%* Mild 17% Moderate 48% Severe 21%
Rosen ²⁷⁴ 1985, US, New York	Prospective Cohort	61	42 ± 3mg	Finnegan score	75%*
Scott ²⁷⁵ 1973, US, Albuquerque	Retrospective Cohort	24	60mg	Not Clearly Defined	41.7%
Scully ¹⁸⁶ 2004, Ireland, Dublin	Retrospective Cohort	85	5-30mg 34.1% 31-50mg 32.9% 51-95mg 32.9% Overall 39.3 ± 23.8mg	Finnegan score	5-30mg 27.6% 31-50mg 42.8% 51-95mg 71.4% Overall 47%*
Seligman ²²⁵ 2008, US, Philadelphia	Retrospective Cohort	303	≤50mg 7.4% 51-100mg 29.9% 101-150mg 35.3% 150-200mg 18.6% >200mg 8.8% Overall mean 124.5 ± 51.5mg	Finnegan score	≤80mg 65.7% >80mg 68.7% Overall 67.9%
Serane ²¹² 2008, Scotland, Greenock	Retrospective Cohort	32	NR	Finnegan score	<20mg 20% ≥20mg 100% Overall 87.5%
Shaw ²³¹ 1994, UK, Liverpool	Retrospective Cohort	32	35mg (5-80)(median)	Not Clearly Defined	≤20mg 25% >20mg 41.7% Overall 37%
Sinha ²¹⁵ 2001, UK, Hull	Retrospective Cohort	22	<20mg 36.4% 20-40mg 45.4% >40mg 18.2%	Rivers score	<20mg 13% 20-40mg 30% >40mg 75%
Statzer ¹⁵⁴ 1972, US, Detroit	Retrospective Cohort	90	45mg (5-110)	Not Clearly Defined	25.50%

Study	Study design	No. neonates	Methadone dose at delivery/last trimester (mean/categories)	Diagnostic criteria	NAS treated
Stimmel ²³³ 1982, US, New York	Retrospective Cohort	79	<50mg 15.2% 50mg 72.2% >50mg 12.6%	Not Clear	<50mg 33.3% 50mg 28.1% >50mg 60% Overall 67.1%
Strauss ¹⁸⁸ 1976, US, Detroit	Retrospective Cohort	70	≤20mg/d 47.1% >20mg/d 52.8%	Not Clearly Defined	≤20mg/d 18.2% >20mg/d 40.5%
Suffet ²⁷ 1984, US, New York	Retrospective Cohort	220	None 8.8% 5-20 mg 38.4% 25-40 mg 44.0% ≥45 mg 8.8%	Green Neonatal Narcotic Withdrawal Index	Approx. 80% diagnosed/25% treated
Vucinovic ²⁷⁶ 2008, Split, Croatia	Retrospective Cohort	15	NR	Not Clear	66.7%*
Wilson ¹³⁸ 1981, US, Houston	Prospective Cohort	39	< 20mg 15.4% 20-60mg 82% 90mg 2.6%	Not Clearly Defined	87.2%
Wolff ¹¹⁷ 2005, UK, Leeds	Prospective Cohort	9	28mg (3-70)	Not Clear	44.4%*

* NAS diagnosed- not specified if also treated

IQR Interquartile Range

DLM Drug Liaison Midwife

MAW Medication assisted withdrawal

NR Not reported

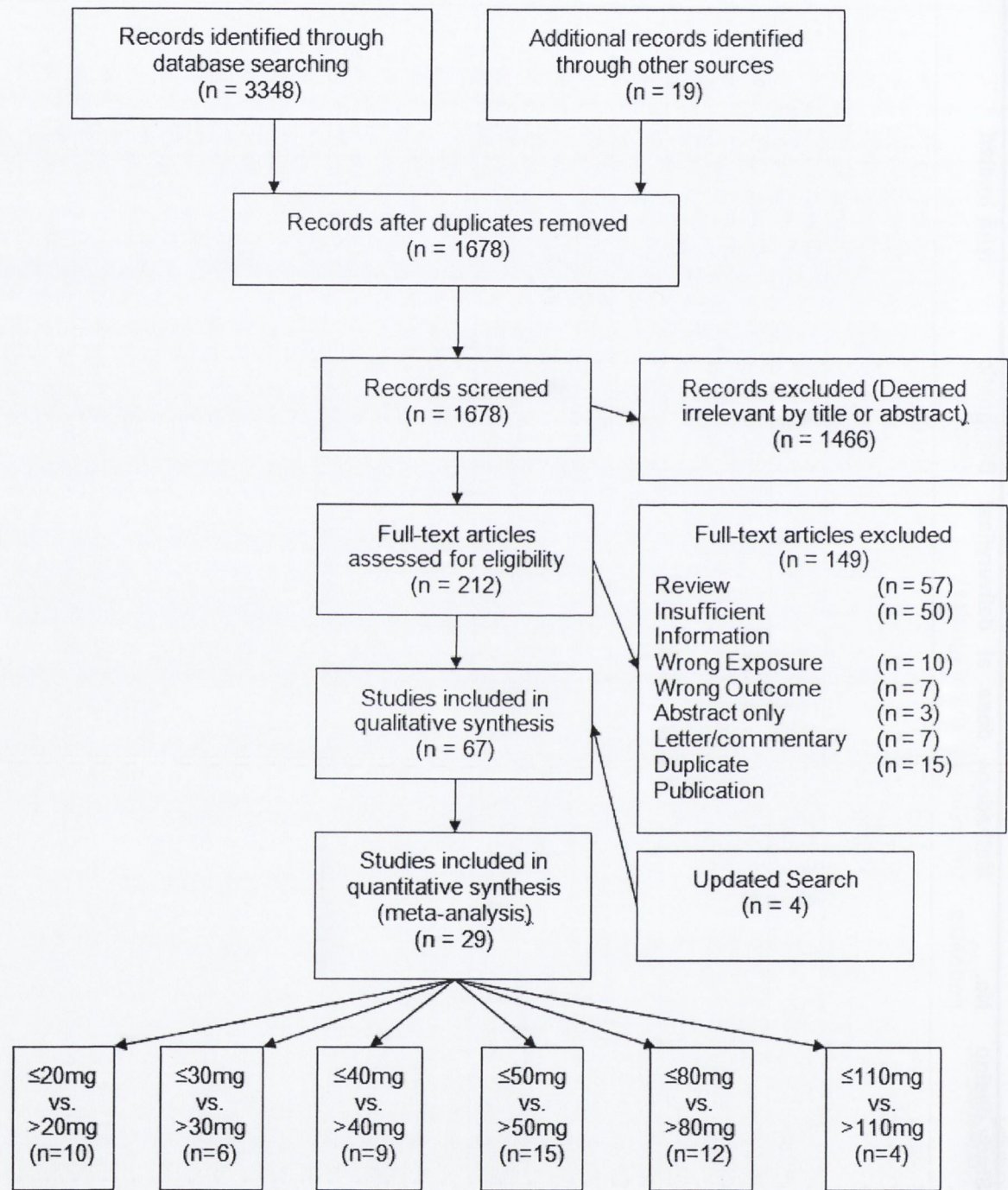


Figure 4-1 Flow of Information through the Phases of the Systematic Review

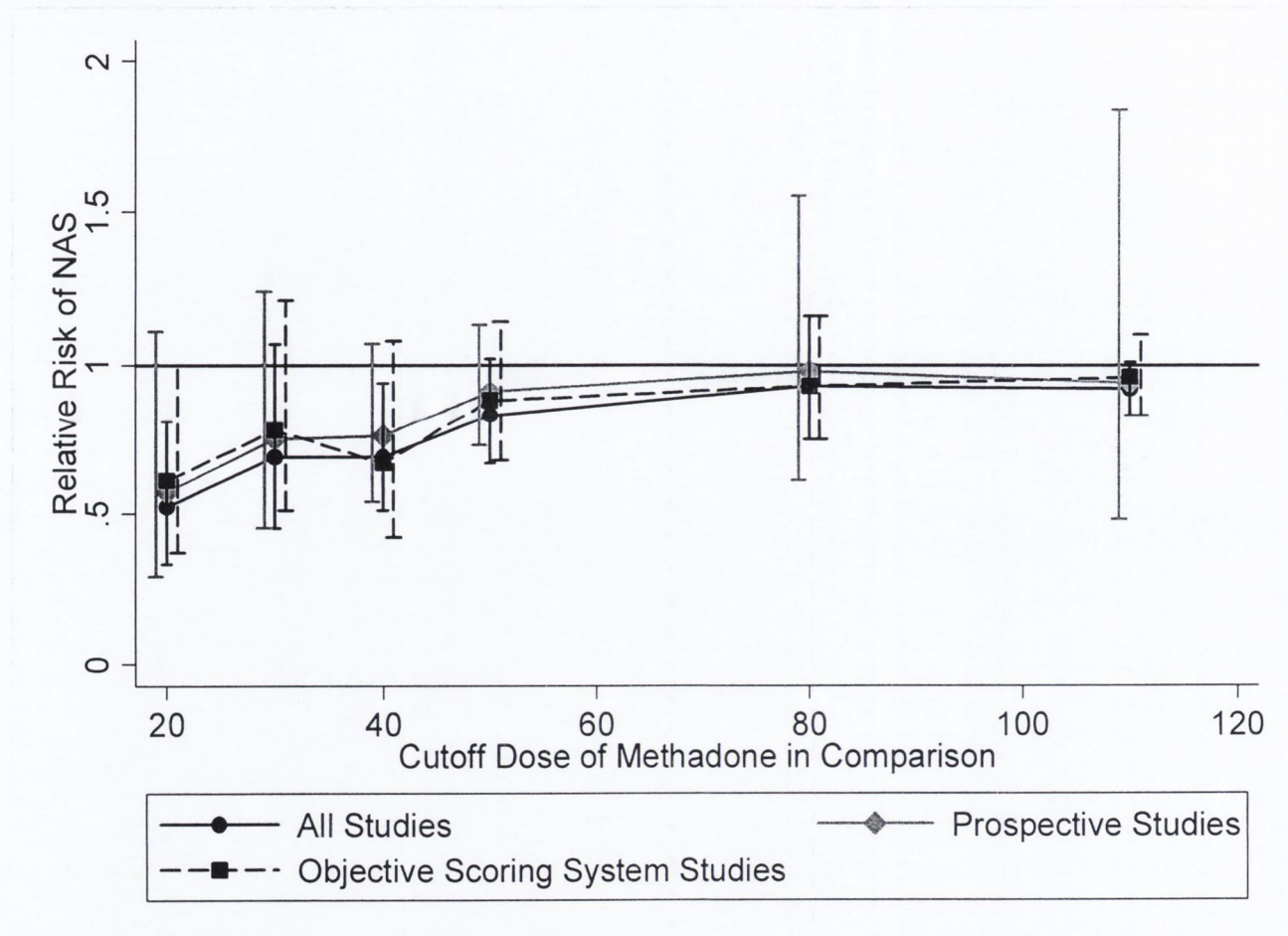


Figure 4-2 Relative Risk of Diagnosed/medically Treated Neonatal Abstinence Syndrome in Neonates Born to Opioid-dependent Pregnant Women Maintained on Lower versus Higher Methadone Doses across a Range of Cut-off Values

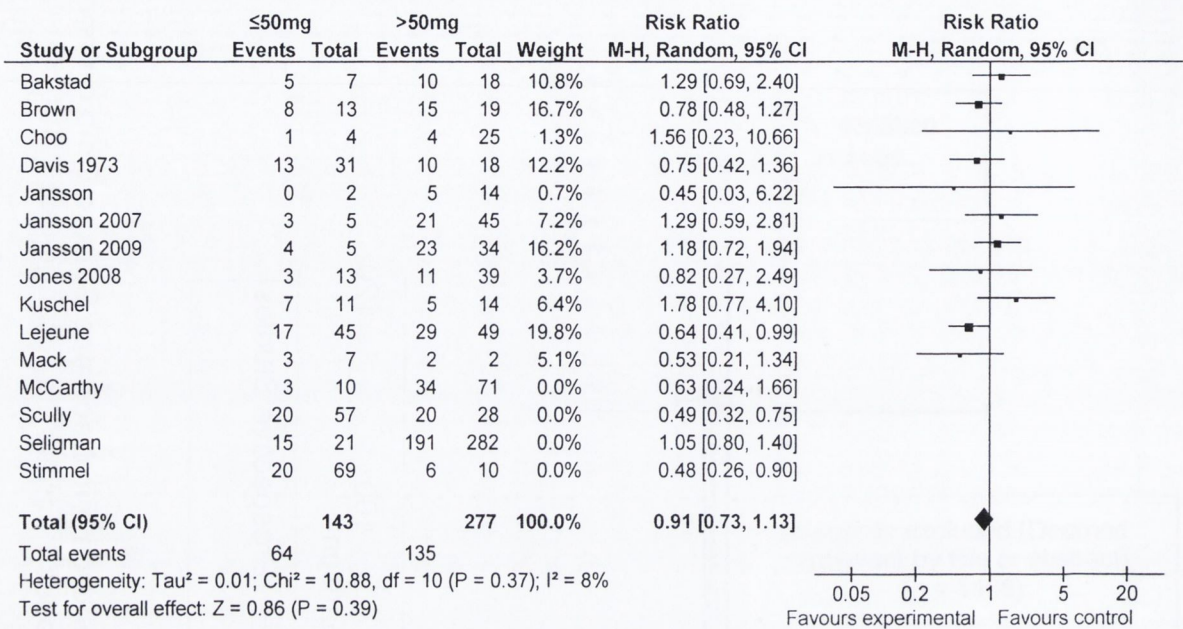


Figure 4-3 Forest Plot- Incidence of Diagnosed/medically Treated Neonatal Abstinence Syndrome in Neonates Born to Opioid-dependent Pregnant Women Maintained on Methadone Doses Above and Below 50mg

CHAPTER 5. RETROSPECTIVE COHORT STUDY: METHADONE AND PERINATAL OUTCOMES

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5.1 Introduction

An estimated 30,000 pregnant women use illicit opioids each year in the European Union.¹¹² Methadone is the treatment of choice for the management of opioid dependence in pregnant women.^{175 176} In the context of optimal care, methadone has been shown to improve engagement with antenatal services, reducing neonatal morbidity and mortality compared with continued illicit drug use.^{26 277} Despite these improvements, methadone-maintained women and their infants appear to be at increased risk of adverse perinatal outcomes compared to the total population. Previous cohort studies report markedly elevated rates of preterm birth of 29-45%^{156 278} and admission of up to half of exposed neonates to the neonatal unit.³⁶ A meta-analysis showed a lower mean birth weight in methadone-exposed neonates compared to controls.¹³⁷ Although it is known that methadone-exposed pregnancies are at greater risk of adverse outcomes, few population-based studies have quantified the likelihood of adverse perinatal outcomes compared to unexposed pregnancies accounting for the effect of confounding sociodemographic factors.

Neonatal abstinence syndrome (NAS) is another important consequence of methadone use in pregnancy, affecting between 13% and 94% of exposed neonates.^{142 145 268} Studies to date have had inconsistent findings about the existence of a relationship between maternal methadone dose and NAS.^{36 141 158 214 225} A recent meta-analysis did not find consistent evidence for a dose-response relationship.²⁷⁹ However, many studies on this topic had limited sample sizes with inadequate power to detect an association between methadone dose and the

occurrence of NAS. It is important to determine if this relationship exists, in order to facilitate optimal dosing of methadone during pregnancy.

Electronic records from a maternity hospital in Dublin, Ireland were used to compare perinatal outcomes for women exposed to methadone with the unexposed population over an eight year period. The first objective was to establish population-based estimates of the risk of adverse perinatal outcomes including preterm birth, intrauterine growth restriction, congenital anomalies, admission to the neonatal unit and perinatal death in methadone-exposed and unexposed pregnancies. A second objective was to explore the determinants of the incidence of NAS in methadone-exposed neonates.

5.2 Methods

A retrospective cohort study was carried out. The cohort included all singleton deliveries in the Coombe Women and Infants University Hospital (CWIUH) between January 1st 2000 and December 31st 2007. This is a tertiary care maternity hospital located in a deprived inner-city area. The hospital serves a catchment area with a population of over 500,000. All women have a booking interview with a midwife at the first antenatal visit. Comprehensive records are routinely available for all deliveries of more than 24 weeks gestation or 500g weight. This study was approved by the hospital's Research Ethics Committee.

Maternal sociodemographic, medical and obstetric characteristics, and perinatal outcomes were recorded from electronic antenatal and delivery records. Information on the following maternal characteristics was extracted: age at delivery, socioeconomic group, nationality, marital status, parity,

planned/unplanned pregnancy, booking gestation, receipt of publicly-funded antenatal care, smoking during pregnancy, alcohol use prior to pregnancy and serology status. Hepatitis B positive serology was defined as a current or past positive result for hepatitis B surface antigen, core antibody, E antigen or E antibody; hepatitis C as current or past positive result for hepatitis C antibody or viral RNA; and HIV as a positive result for HIV antigen or antibody.

Opioid-dependent pregnant women are routinely referred to a Drug Liaison Midwife who co-ordinates the woman's care, liaising between the addiction and obstetric services.¹⁸⁶ Multiple sources of ascertainment were used to identify women using methadone at the time of delivery, including antenatal records, controlled drug registers and prescription records. Methadone dose at delivery was recorded from controlled drug registers or prescription records. Controlled drug registers must be used to record all doses of methadone dispensed in the hospital. Women were categorised as methadone-exposed based on use at the time of delivery. More longitudinal data on methadone dosage throughout pregnancy or during the last trimester are not routinely available within hospital records.

Maternal and perinatal outcome measures included mode of delivery; gestational age at delivery; weight for gestational age; infant's condition at birth (Apgar scores at 1 and 5 minutes and whether resuscitation was required); admission to neonatal special/intensive care; congenital anomalies and perinatal death. Every woman had an ultrasound scan at the antenatal booking visit. Gestational age was estimated from the calculation based on first day of the last menstrual period but the booking ultrasound scan estimate was preferred if the dates were uncertain or

there was a discrepancy of more than seven days. Preterm birth was defined as the birth of a live baby at less than 37 weeks gestation. Very preterm birth was defined as the birth of a live baby at less than 32 weeks gestation. Preterm births were further categorised according to whether preterm labour was spontaneous or not. Birth weight centiles were calculated using the GROW-Centile calculator that yields centiles customised for maternal height, weight, ethnicity, parity, infant sex and delivery gestation.²⁸⁰ Population mean maternal height and weight were used for centile calculations where data were missing for any individual pregnancy. Birth weights below the customised tenth centile were defined as small for gestational age (SGA). Further neonatal outcome information was available for neonates admitted to the neonatal unit, including main reason for admission and congenital anomaly diagnoses. The perinatal death register was used for the ascertainment of stillbirths and neonatal deaths, along with electronic delivery suite records. Stillbirth was defined as delivery of a baby showing no signs of life at or after 24 weeks gestation. Neonatal death was defined as the death of a baby within the first seven days of life. Congenital anomalies were identified from records of a physical examination of all babies after delivery and from neonatal unit discharge records. Congenital anomalies were categorised as major, minor or chromosomal, based on the EUROCAT classification system.¹⁰⁶

During the study period neonates were initially monitored for NAS on the postnatal ward using a 17-item scoring system adapted from Finnegan *et al*²⁴³ by removing the moro reflex, sweating and mottling items. Neonates with suspected NAS were admitted to the neonatal unit for assessment and treatment if necessary. NAS was normally diagnosed if the neonate had two or more successive Finnegan scores of

eight or above, or a single score of 12 or above. Diagnosis of NAS was ascertained from multiple fields in the electronic neonatal discharge register including main diagnosis, central nervous system diagnosis, unresolved problems at discharge, other diagnoses and discharge medications. Neonatal urine toxicology screening for opiates (excludes methadone), benzodiazepines, cannabis, cocaine, amphetamines and alcohol was performed when clinically indicated in the first days of life.

Basic descriptive statistics were used to describe maternal characteristics and perinatal outcomes for the exposed and unexposed groups. Continuous variables were tested for normality using the *sktest* function in STATA IC 10 (Skewness and Kurtosis test for normality) or Shapiro Wilk tests as appropriate. Differences in means or medians were assessed using independent samples Student's t-tests or Mann Whitney U tests. Univariable and multivariable logistic regression analyses were used to determine crude and adjusted odds ratios and 95% confidence intervals for the association between methadone exposure status, maternal characteristics and a range of perinatal outcomes. Only maternal characteristics that differed significantly between the exposed and unexposed groups were included in the final multivariable models. The analysis was repeated excluding women with diabetes during the pregnancy or a history of epilepsy, conditions known to be associated with adverse perinatal outcomes.

Separate univariable and multivariable logistic regression analyses were carried out to examine the determinants of NAS in methadone-exposed neonates. Variables found to have a potential impact on the incidence of NAS in the univariable analyses ($p < 0.1$) were included in the multivariable models. Likelihood

ratio tests were used to test for evidence of interactions. Subgroup analyses were carried out examining the determinants of NAS excluding infants with urine toxicology results positive for opiates, benzodiazepines, cannabis or cocaine exposure. These were *post hoc* analyses as it was unclear at the outset what level of toxicology data would be available. A separate logistic regression analysis with methadone dose group as an ordinal variable (<21mg, 21-50mg, 51-80mg, 81-100mg and >100mg) was used to test for a dose-response relationship between methadone and the occurrence of NAS.

A sample size calculation estimated that with 618 methadone-exposed pregnancies, the study would have 80% power, at an α of 0.05, to detect a relative risk of NAS of 1.3 or greater assuming a 35% rate of NAS in the low dose group and an equal number of women in each group. The rate of NAS in the low dose group is based on an earlier study in the same population¹⁸² and similar studies identified in a systematic review.²⁷⁹

STATA IC 10 was used for all statistical analysis (StataCorp. 2001. Statistical Software: Release 10.1. College Station, TX: Stata Corporation). The STATA command `xtmelogit` was used to carry out mixed effects logistic regression in order to generate odds ratios adjusted for the lack of independence in perinatal outcomes for women with more than one delivery in the study period. These regression models adjusted for the fact that some women may have had more than one infant in the cohort during the study period.

5.3 Results

Of 61030 singleton deliveries between 2000 and 2007, 618 (1%) were to women on methadone at delivery. A further 13 women with a history of methadone use were excluded from the study due to unavailability of medical records.

Maternal characteristics are outlined in Table 5-1. The median (IQR) ages at delivery in the methadone-exposed and unexposed groups were 26 (23-28) and 31 (26 to 34) ($p<0.01$), respectively. The comparison group of non-exposed women were mostly Irish, two thirds were married, four in ten were nulliparous and three quarters were in receipt of publicly-funded obstetric care. Compared to women in the unexposed population, those using methadone at delivery were more likely to be unemployed, Irish, parous, smokers, to have an unplanned pregnancy and publicly-funded obstetric care. Serological evidence of viral blood-borne disease, particularly Hepatitis C, was more likely in methadone-exposed women than in the non-exposed population.

Maternal and perinatal outcomes are described in Table 5-2. Methadone exposure was associated with preterm birth (adjusted odds ratio 2.47, 95% confidence interval 1.97-3.11) and very preterm birth (<32 weeks) (aOR 2.27, 95% CI 1.40-3.69). Methadone-exposed neonates were more likely to be small for gestational age (aOR 2.21, 95% CI 1.85-2.64). Admission to the neonatal unit was much more likely if the neonate had been exposed to methadone (aOR 6.15, 95% CI 5.14-7.36). Diagnosis of a major congenital anomaly was more likely in methadone-exposed neonates. The occurrence of major congenital anomaly subgroups is compared in Table 5-3. After examining individual major congenital anomalies it was apparent that Pierre Robin sequence, a congenital facial anomaly consisting

of a combination of small lower jaw (micrognathia), displacement of the tongue upwards and towards the back of the oral cavity, and cleft palate, was over-represented with four cases among the 618 methadone-exposed neonates (1 in 155) and eight cases in the unexposed group (1 in 7,552).

Adjustment for interdependence of perinatal outcomes in women with more than one delivery during the study period using mixed effects binary logistic regression resulted in marginal changes in the odds ratios for most outcomes with the exception of preterm delivery, being small for gestational age and admission to the neonatal unit. For these outcomes, the adjusted odds ratios were changed to: preterm birth <37 weeks (aOR 3.07, 95% CI 2.28-4.14), spontaneous preterm birth <37 weeks (aOR 3.23, 95% CI 2.32-4.50), very preterm birth <32 weeks (aOR 2.47, 95% CI 1.40-4.34), spontaneous preterm birth <32 weeks (aOR 3.19, 95% CI 1.67-6.08), being small for gestational age (aOR 3.27, 95% CI 2.49-4.28) and admission to the neonatal unit (aOR 9.14, 95% CI 7.21-11.57). No evidence of exposure-confounder interaction was found. Repeating the analysis excluding women with diabetes during the pregnancy or a history of epilepsy did not materially change the results.

The median (IQR) methadone doses in mothers of neonates with and without a diagnosis of NAS were 63.5mg (40-80) and 50mg (30-70), respectively ($p < 0.01$). Compared to neonates born to women on very low doses (<21mg), those born to women on higher doses were more likely to have a recorded diagnosis of NAS with a clear dose-response relationship (Table 5-4). The rate of diagnosis of NAS ranged from 23.3% in the very low dose group to 73.3% in the highest dose group (see Figure 5-1). An NAS diagnosis was more likely among neonates born before

37 weeks gestation or with a birth weight below the 10th centile. The effect of methadone dose on the incidence of NAS was also present when neonates were dichotomised into low and high dose groups with 50mg and 80mg cut off points. After adjustment for preterm birth and having a birth weight below the 10th centile the odds ratios for NAS in neonates born to women on doses above and below 50mg and 80 mg were aOR 2.10, 95% CI 1.49-2.98 and aOR 1.73, 95% CI 1.04-2.87, respectively. Maternal smoking and alcohol use were not associated with NAS.

Neonatal urine toxicology results were available for 254 (41.1%) of the methadone-exposed neonates. Of these 79 (31.1%) were opiate positive, 72 (28.3%) benzodiazepine positive, 15 (5.9%) cannabis positive and 5 (2.0%) cocaine positive. A relationship between the maternal methadone dose at delivery and occurrence of NAS was still evident with doses above and below 50mg in subgroup analyses excluding neonates with urine toxicology results positive for opiates, benzodiazepines, cannabis or cocaine ($\leq 50\text{mg}$ compared with $>50\text{mg}$ aOR 1.71, 95% CI 1.13-2.55; $\leq 80\text{mg}$ compared with $>80\text{mg}$ aOR 0.76, 95% CI 0.37-1.58). Tests for a relationship between methadone dose band and diagnosis of NAS using logistic regression analyses found evidence of a dose-response effect when all the methadone-exposed neonates were included in the analysis ($p < 0.001$) and when neonates with positive urine toxicology were excluded ($p = 0.02$).

5.4 Discussion

Maternal methadone use during pregnancy was associated with a range of adverse perinatal outcomes even after known socio-demographic risk factors were

accounted for. Adverse outcomes included preterm and very preterm birth, being small for gestational age, low Apgar scores, neonatal unit admission and diagnosis of a major congenital anomaly. The incidence of NAS was related to maternal methadone dose at delivery.

This study examined perinatal outcomes in a geographical cohort of women delivering in a large maternity hospital. The hospital's catchment area includes areas of inner-city deprivation with relatively high rates of illicit drug use, facilitating the identification of a large cohort of methadone-exposed pregnancies. The results of this study should be generalisable to similar groups of methadone-maintained opioid-dependent women. In some settings methadone is infrequently initiated before pregnancy.²⁸¹ This is in contrast to the population examined here, the majority of whom are on methadone maintenance treatment prior to pregnancy. The rate of methadone use is likely to be lower in other Irish cities and rural locations, however the characteristics of individual users and potential for adverse perinatal outcomes are unlikely to differ significantly. Multiple sources of ascertainment were used to ensure as complete identification of methadone-exposed pregnancies as possible. The large sample size facilitated an assessment of the effect of methadone on perinatal outcomes and the incidence of NAS which may be missed in smaller studies.

As this retrospective study used routinely collected data, not all information relevant to the research questions was available. Limited information was available on maternal nutrition, which may account for some of the adverse perinatal outcomes. Also, there were limited data on neonatal urine toxicology, with only a minority of neonates having urinalysis performed, and no data on

maternal toxicology testing or prescription medication use, limiting the ability to adjust for the effect of concomitant licit and illicit drug exposure on perinatal outcomes. Neonatal urinalysis has a limited window of detection for illicit drug use, reflecting use in the days prior to delivery.²⁸² There is also potential for false positive results due to urinalysis after oral morphine has been initiated for NAS or due to use of opioid analgesics in a breastfeeding mother. It is possible that there is residual confounding relating to socioeconomic differences between the two groups of women that could contribute to the findings. Ascertainment of NAS diagnoses was reliant on electronic records and there was no information on the number of neonates with medically treated NAS, or the severity or duration of NAS. Ascertainment of congenital anomalies was likely to be incomplete, as information was only available on anomalies diagnosed before first hospital discharge. Some of the effect of methadone on adverse perinatal outcomes may be explained by detection bias, with a greater detection of some study outcomes in the methadone-exposed group due to a higher rate of admission to the neonatal unit.

Rates of adverse perinatal outcomes such as preterm birth, lower birth weight and admission to the neonatal unit are higher in methadone-exposed pregnancies than in the overall population.^{36 137 158 278} The 20.4% estimate of the incidence of preterm birth is in agreement with the 20.3% rate reported by Dryden and her colleagues for a similar cohort in Glasgow,³⁶ though other studies have reported higher rates.¹⁵⁶ Serological evidence of hepatitis C infection was also quite common in Dryden's study.³⁶ This study shows that after adjusting for a variety of maternal characteristics that may adversely affect the risk of preterm birth,

methadone treatment was independently associated with preterm and very preterm delivery. This effect was also present when spontaneous delivery before 37 and 32 weeks was considered as the outcome. Almario et al found that the risk of preterm birth rose with the number of supplemental drugs used by the mother in addition to methadone.²⁷⁸

Other adverse perinatal outcomes such as growth restriction and low Apgar scores were also more likely with exposure to methadone. Previous reports have demonstrated lower birth weights in this population.^{137 283} Like previous studies, neonatal unit admission was common for methadone-exposed neonates.³⁶ This has important consequences for health system resources, with long durations of hospitalisation reported in a variety of settings.^{36 156}

Methadone is not generally considered to be teratogenic.^{133 195} The present analysis found that methadone exposure increased the likelihood of a major congenital anomaly diagnosis. Many previous studies in this area did not systematically report congenital anomalies as a study outcome. Small sample sizes also limit the potential to examine rare outcomes such as congenital anomalies. Unexpectedly we found that there was an elevated rate of Pierre Robin Sequence in the methadone-exposed group. The rate in the unexposed group was similar to rates reported internationally of 1 in 8,500 and 1 in 14,000.^{284 285} This incidental finding is not sufficient to link methadone causally to Pierre Robin Sequence. Future studies are required to verify or reject this finding.

Many previous studies have examined the relationship between methadone and NAS. In agreement with some studies, this study finds that there is a relationship

between maternal methadone dose at delivery and NAS.^{36 155 156 186 214} Other authors have not reported such a relationship.^{141 157 158 225 228} The dose-response effect could be explained by greater concomitant illicit drug use in women on higher methadone doses, but the effect persisted in subgroup analyses excluding neonates with definite illicit drug exposure. It is possible that studies with smaller sample size might miss a true dose-response effect, or perhaps some studies with high mean methadone doses missed a dose-response relationship, due to a ceiling effect. Some authors have demonstrated a relationship between maternal smoking and the severity or duration of NAS.^{242 286} Smoking was not associated with NAS in this study, although the confidence intervals for the odds ratios were wide as the majority of the methadone-exposed women smoked.

Methadone's beneficial effects of minimising illicit drug use and fostering engagement with antenatal care outweigh the risks of adverse perinatal outcomes found in this study. The increased incidence of very preterm birth and low Apgar scores have important implications as they are associated with adverse consequences in the short and long-term. The incidence of congenital anomalies in methadone-exposed neonates should be routinely assessed and reported in future studies. Although an association is reported between methadone dose and the incidence of NAS, it is important not to view NAS in isolation. NAS is a short-term, treatable condition. Although it is an important outcome, it is not the only one to consider when making decisions on optimal methadone doses in pregnancy. Continued stability or cessation of drug use, and associated risk behaviours, currently take precedence over endeavours to minimise NAS. It is possible that there is a subgroup of motivated, stable women within this population, for whom

careful, supervised dose reductions may reduce the likelihood of NAS, but this potential benefit needs to be balanced against the risk of decreased methadone doses leading to relapse of illicit drug use.

In conclusion, methadone exposure in pregnancy is associated with a range of adverse perinatal outcomes, even after accounting for the effects of maternal sociodemographic risk factors. This vulnerable group of women and their neonates require dedicated, well-resourced, multidisciplinary care in order to improve perinatal and long term outcomes.

Table 5-1 Maternal Characteristics among Pregnancies Exposed and Not Exposed to Methadone

		Exposed n=618 (1.01%)	Non-exposed n=60412 (98.99%)	Odds Ratio	95% CI
	N=61030				
Age at delivery	611030				
<20 years		20 (3.2)	3052 (5.0)	0.35	0.22-0.56
20-24 years		211 (34.1)	8640 (14.3)	1.32	1.10-1.59
25-29 years		267 (43.2)	14461 (23.9)	1	-
30-34 years		96 (15.5)	20254 (33.5)	0.26	0.20-0.32
35-39 years		18 (2.9)	11830 (19.6)	0.08	0.05-0.13
≥40 years		6 (1.0)	2175 (3.6)	0.15	0.06-0.34
Socioeconomic group	60995				
Home duties		43 (7.0)	12833 (21.2)	1	-
Professional, Manager, Employer		5 (0.8)	13945 (23.1)	0.11	0.04-0.27
Non-Manual		48 (7.8)	19087 (31.6)	0.75	0.50-1.13
Manual		18 (2.9)	2447 (4.0)	2.19	1.26-3.81
Unemployed		449 (72.6)	8696 (14.4)	15.4	11.2-21.1
Non-classifiable		55 (8.9)	3369 (5.6)	4.87	3.26-7.27
Nationality- Irish	59582	556 (94.7)	46687 (79.1)	4.73	3.29-6.79
Married	60640	26 (4.3)	39287 (65.4)	0.02	0.01-0.03
Nulliparous	61027	187 (30.3)	25275 (41.8)	0.60	0.51-0.72
Unplanned pregnancy	59921	429 (70.9)	20662 (34.8)	4.56	3.82-5.44
Booking gestation (weeks)	59625				
< 12 weeks		114 (19.7)	12465 (21.1)	1.07	0.86-1.33
12 - 20 weeks		322 (55.5)	37718 (63.9)	1	-
> 20 weeks		144 (24.8)	8862 (15.0)	1.90	1.56-2.32
Publicly-funded obstetric care	60069	604 (99.8)	44184 (74.3)	208.9	29.4-1485
Smoked During Pregnancy	60213	569 (93.7)	13109 (22.0)	53.1	38.2-73.8
Periconceptional Alcohol Use (units per week)	60246				
Never		202 (33.3)	11235 (18.8)	1	-
Occasional		254 (41.8)	25337 (42.5)	1.26	1.04-1.51
1 - 5		89 (14.6)	17049 (28.6)	0.29	0.23-0.37
6 - 9		34 (5.6)	4626 (7.8)	0.41	0.28-0.59
10 - 14		8 (1.3)	1014 (1.7)	0.44	0.21-0.89
15 - 20		10 (1.6)	275 (0.5)	2.02	1.06-3.86
>20		10 (1.6)	103 (0.2)	5.40	2.78-10.49
Hepatitis B Positive Serology [§]	31972	20 (3.5)	326 (1.0)	3.47	2.19-5.49
Hepatitis C Positive Serology [‡]	31973	275 (48.2)	193 (0.6)	150.2	120.9-186.6
HIV Positive*	56781	33 (5.8)	171 (0.3)	20.3	13.8-29.7

[§] Current or past hepatitis B surface antigen, core antibody, E antigen or E antibody positive

[‡] Current or past hepatitis C antibody or polymerase chain reaction positive

* HIV antigen or antibody positive

Table 5-2 Maternal & Perinatal Outcomes among Pregnancies Exposed and Not Exposed to Methadone

		Exposed n=61030 n=618 (1.01%)	Non-exposed n=60412 (98.99%)	OR	95% CI	aOR [†]	95% CI
Mode of Delivery	60832						
SVD		431 (69.8)	38535 (64.0)	1	-	1	-
Elective LSCS		40 (6.5)	4713 (7.8)	0.76	0.55-1.05	1.72	1.20-2.48
Emergency LSCS		71 (11.5)	7496 (12.4)	0.85	0.66-1.09	1.26	0.94-1.68
Forceps/ventouse		75 (12.1)	9471 (15.7)	0.71	0.55-0.90	1.45	1.10-1.91
Meconium Stained Liquor	60533	76 (12.6)	9076 (15.1)	0.81	0.63-1.03	0.68	0.52-0.88
Preterm birth < 37 weeks	60978	126 (20.4)	3382 (5.6)	4.32	3.54-5.27	2.47	1.97-3.11
Spontaneous Preterm Labour		93 (15.1)	2036 (3.4)	5.08	4.06-6.36	2.68	2.06-3.49
Very preterm birth < 32 weeks	60978	27 (4.4)	727 (1.2)	3.75	2.53-5.56	2.27	1.40-3.69
Spontaneous Preterm Labour		22 (3.6)	363 (0.6)	6.11	3.94-9.47	2.99	1.69-5.29
Small for gestational age < 10 th centile [†]	59877	268 (45.9)	8379 (14.1)	5.15	4.37-6.07	2.21	1.85-2.64
Apgar score <3 at 1 minute	60725	20 (3.3)	636 (1.1)	3.18	2.02-5.00	1.94	1.12-3.37
Apgar score <7 at 5 minutes	60668	22 (3.6)	680 (1.1)	3.28	2.13-5.06	2.07	1.23-3.48
Ventilation required at resuscitation	60977	6 (1.0)	398 (0.7)	1.48	0.66-3.32	0.92	0.33-2.55
Admitted to neonatal unit	61029	328 (53.1)	8735 (14.5)	6.69	5.70-7.85	6.15	5.14-7.36
Congenital anomaly	61029						
Any		47 (7.61)	1778 (2.94)	2.71	2.01-3.67	2.20	1.54-3.14
Minor anomalies		22 (3.56)	842 (1.39)	2.61	1.70-4.02	2.12	1.26-3.56
Major anomalies		19 (3.07)	647 (1.07)	2.92	1.84-4.65	1.94	1.10-3.43
Chromosomal anomalies		1 (0.16)	150 (0.25)	0.65	0.09-4.66	1.48	0.19-11.4
Unclassified anomalies		5 (0.81)	101 (0.17)	4.87	1.98-12.0	7.26	2.58-20.4
Perinatal Death*	61030	15 (2.43)	491 (0.81)	3.04	1.80-5.11	1.70	0.87-3.30
Neonatal abstinence syndrome	61029	247 (40.0)	39 (0.06)	1030	724-1466	426	249-728

[†] adjusted for age at delivery (years), socioeconomic group, Irish nationality, marital status, nulliparity, planning of pregnancy, booking gestation (weeks), receipt of publicly funded healthcare, number of cigarettes per day (none, 1-9 a day, greater than 10 a day), and units of alcohol used per week in the periconceptional period (none, 1-9 units, greater than 10 units)

[†] birth weight centiles were calculated using GROW-Centile, a customised weight centile calculator

* includes stillbirths and neonatal deaths. Stillbirth was defined as delivery of a baby showing no signs of life at or after 24 weeks gestation. Neonatal death was defined as the death of a baby within the first seven days of life; LSCS: lower segment cesarean section

Table 5-3 Frequency of Occurrence of Major Congenital Anomaly Subgroups in Methadone-exposed and Unexposed Neonates

Anomaly Subgroup	Exposed n=618 (1.01%)	Non-exposed n=60412 (98.99%)
Nervous system	2 (0.3)	105 (0.2)
Eye	0 (0)	8 (0)
Ear, face and neck	1 (0.2)	43 (0.1)
Congenital heart disease	4 (0.6)	103 (0.2)
Respiratory	0 (0)	11 (0)
Oro-facial clefts	3 (0.5)	54 (0.1)
Digestive system	0 (0)	45 (0.1)
Abdominal wall defects	0 (0)	33 (0.1)
Urinary	1 (0.2)	46 (0.1)
Genital	0 (0)	72 (0.1)
Limb	4 (0.6)	129 (0.2)
Musculo-skeletal	0 (0)	23 (0)
Other malformations	0 (0)	6 (0)
Teratogenic syndromes with malformations	0 (0)	4 (0)
Genetic syndromes and microdeletions*	4 (0.6)	12 (0)

*Includes Pierre Robin Sequence

Table 5-4 Determinants of Neonatal Abstinence Syndrome in Methadone-Exposed Neonates

		NAS	No NAS						
	n=618	n=247 (40.0%)	n=371 (60.0%)	OR	95% CI	aOR	95% CI	aOR*	95% CI
Preterm birth < 37 weeks	617	70 (55.6)	56 (44.4)	2.22	1.49-3.30	2.03*	1.34-3.08	2.10*	1.32-3.34
Very preterm birth < 32 weeks	617	12 (44.4)	15 (55.6)	1.21	0.56-2.63	1.10*	0.48-2.89	1.07*	0.44-2.66
Small for gestational age < 10 th centile	584	121 (45.2)	147 (54.8)	1.56	1.12-2.18	1.46*	1.03-2.07	1.55*	1.03-2.32
Male Sex	618	135 (41.8)	188 (58.2)	1.17	0.85-1.62	1.34 [†]	0.94-1.91	1.38 [†]	0.93-2.03
Methadone dose band at delivery	615								
Less than 21mg		19 (23.8)	61 (76.2)	1	-	1 [§]	-	1 [§]	-
21-50mg		73 (33.3)	146 (66.7)	1.60	0.89-2.89	1.62	0.86-3.05	1.68	0.84-3.34
51-80mg		117 (47.4)	130 (52.6)	2.88	1.63-5.12	2.83	1.52-5.29	3.06	1.51-6.18
81-100mg		26 (48.1)	28 (51.8)	2.98	1.42-6.26	2.90	1.32-6.40	3.09	1.28-7.44
Greater than 100mg		11 (73.3)	4 (26.7)	8.83	2.52-30.97	8.35	2.27-30.68	9.81	2.24-42.9
Maternal Smoking During Pregnancy	608								
None		11 (28.2)	28 (71.8)	1	-	1 [†]	-	1 [†]	-
1-10 a day		103 (37.1)	175 (62.9)	1.50	0.72-3.14	1.16	0.52-2.60	1.14	0.48-2.74
Greater than 10 a day		128 (44.0)	163 (56.0)	2.00	0.96-4.17	1.40	0.63-3.11	1.38	0.58-3.30
Periconceptional Alcohol Use	607								
None		86 (42.6)	116 (57.4)	1	-	1 [†]	-	1 [†]	-
Light (≤9 units per week)		144 (38.2)	233 (61.8)	0.83	0.59-1.18	0.84	0.58-1.22	0.83	0.55-1.25
Moderate/heavy (≥10 units per week)		12 (42.9)	16 (57.1)	1.01	0.45-2.25	0.84	0.34-2.07	0.81	0.30-2.19

* adjusted for methadone dose band at delivery and amount smoked

† adjusted for methadone dose band at delivery, being small for gestational age (< 10th centile), preterm birth (<37 weeks) and amount smoked

§ adjusted for being small for gestational age (< 10th centile), preterm birth (<37 weeks) and amount smoked

● mixed effects logistic regression used to adjust for the interdependence of outcomes for women who delivered more than once during the study period

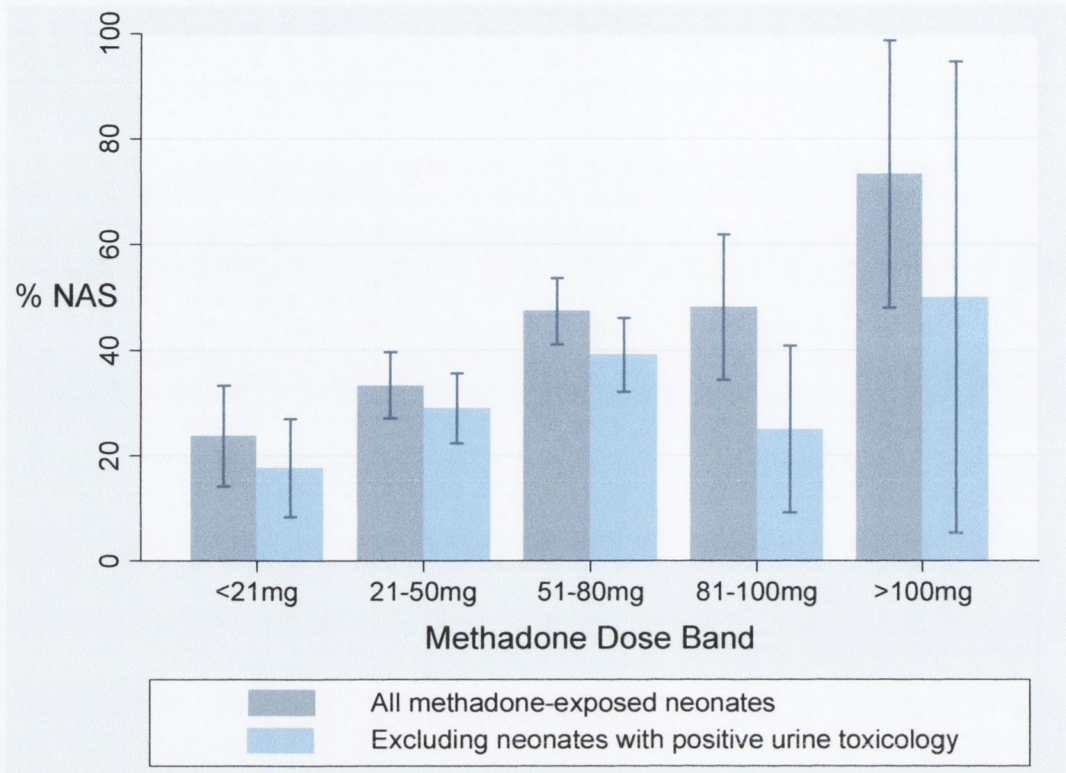


Figure 5-1 Incidence of Neonatal Abstinence Syndrome by Methadone Dose Band at Delivery

CHAPTER 6. PROSPECTIVE COHORT STUDY: METHADONE AND PERINATAL OUTCOMES

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6.1 Introduction

Opioid dependence is an important public health issue, with an estimated 750,000 to 1 million active injecting drug users in the European Union.²⁸⁷ In some settings methadone-maintained opioid-dependent women represent 3% of all deliveries.³⁶ Dependence on opioids during pregnancy has serious potential consequences for perinatal outcomes.²⁷⁷ Methadone maintenance treatment is an established treatment option for opioid-dependent pregnant women.¹⁷⁶ Compared to ongoing heroin use, methadone maintenance treatment, in the context of multidisciplinary care including antenatal care, has been associated with improved perinatal outcomes including higher birth weights, fewer obstetric complications, less preterm birth and reduced neonatal morbidity.²⁶ Despite these improvements, adverse perinatal outcomes remain more common in methadone-exposed pregnancies than in non-exposed pregnancies.²⁸⁸

A consistent finding in previous studies of methadone use during pregnancy is the frequent occurrence of NAS, with an incidence ranging from 13% to 94%.^{142 145-149} The determinants of the incidence, severity and duration of this abstinence syndrome are not completely understood. Studies which have examined the use of methadone during pregnancy to date have had inconsistent findings on the association between methadone dosage and the incidence of NAS.^{36 141 158 214 225}

²⁸⁸ A recent meta-analysis did not find consistent evidence for a dose-response relationship.²⁷⁹ Few studies have considered potential confounding factors or effect modifiers that may impact on the incidence, severity or duration of the abstinence syndrome such as preterm birth,¹⁴⁶ or smoking.²⁴² Previous studies have also been limited by incomplete recording of concomitant exposures that

may affect NAS including the use of antidepressant medications,²⁸⁹⁻²⁹² benzodiazepines,²²⁵ and illicit drugs.

The aim of this study was to examine perinatal outcomes and neonatal abstinence syndrome in relation to concomitant drug use in addition to methadone and maternal methadone dose at delivery. Specific objectives included describing maternal characteristics, addiction profiles and perinatal outcomes for the cohort; comparing perinatal outcomes and NAS for women stabilised on methadone only and those with concomitant exposure to other drugs; comparing perinatal outcomes and NAS for women on low and high methadone doses; and examining the influence of clinical characteristics such as preterm birth, being small for gestational age and smoking on the incidence of NAS.

6.2 Methods

6.2.1 *Assembly of multidisciplinary team*

A multidisciplinary team was assembled across the two study centres, the Coombe Women and Infants University Hospital (CWIUH) and the Rotunda Hospital. The team incorporated Obstetricians responsible for specialised antenatal clinics for opioid-dependent pregnant women (Dr. Maeve Eogan and Dr. Michael O'Connell), Drug Liaison Midwives (Deirdre Carmody and Justin Gleeson), Neonatologists (Prof. Tom Clarke and Dr. Martin White) and Neonatal Unit Advanced Nurse Practitioners (Christine McDermott and Anne O'Sullivan). There was academic input from collaborators with backgrounds in Obstetrics (Prof. Deirdre Murphy), Pharmacy Practice (Prof. Paul Gallagher and Judith Strawbridge) and Primary Care (Prof. Tom Fahey).

6.2.2 *Study design and participants*

A prospective cohort study was carried out in two maternity hospitals in Dublin, Ireland. The two study centres provide maternity services to a catchment area with a population of approximately 1 million, delivering approximately 17,000 babies annually. Opioid-dependent pregnant women receive antenatal care in dedicated clinics staffed by Obstetricians, Infectious Disease Midwives and Physicians, Social Workers and Drug Liaison Midwives who ensure continuity of care between the Maternity and Addiction services.¹⁸⁶ Women were recruited from these specialised antenatal clinics between July 2009 and July 2010. Women were eligible for inclusion in the study if they were on methadone maintenance treatment during pregnancy and were greater than 28 weeks gestation. Women were excluded if they were aged under-18 or if they were deemed unable to give informed consent to participate in the study by their Obstetrician.

6.2.3 *Ethical issues*

Potential study participants were opioid-dependent pregnant women and newborn infants, a vulnerable group of individuals. The exposures of interest related to prescribed methadone and concomitantly used illicit drugs and other medications. The outcomes of interest were adverse perinatal events including NAS. Both the exposures and outcomes were of a sensitive nature.

Each potential study participant was informed about the study in the first instance by a clinician in the specialised antenatal clinics. Women were given a written patient information leaflet (see Appendix VI) and were encouraged to ask the researcher (BC) more detailed questions if necessary. The information sheet addressed the purpose of the project, expected duration, procedures involved,

risks or discomforts, benefits for the women/infants and others, indemnity cover, disclosure of incidental findings, confidentiality and contact details for a named researcher to deal with any queries. Women had a minimum of 24 hours to consider participation in the study. In practice, women were provided with the information leaflet at an antenatal visit and informed consent was sought prior to the research interview at the next visit (one to four weeks later).

The patient information leaflet and consent form were carefully designed and written to ensure clarity for potential study participants. The documentation was designed to maximise the Flesch reading ease score and ensure accessibility to all potential participants. Women with reading difficulties had the explanatory documentation read to them. Women were assured that participation was entirely voluntary and that declining participation would not affect the care of her or her baby in any way. Women were given another opportunity to have any concerns addressed by a researcher before written informed consent was obtained at the third trimester study interview.

Women were advised that data collected as part of the study would remain confidential. However, safeguards allowed for disclosure of information where a study participant reported behaviour that posed a serious risk to herself or her unborn child/infant. The following disclosure statement outlining when confidentiality must be breached was incorporated into the patient information leaflet:

“Only in circumstances where from the interview disclosure is needed urgently to prevent injury or damage to the health of a

person, for example child protection concerns, would there be disclosure to the appropriate agency. Any such concern would be discussed fully with you."

Ethical approval for the study was obtained from Ethics Committees at the Coombe Women and Infants University Hospital, The Rotunda Hospital and the Drug Treatment Centre Board (See Appendix V). The electronic study dataset did not include personally identifiable information such as name, address, hospital number or medical card number. Women and infants were identified by a study number in the electronic dataset which was recorded along with the patient's name and hospital number on a paper-format study participant register. Electronic records were stored on a networked, password-protected computer with daily data backups.

6.2.4 Explanatory variables

Data on the following maternal and neonatal explanatory variables were collected during the study interview and from medical records:

Maternal

- Demographics
- Illicit drug use
- Prescribed medication use
- Cigarette smoking/Fagerström Test for Nicotine Dependence score
- History of NAS in previous child
- Urine toxicology results
- Methadone dose at delivery

Neonatal

- Delivery gestation
- Urine toxicology results

Data on maternal demographics, smoking history and alcohol consumption were extracted from routinely collected information in medical charts and electronic hospital records. Information on maternal characteristics was collected for women who did not consent to participate in the research interview to determine if the participants differed systematically from the women who did participate. All participants took part in a structured interview carried out in the third trimester by one researcher (BC). The drug use question from the Addiction Severity Index, modified to reflect local drug names, was used to examine drug use history and current use of medications and illicit drugs.²⁹³ The Fagerström Test for Nicotine Dependence (FTND) was used to assess current smoking status and provide a proxy indication of biochemical measures of the extent of maternal smoking.²⁹⁴ The Objective Opiate Withdrawal Scale was completed by the interviewer to assess any evidence of maternal withdrawal present during the interview.²⁹⁵ Women were also asked if they had previous children while they were on methadone maintenance treatment who were medically treated for NAS. Methadone dose at delivery was determined from hospital records.

Enzyme immunoassay was used for maternal and neonatal urine toxicology testing to detect the presence of opiates (excludes methadone), benzodiazepines, or cocaine. Samples were screened with CEDIA[®] immunoassay kits using a Beckman Coulter[®] AU2700 clinical chemistry analyzer. Information on the presence of any positive maternal urine toxicology results in the four weeks before delivery was extracted from Addiction Service records. Women usually underwent weekly urinalysis during the study period. Information on neonatal urine toxicology

screening, carried out when clinically indicated in the first days of life, was extracted from hospital laboratory records.

6.2.5 Outcome variables

Perinatal outcomes and outcomes related to NAS were recorded from maternal and neonatal medical records. Perinatal outcome measures included mode of delivery, amniotic fluid status, gestational age at delivery, birth weight, weight for gestational age, occipitofrontal circumference, length, Apgar scores at 1 and 5 minutes and admission to the neonatal unit (special/intensive care). Gestational age was estimated from an ultrasound scan performed at the first antenatal appointment. Preterm birth was defined as the birth of a live baby at less than 37 weeks gestation. Preterm births were further categorised according to whether preterm birth was spontaneous or indicated medically. Birth weight centiles were estimated using the GROW-Centile calculator that yields centiles customised for maternal height, weight, ethnicity, parity, infant sex and delivery gestation.²⁸⁰ Mean maternal height and weight of the participant group were used for centile calculations where data were missing for any individual pregnancy. Birth weights below the customised tenth centile were defined as small for gestational age (SGA). Occipitofrontal circumference and length centiles were estimated from UK-WHO Growth Charts.²⁹⁶

Outcomes selected to reflect the incidence, severity and duration of NAS included the incidence of medically treated NAS; peak Finnegan score and cumulative dose of NAS treatment; and duration of hospitalisation. Some variables that were considered as outcome variables in relation to perinatal outcomes, e.g. preterm

birth, were also considered as potential confounders or effect modifiers in relation to NAS.

During the study period neonates were initially monitored for NAS every 4-6 hours by midwifery staff on the postnatal ward using a 17-item scoring system adapted from Finnegan et al ²⁴³ by removing the moro reflex, sweating and mottling items. Neonates with suspected NAS were admitted to the neonatal unit for assessment and treatment if necessary. Initiation of oral morphine treatment for NAS was at the Clinician's discretion. Treatment was usually initiated in response to two consecutive Finnegan scores of eight or above, or a single score of 12 or above. Phenobarbitone was used as a second line treatment when there was an inadequate response to morphine, when seizures occurred or when poly-drug abuse was suspected. Peak NAS scores, cumulative dose of NAS treatment and length of stay were extracted from neonatal medical records. Primary indications for increased length of stay other than NAS were recorded.

6.2.6 Statistical methods

Descriptive statistics were used to describe maternal characteristics and perinatal outcomes. Continuous variables were tested for evidence of deviation from normality using Shapiro-Wilk tests. Mean values and standard deviations (SD) are reported for normally distributed continuous variables. Median values and interquartile ranges (IQR) are reported for continuous variables with evidence of non-normal distribution.

Maternal characteristics of study participants were compared with all women who delivered in the two study hospitals in 2008, the most recent year for which

complete data were available. Differences in means or medians of continuous variables were assessed using independent samples Student's t-tests or Mann-Whitney U-Tests as appropriate. Chi-squared tests or exact tests were used to compare differences in categorical variables between groups. Study participants and non-participants were then compared to identify any maternal characteristics that differed significantly between the two groups of methadone-maintained women and assess the external validity of the study. Univariable logistic regression analyses were used to generate crude odds ratios (OR) and 95% confidence intervals (CI) for the association between maternal characteristics and study participation status.

Two comparisons were carried out to examine the impact of methadone use on perinatal outcomes and NAS. The first compared outcomes among women maintained exclusively on methadone (methadone only group) with outcomes among women using concomitant opiates, benzodiazepines or cocaine in addition to methadone (concomitant drug use group). Women were assigned to the methadone only or the concomitant group based on maternal urine toxicology screening in the four weeks before delivery and neonatal screening in the first days of life. If a neonate had a urine screen positive for opiates due to initiation of morphine treatment for NAS prior to taking the urine sample, they were included in the methadone only group, provided that there was no other evidence of concomitant drug use from maternal or neonatal urine toxicology. The second comparison examined perinatal outcomes and NAS for women on low and high methadone doses. A cut off point of $\geq 80\text{mg}$ was selected as it has been commonly used in similar studies.²⁷⁹

Univariable logistic regression analyses were used to estimate unadjusted odds ratios and 95% confidence intervals for the association between concomitant drug use and perinatal outcomes or NAS. Separate univariable and multivariable logistic regression analyses were carried out to examine the association between methadone dose (above and below 80mg) and perinatal outcomes or NAS with adjustment for concomitant drug use. Univariable logistic regression analyses with methadone dose band as an ordinal variable were used to test for a relationship between methadone dose and concomitant drug use, and for a relationship between methadone dose and the incidence of medically treated NAS. The methadone dose bands used as an explanatory variable in these analyses were: $\leq 20\text{mg}$, 21-50mg, 51-80mg, 81-100mg and $>100\text{mg}$. Multivariable logistic regression was used to test for a relationship between methadone dose and the incidence of medically treated NAS with adjustment for concomitant drug use. Further logistic regression analyses were used to examine the relationship between clinical characteristics and the incidence of medically treated NAS with adjustment for concomitant drug use and methadone dose band at delivery.

A sample size calculation estimated that a sample size of 120 patients would be required to have 80% power with an α of 0.05 to detect a difference in the incidence of NAS between the low and high methadone dose groups of 25%, assuming that 35% of the infants in the low dose group develop NAS (i.e. 35% versus 60%). The assumed rate of treated NAS was based on a studies in a similar population^{288 182} and data from other studies included in a systematic review of methadone dose and NAS.²⁷⁹ SPSS version 16 (SPSS Inc., Chicago, Illinois) was used for all analyses. Analysis and reporting of the study were carried

out in accordance with guidelines for the reporting of observational studies in epidemiology.²⁹⁷

6.3 Results

6.3.1 Participants

During the study period 144 women were potentially eligible for inclusion in the study. Of these, 117 women consented to participate. The remaining women either refused participation (16), or could not be recruited due to poor attendance at antenatal clinics, preterm delivery or intrauterine death (11). Among the participants there were two intrauterine deaths and one woman transferred to another hospital for antenatal care after recruitment; data were therefore available on 114 live born neonates. The two intrauterine deaths occurred at 36 and 38 weeks gestation. Autopsies were carried out, but further details of the two cases are currently unavailable as they are still *sub judice* in the Coroner's Court. Of the 117 participants, 15 women were interviewed after delivery while still an inpatient on the postnatal ward. The mean gestation at maternal interview was 34.8 weeks (standard deviation 3.4).

6.3.2 Maternal characteristics and addiction history

The maternal characteristics of study participants and the total population delivering in the two study centres in 2008 are presented in Table 6-1. Compared to the total population, there were differing age distributions and higher levels of unemployment, multiparity, unplanned pregnancy, smoking and viral blood borne diseases in the methadone-maintained women. Maternal characteristics of study participants and non-participants are compared in Table 6-2. The mean age at delivery was 30.1 (SD 4.3) for the participants and 30.3 (SD 4.7) for the non-participants ($p=0.87$). There were no significant differences in maternal characteristics between the two groups. Non-participants appeared more likely to

have five or less antenatal visits, though this difference was not statistically significant. The distribution of methadone doses was similar for the two groups. The mean methadone dose at delivery was 69.3mg (SD 27.8) for participants and 71.6mg (SD 34.0) for non-participants ($p=0.71$).

Depression and asthma were among the more commonly reported medical disorders in the antenatal booking records, with history of depression or current depression reported by 61 (52.6%) women and asthma reported by 25 (21.6%) women. At the study interview in the third trimester, prescription medication use (apart from methadone) was reported by 56 (48.3%) women. Antidepressant use was reported by 16 (13.8%) women.

Self-reported addiction histories of study participants are described in Table 6-3 . Women had been on methadone for a median of 7.0 years (IQR 3.0-10.0). Six women were started on methadone treatment during pregnancy. Use of heroin and benzodiazepines in the 30 days before the interview was reported by 34 (29.6%) and 44 (37.9%) women, respectively. Forty one women (35.3%) had smoked cannabis in the previous 30 days. Signs of withdrawal, as measured by the Objective Opiate Withdrawal Scale (OOWS), were present for 12 (10.3%) women. Among these women withdrawal was mild with a maximum OOWS score of two. There was no significant difference in the mean methadone dose at delivery in women with and without signs of opioid withdrawal ($p=0.73$). Maternal and neonatal urine toxicology results are summarised in Table 6-4. Results of urine toxicology testing in the four weeks before delivery were available for 107 women, of these 39 (36.4%) were opiate positive (excludes methadone). Urine

toxicology testing was carried out for 61 of the neonates, of these 32 (52.5%) were opiate positive.

6.3.3 *Perinatal outcomes and NAS*

The mean gestational age at delivery and birth weight were 39.0 weeks (SD 1.76) and 2965 g (SD 517), respectively. A high proportion of neonates were small for gestational age, with 49 (42.2%) having a birth weight below the customised tenth centile. Fifty six (48.3%) neonates required admission to the neonatal unit. The mean methadone dose at delivery was 69.3mg (SD 27.8). The overall rate of medically treated NAS was 25.4% (29 neonates). The rate did not differ between study centres (25.5% in CWIUH and 25.4% in the Rotunda).

Maternal and neonatal outcomes for women in the methadone only and concomitant drug use groups are compared in Table 6-5. Three neonates who had a urine sample positive for opiates were included in the methadone only group as their opiate-positive urine screen was most likely due to their urine samples being taken after initiation of oral morphine treatment for NAS. Compared to the methadone only group, perinatal outcomes did not differ significantly for the group with concomitant exposure to opiates, benzodiazepines or cocaine. The rate of preterm birth appeared higher in neonates exposed to concomitant drugs, although the difference was not statistically significant. There was a longer median duration of hospital stay in neonates exposed to concomitant drugs. Social reasons for prolonged stay such as custody arrangements or lack of accommodation were more common in the concomitant drug use group (11% versus 0%, $p=0.05$). The incidence of medically treated NAS, mean peak Finnegan scores and cumulative dose of NAS treatment did not appear to differ

with concomitant drug use. Methadone use at delivery is compared for the methadone only and concomitant drug use groups in Table 6-6. Women with evidence of concomitant drug use had higher mean methadone doses at delivery (73.7mg [SD 26.9] compared with 60.5mg [SD 27.8], $p=0.02$). There was a statistically significant increase in concomitant drug use with increasing methadone dose band at delivery ($p=0.02$).

The second comparison examined maternal and neonatal outcomes for low and high methadone dose groups with a cut-off of ≥ 80 mg (Table 6-7). Perinatal outcomes did not differ between the two groups. There was a higher median cumulative dose of morphine treatment for NAS in the high dose group. No other statistically significant differences were found between the two dosage groups with respect to the incidence of medically treated NAS, the mean peak Finnegan score or the total length of hospital stay. The incidence of medically treated NAS in relation to methadone dose band at delivery is presented in Figure 6-1. There was no association between increasing maternal methadone dose band at delivery and the incidence of medically treated NAS in the univariable analysis ($p=0.75$) or in the multivariable analysis with adjustment for concomitant drug use ($p=0.60$). Within the methadone only group 4 of 26 (15.4%) neonates in the low dose group required medical treatment for NAS compared with 4 of 14 (28.6%) in the high dose group ($p=0.42$).

The results of logistic regression analyses examining the association between clinical factors that might influence the incidence of medically treated NAS are outlined in Table 6-8. None of the tested potential determinants had a significant effect on the incidence of medically treated NAS in univariable analyses or in

multivariable analyses that adjusted for methadone dose and concomitant drug use.

Three congenital anomalies were recorded in the 114 live born neonates, including one case each of trigonocephaly, ventricular septal defect and congenital melanocytic naevus. Neonatal follow up was limited to the duration of the postnatal hospital stay; however two deaths were reported after hospital discharge at 3 weeks and 5 months of age, both from suspected sudden infant death syndrome.

6.4 Discussion

This prospective cohort study reported on perinatal outcomes and NAS in a group of opioid-dependent pregnant women treated in two maternity hospitals in Dublin, Ireland. Adverse perinatal outcomes were common among the study participants, with four in ten neonates being small for gestational age and nearly half admitted to the neonatal unit. Neonates exposed to methadone only had a shorter duration of hospitalisation than those exposed to methadone and concomitant opiates, benzodiazepines, or cocaine. The incidence or severity of NAS did not differ significantly for neonates exposed to methadone only and those exposed to methadone and concomitant drugs. Concomitant use of opiates, benzodiazepines or cocaine was more likely with increasing methadone dose. Neonates exposed to methadone doses of 80mg or above required higher cumulative doses of morphine treatment for NAS than those exposed to lower doses. The incidence and duration of NAS did not differ with maternal methadone doses above and below 80mg. None of the tested clinical factors were statistically significant determinants of the incidence of medically treated NAS. Of note, the occurrence of two intrauterine deaths and two postnatal deaths seems high for a group this size.

6.4.1 *Strengths and weaknesses*

This study had the strength of prospective design, with the ability to collect detailed data on exposures and outcomes which would not be available with retrospective study designs. Information was available on methadone and other prescribed medication use along with objective measures of concomitant drug use, allowing an assessment of the independent effects of methadone and concomitant exposures on perinatal outcomes. Data were available on maternal characteristics

and other factors which may affect the incidence, severity or duration of NAS such as preterm birth,¹⁴⁶ smoking,²⁴² use of antidepressant medications,²⁸⁹⁻²⁹² and concomitant illicit drug use. Many previous retrospective studies in this context have failed to adjust for the effect of these putative confounding factors when assessing the relationship between maternal methadone dose and NAS. There was a uniform multidisciplinary approach to the treatment of mothers and neonates during the study period across the two study centres. Assessment of the incidence of NAS was based on an objective scoring system.²⁴³ Data on medications used to treat NAS and peak Finnegan scores were available as indices of the incidence and severity of NAS. Information on duration of hospital stay was available as a proxy indicator of the duration of treatment of NAS. Women who declined participation in the study did not appear to differ significantly from participants, therefore the results are likely to be generalisable to similar populations of opioid-dependent women.

Although this was one of the largest prospective cohort studies of methadone use in pregnancy reported to date, it had limited power to detect differences in the incidence of NAS and examine the determinants of NAS as the incidence of medically treated NAS was lower than anticipated in the *a priori* sample size calculation and in relation to similar studies.²⁷⁹ Nevertheless, the pattern of medically treated NAS across the reported dosage bands does not suggest that there was a relationship that went undetected due to insufficient power. Nurses and midwives assessing the severity of NAS and neonatologists initiating medical treatment were not blinded to maternal methadone dose and use of concomitant drugs. Though an objective scoring system was used, this knowledge may have

biased estimates of the severity of NAS and decisions to initiate treatment. Policies to discharge some neonates on phenobarbitone treatment for NAS in the two study centres meant that the duration of hospitalisation is not necessarily an accurate reflection of total duration of treatment. Disentangling the effects of methadone dose on perinatal outcomes and NAS from those of concomitant use of heroin, benzodiazepines, cannabis, cocaine, alcohol and prescribed medications (e.g. antidepressants) is complex. Maternal and neonatal urinalysis had limitations in this study. Maternal results were only available as a binary variable for any positive result in the four weeks before delivery. There was insufficient data on compliance with urinalysis and any concomitant use prior to four weeks before delivery would have been missed. The window of detection for illicit drug use in neonatal urinalysis is limited, reflecting use in the days prior to delivery.²⁸² There is also potential for false positive results due to urinalysis after morphine treatment for NAS has been initiated or due to use of opioid analgesia in a breastfeeding mother. Outcomes besides NAS such as growth restriction are likely to be significantly affected by other maternal characteristics such as smoking, which is very common in this group and maternal nutritional status, which was not assessed in this study. As a range of outcomes were examined in this study, the issue of multiple testing and the associated risk of type I errors become relevant. For this reason, this study provides hypotheses that require further testing in future studies.

6.4.2 *Comparison with other Studies*

With regard to perinatal outcomes, the preterm birth rate of 10.3% was lower than some international estimates of 20 to 45% in methadone maintained women.^{36 156}

This rate is also lower than a previous estimate of 20.4% from CWIUH.²⁸⁸ The low incidence could be partially explained by the fact that women with very preterm delivery were less likely to be recruited for the study. If non-participants were included, however, the rate of preterm birth would only increase to 11.4%. This difference may be a chance finding. An alternative explanation is the introduction of a dedicated antenatal clinic for women with opioid dependence in CWIUH since the previous study. Greater continuity of care and better compliance with antenatal care may have a positive effect on preterm birth.

A considerable proportion of the neonates were small for gestational age, with 42% of neonates having a birth weight below the customised 10th centile. A similar proportion was reported in an earlier study from CWIUH.²⁸⁸ Dryden *et al* reported that 23% of infants delivered at a Glasgow maternity hospital weighed less than the ninth centile.³⁶ Low birth weight is a common feature in studies of methadone maintenance treatment in pregnancy.^{137 283} An excessive number of neonates also had head circumferences or lengths below the 10th centile. Similar findings relating to reduced head circumference²⁹⁸ and length measurements²⁹⁹ have been reported previously. Methadone exposure may not affect growth directly, some studies have indicated that intrauterine growth restriction is related to maternal body mass index rather than methadone use.²⁸⁵

Concomitant drug use and methadone dose at delivery were found to have an impact on the duration of hospitalisation and severity of NAS, respectively. Neonates exposed to concomitant drugs had a longer hospital stay than those exposed to methadone only. Duration of hospitalisation is likely to have multiple contributing factors other than NAS, including social reasons for prolonged stay

and possibly a greater incidence of preterm birth after exposure to concomitant drugs. An increased duration of hospitalisation for neonates with exposure to concomitant drugs was reported by Dryden and colleagues who found that duration of hospital stay was longer for neonates of polydrug-misusing women.³⁶ Seligman *et al* also reported that concomitant benzodiazepine use was a significant predictor of length of NAS treatment.²²⁵ Other studies that examined the impact of methadone dose on duration of hospitalisation have had conflicting findings with some reporting longer length of stay with higher methadone doses¹⁵⁶²¹⁴ and others reporting no relationship.¹⁵⁸¹⁴¹ Neonates exposed to higher methadone doses required a greater amount of morphine for the treatment of NAS. Previous studies that quantified morphine use as a proxy measure for the severity of NAS did not assess the impact of methadone dose on morphine requirements.¹⁷²¹⁷³

The incidence of medically treated NAS was low in comparison to previous reports, most of which had overall rates in the 60-80% range.¹⁵⁵¹⁵⁸²¹⁷²²⁴²²⁸²³⁴²⁴⁷²⁶⁵²⁷³³⁰⁰ Some reports have had a lower overall level of medically treated NAS closer to the level reported here.¹⁴²¹⁴⁵²²⁹²⁵⁰ Differences in rates of medically treated NAS may be partially explained by varying treatment thresholds in individual neonatal units. Findings in relation to the impact of maternal methadone dose on the incidence of NAS are similar to previous studies reporting no relationship.³²¹⁴¹¹⁵⁷¹⁵⁸¹⁷⁰²²⁶²³¹²³³ The findings are in conflict, however, with two studies previously conducted in CWIUH¹⁸⁶²⁸⁸ and other studies that have reported a relationship.²⁷³⁶¹⁴⁰¹⁴⁸¹⁵⁵²¹²²¹⁴²¹⁷²²¹²²² Differences in findings between this study and the two studies previously conducted in CWIUH could be partially

explained by temporal trends in the diagnosis and treatment of NAS in the study hospitals. The former studies also had different sources of outcome ascertainment, with one reporting on recorded diagnoses of NAS in an electronic hospital discharge register rather than actual medical treatment determined by an objective scoring system²⁸⁸ and the other not clearly defining NAS.¹⁸⁶ These studies did not report on the severity or duration of NAS.

Concomitant drug use was more likely among women on higher methadone doses. The relationship between concomitant drug use and methadone dose in opioid-dependent pregnant women is not completely understood. Some authors have reported conflicting findings of less use of concomitant drugs with higher methadone doses.¹⁴¹ In the non-pregnant population, higher methadone doses are associated with reduced use of concomitant drugs.³⁰¹

Among the 116 study participants there were two intrauterine deaths and two deaths from suspected Sudden Infant Death Syndrome. Few studies have estimated the effect of methadone on perinatal or infant mortality rates.²³⁵ A previous estimate of the perinatal mortality rate after methadone use in pregnancy in CWIUH was 24 per 1000 births.²⁸⁸ Methadone use during pregnancy has been associated with an elevated infant mortality rate of 24 per 1000 live births, mostly as a result of Sudden Infant Death Syndrome.¹⁶⁶

6.4.3 *Clinical implications*

This study adds to the existing body of knowledge concerning perinatal outcomes and NAS following methadone use in pregnancy. Adverse perinatal outcomes, such as being small for gestational age and admission to the neonatal unit, are

common in this group. Compared to the total population there may be an elevated risk of perinatal and infant mortality after methadone maintenance treatment for opioid-dependence in pregnancy. Every attempt should be made to facilitate optimal engagement with antenatal care to ensure that modifiable risk factors for these adverse outcomes are addressed. As psychiatric co-morbidity was common among study participants, with over half reporting current depression or a history of depression, appropriate monitoring and treatment during and after pregnancy is important. The rate of unplanned pregnancy in study participants was very high. Clinicians should regularly assess the contraceptive needs of opioid-dependent women.

Concomitant drug use, which was associated with an increased duration of hospitalisation for the neonate, was common in this study. There was also some evidence of non-compliance with methadone maintenance treatment. Opioid-dependent pregnant women should be counselled on the potential risks of concomitant drug use during pregnancy. Contingency management approaches, which use increasing value food vouchers to incentivise continued abstinence from concomitant illicit drug use and treatment compliance, have been shown to be effective in this setting.³⁰²

The issue of reducing methadone doses during pregnancy is controversial.¹⁶⁸ A considerable proportion of patients seek to have their dose reduced during pregnancy in the hope of attenuating NAS. Though there was some evidence of increased severity of NAS with higher methadone doses in this study, methadone dose did not appear to affect the incidence or duration of NAS. There is no robust evidence available that demonstrates that lowering methadone doses during

pregnancy leads to reductions in the incidence, severity or duration of NAS. It is important not to consider NAS as the only factor influencing methadone dosage decisions during pregnancy. Relief of maternal withdrawal symptoms and blockage of further opioid use are of primary importance. The findings of this study support the approach of prescribing an appropriate methadone dose that stops or minimises illicit drug use which is endorsed by international treatment guidelines from the US,¹⁷⁵ the UK,¹⁷⁶ and Australia.¹⁷⁷

6.4.4 *Implications for future research*

Ideally a sufficiently powered randomised study would compare adverse perinatal outcomes, and the incidence, severity and duration of NAS for women randomised to high and low dose methadone groups. There are serious ethical and practical difficulties in carrying out such a trial. In the absence of a randomised study, a definitive multicentre prospective cohort study of adverse perinatal outcomes in general and the determinants of NAS in particular should be carried out. This study would have to overcome the limitations of research to date including small sample sizes and failure to control for factors besides methadone use that may affect perinatal outcomes and NAS. The association between higher methadone doses and greater use of concomitant drugs is a particular challenge that would need to be addressed in the study protocol. There have been calls previously for an international collaborative prospective cohort study, with objective, blinded assessment of outcomes and detailed recording of potential confounders or effect modifiers.^{35 288} Such a study could build on the experience of international collaborations such as the MOTHER project, a double-blind, double-dummy, flexible-dosing, randomised clinical trial of methadone versus buprenorphine for

the management of opioid-dependent pregnant women.¹⁷⁴ International collaboration would afford the opportunity to include patients from diverse settings treated with a wide range of methadone doses with a common follow up protocol.

There is a need to investigate further inter-patient variations in methadone pharmacokinetic parameters such as metabolic capacity¹²⁰ and genetic polymorphisms known to affect placental transfer of methadone¹²⁴ as potential determinants of NAS. Further pharmacoepidemiological studies of the relationship of methadone use in pregnancy with perinatal and infant mortality are also needed in order to identify potentially modifiable risk factors in this group of women. A recent population-based Australian study identified heavy smoking, not accessing antenatal care and having a birth weight below the 10th centile for gestational age as risk factors for death in methadone-exposed infants.¹⁶⁶ Some of these risk factors may be amenable to intervention with adequately-resourced multi-disciplinary antenatal care.

In conclusion, this study suggested that adverse perinatal outcomes such as being small for gestational age and admission to the neonatal unit were common in this group. The duration of hospitalisation for the neonate was affected by maternal use of opiates, benzodiazepines and cocaine. The incidence and duration of NAS were not affected by methadone dose, though the severity of NAS, as indicated by the amount of morphine required for treatment, was increased with higher doses.

Table 6-1 Maternal Characteristics of Study Participants and the Total Population

		Study Participants	Total Population [#]	
	n	n=116	n=16884	p
Age at delivery	116			
<20 years		1 (0.9)	704 (4.2)	0.07
20-24 years		10 (8.6)	2417 (14.3)	0.08
25-29 years		43 (37.1)	4233 (25.1)	<0.01
30-34 years		45 (38.8)	5310 (31.4)	0.09
35-39 years		15 (12.9)	3520 (20.8)	0.04
>40 years		2 (1.7)	700 (4.1)	0.19
Unemployed	116	73 (63.5)	4553 (27.0)	<0.01
Nulliparous	116	16 (13.8)	7582 (44.9)	<0.01
Unplanned pregnancy	87	63 (72.4)	2968/9206 [*] (32.2)	<0.01
Non-Smoker	116	11 (9.5)	7672/9206 [*] (83.3)	<0.01
Hepatitis B Positive Serology [*]	115	3 (2.6)	128 (0.8)	0.02
Hepatitis C Positive Serology [‡]	115	56 (48.7)	135 (0.8)	<0.01
HIV Positive [§]	115	5 (4.3)	57 (0.3)	<0.01

[#] Total number of women with deliveries >500g in both study centres

^{*} CWIUH Only- denominator relates to all women booking for antenatal care

^{*} Current or past hepatitis B surface antigen, core antibody, E antigen or E antibody positive

[‡] Current or past hepatitis C antibody or polymerase chain reaction positive

[§] HIV antigen or antibody positive

Table 6-2 Maternal Characteristics of Study Participants and Non-participants

	n	Study Participants n=116 (81.1%)	Non- participants n=27 (18.9%)	OR	95% CI	p
Age at delivery	143					
<20 years		1 (0.9)	1 (3.7)	0.21	0.01-3.67	0.28
20-24 years		10 (8.6)	1 (3.7)	2.09	0.24-18.5	0.51
25-29 years		43 (37.1)	9 (33.3)	1	-	-
30-34 years		45 (38.8)	11 (40.7)	0.86	0.32-2.27	0.75
35-39 years		15 (12.9)	5 (18.5)	0.63	0.18-2.17	0.46
>40 years		2 (1.7)	0 (0)	-	-	-
Socioeconomic group	142					
Home duties		29 (25.2)	4 (14.8)	1	-	-
Unemployed		73 (63.5)	19 (70.4)	0.53	0.17-1.69	0.28
Employed		13 (11.3)	4 (14.8)	0.45	0.10-2.08	0.30
Nulliparous	143	16 (13.8)	4 (14.8)	0.92	0.28-3.01	0.89
Unplanned pregnancy	111	63 (72.4)	17 (70.8)	0.92	0.34-2.51	0.88
Booking gestation (weeks)	143					
< 12 weeks		44 (37.9)	12 (44.4)	1	-	-
12 - 20 weeks		52 (44.8)	10 (37.0)	1.42	0.56-3.60	0.46
> 20 weeks		20 (17.2)	5 (18.5)	1.09	0.34-3.51	0.88
Five or less antenatal visits	142	26 (22.6)	11 (40.7)	0.42	0.18-1.03	0.06
Three or more missed antenatal appointments	139	49 (43.8)	14 (51.9)	0.77	0.31-1.68	0.45
Smoking status at booking (cigarettes per day)	143					
Non-Smoker		19 (16.4)	2 (7.4)	1	-	-
1-10		46 (39.7)	9 (33.3)	0.54	0.11-2.73	0.45
11-20		33 (28.4)	12 (44.4)	0.29	0.06-1.43	0.13
>20		18 (15.5)	4 (14.8)	0.47	0.07-2.91	0.42
Periconceptional Alcohol Use (units per week)	62					
Never		18 (42.9)	7 (35.0)	1	-	-
Occasional		7 (16.7)	4 (20.0)	0.68	0.15-3.07	0.62
1 - 5		12 (28.6)	6 (30.0)	0.78	0.21-2.89	0.71
6 - 10		3 (7.1)	2 (10.0)	0.58	0.08-4.27	0.60
11 - 20		0 (0)	1 (5.0)	-	-	-
>20		2 (4.8)	0 (0)	-	-	-
Hepatitis B Positive Serology*	142	3 (2.6)	0 (0)	-	-	-
Hepatitis C Positive Serology [†]	142	56 (48.7)	13 (48.1)	1.02	0.44-2.36	0.96
HIV Positive [§]	141	5 (4.3)	1 (3.8)	1.14	0.13-10.16	0.91
Body Mass Index	130					
<18.5		8 (7.6)	1 (4.0)	2.43	0.28-20.82	0.42
18.5-24		56 (53.3)	17 (68.0)	1	-	-
25-29		27 (25.7)	2 (8.0)	4.10	0.88-19.03	0.07
>30		14 (13.3)	5 (20.0)	0.85	0.27-2.70	0.78
Methadone Dose at Delivery	143					
≤20mg		8 (6.9)	3 (11.1)	1	-	-
21-50mg		27 (23.3)	5 (18.5)	2.02	0.40-10.4	0.38
51-80mg		45 (38.8)	9 (33.3)	1.88	0.42-8.47	0.41
81-100mg		28 (24.1)	7 (25.9)	1.50	0.31-7.17	0.61
>100mg		8 (6.9)	3 (11.1)	1.00	0.15-6.53	1.00

* Current or past hepatitis B surface antigen, core antibody, E antigen or E antibody positive

[†] Current or past hepatitis C antibody or polymerase chain reaction positive[§] HIV antigen or antibody positive

Table 6-3 Addiction History as Reported at the Third Trimester Study Interview

	n	Median (Interquartile range) Number (%)
Methadone		
Age at first use	116	21.0 (18.0-25.0)
Dose missed in last 30 days	116	11 (9.5%)
Duration of use (years)	112	7.0 (3.0-10.0)
Heroin		
Age at first use	115 [‡]	17 (15.0-21.0)
Ever injected	115	69 (59.5%)
Age at first injection	69	20 (17.0-23.5)
Current use (last 30 days)	115	34 (29.6%)
Duration of use (years)	115	6 (3.0-9.0)
Cocaine		
Age at first use	85	20 (16.0-24.5)
Current use (last 30 days)	116	4 (3.4%)
Benzodiazepines		
Age at first use	86	19.0 (16.0-23.5)
Current use (last 30 days)	116	44 (37.9%)
Duration of use (years)	56	6 (2.0-10.0)
Cannabis		
Age at first use	99	15 (13.0-17.0)
Current use (last 30 days)	116	41 (35.3%)
Duration of use (years)	45	7.0 (3.0-13.5)
Alcohol		
Any use (last 30 days)	116	32 (27.6%)

[‡] One participant reported a primary addiction to methadone (heroin never used)

Table 6-4 Maternal and Neonatal Urine Toxicology Results

	n	Positive Results Number (%)
Maternal*		
Opiates†	107§	39 (36.4)
Benzodiazepines	106	51 (48.1)
Cocaine	107	4 (3.7)
Neonatal		
Opiates†	61§	32 (52.5)
Benzodiazepines	61	17 (27.9)
Cocaine	61	6 (9.8)

* Any positive result in the four Weeks before Delivery

† Does not include methadone

§ Maternal and neonatal urine toxicology results not available for all mothers and neonates

Table 6-5 Perinatal Outcomes and Neonatal Abstinence Syndrome in Relation to Concomitant Drug use in addition to Methadone

	n	Methadone Only n=40 (34.8%)	Concomitant drug use [§] n=75 (65.2%)	OR	95% CI	p
Mode of delivery	115 [†]					
SVD		28 (70.0)	48 (64.0)	1	-	-
Elective LSCS		5 (12.5)	6 (8.0)	0.70	0.20-2.50	0.58
Emergency LSCS		5 (12.5)	14 (18.7)	1.63	0.53-5.02	0.39
Forceps/ventouse		2 (5.0)	7 (9.3)	2.04	0.40-10.52	0.39
Meconium stained liquor	106	2 (5.7)	5 (7.0)	1.25	0.23-6.79	0.80
Preterm birth < 37 weeks	115	2 (5.0)	10 (13.3)	2.92	0.61-14.05	0.18
Spontaneous preterm labour	115	1 (2.5)	5 (6.7)	2.78	0.31-24.70	0.36
Weight for gestational age < 10 th centile	114	15 (37.5)	34 (45.9)	1.42	0.64-3.11	0.38
Occipitofrontal circumference < 10 th centile	111	11 (29.7)	27 (36.5)	1.36	0.58-3.17	0.48
Length < 10 th centile	81	7 (25.9)	19 (35.2)	1.55	0.56-4.33	0.40
Apgar score <3 at 1 minute	108	1 (2.7)	0	-	-	-
Apgar score <7 at 5 minutes	108	0	0	-	-	-
Admitted to neonatal unit	113	19 (47.5)	37 (50.7)	1.14	0.52-2.46	0.75
Pharmacological treatment for NAS	113	8 (20.0)	21 (28.8)	1.62	0.64-4.08	0.31
Length of stay*	113	5.0 (5.0-7.0)	6.0 (5.0-22.5)	-	-	0.03 [‡]
Peak Finnegan score*	109	8.0 (5.0-11.0)	9.0 (6.0-12.0)	-	-	0.34 [‡]
Cumulative dose of morphine treatment (mg)*	29	15.1 (10.7- 29.4)	17.2 (12.4- 30.5)	-	-	0.63 [‡]
Cumulative dose of phenobarbitone treatment (mg)*	12	224 (-)	321 (191-407)	-	-	0.39 [‡]

* Median (Interquartile Range)
† One mother-neonate pair did not have any urine toxicology data and could not be categorised
§ Evidence of concomitant opiate, benzodiazepine or cocaine use (maternal urine toxicology testing in the four weeks before delivery or neonatal urine toxicology testing in the first days of life)
‡ Mann-Whitney U-Test
LSCS Lower segment Caesarean section

Table 6-6 Maternal Methadone Dose at Delivery in Relation to Concomitant Drug use

	Methadone Only n=115 [†]	n=40 (34.8%)	Concomitant drug use [§] n=75 (65.2%)	OR	95% CI	p
Methadone dose at delivery (mg)	60.5 (27.8) *		73.7 (26.9)	-	-	0.02 [‡]
Methadone dose band at delivery						
Less than 21mg	5 (12.5)		3 (4.0)	1	-	-
21-50mg	12 (30.0)		15 (20.0)	2.08	0.41-10.5	0.38
51-80mg	14 (35.0)		31 (41.3)	3.69	0.77-17.6	0.10
Greater than 80mg	9 (22.5)		26 (34.7)	4.82	0.95-24.3	0.06

* Mean (Standard Deviation)
† One mother-neonate pair did not have any urine toxicology data and could not be categorised
§ Evidence of opiate, benzodiazepine or cocaine use in addition to methadone in maternal urine toxicology testing in the four weeks before delivery or neonatal urine toxicology testing in the first days of life
‡ Independent samples T-Test

Table 6-7 Perinatal Outcomes and Neonatal Abstinence Syndrome in Relation to Methadone Dose at Delivery

	n	Methadone Dose at Delivery		OR	95% CI	p	aOR [†]	95% CI	p
		<80mg n=65 (56.0%)	≥80mg n=51 (44.0%)						
Mode of Delivery	116								
SVD		46 (70.8)	31 (60.8)	1	-	-	1	-	-
Elective LSCS		4 (6.2)	7 (13.7)	2.60	0.70-9.63	0.15	2.87	0.76-10.9	0.12
Emergency LSCS		10 (15.4)	9 (17.6)	1.33	0.49-3.66	0.57	1.31	0.47-3.63	0.61
Forceps/ventouse		5 (7.7)	4 (7.8)	1.19	0.30-4.77	0.81	1.13	0.28-4.62	0.86
Meconium Stained Liquor	107	5 (8.2)	2 (4.3)	0.51	0.09-2.75	0.43	0.50	0.09-2.75	0.43
Preterm birth < 37 weeks	116	7 (10.8)	5 (9.8)	0.90	0.27-3.02	0.86	0.82	0.24-2.81	0.76
Spontaneous Preterm Labour	116	4 (6.2)	2 (3.9)	0.62	0.11-3.54	0.59	0.57	0.10-3.29	0.53
Weight for gestational age < 10 th centile [†]	115	26 (40.0)	23 (46.0)	1.28	0.61-2.69	0.52	1.28	0.60-2.73	0.52
Occipitofrontal Circumference < 10 th centile	112	21 (33.9)	17 (34.0)	1.00	0.46-2.21	0.99	1.00	0.45-2.22	1.00
Length < 10 th centile	82	11 (25.6)	15 (38.5)	1.82	0.71-4.66	0.21	1.84	0.71-4.77	0.21
Apgar score <3 at 1 minute	109	1 (1.7)	0	-	-	-	-	-	-
Apgar score <7 at 5 minutes	109	0	0	-	-	-	-	-	-
Admitted to neonatal unit	114	29 (45.3)	27 (54.0)	1.42	0.67-2.98	0.36	1.47	0.69-3.12	0.32
Pharmacological treatment for NAS	114	15 (23.4)	14 (28.0)	1.27	0.54-2.96	0.58	1.24	0.53-2.93	0.62
Length of stay*	114	6 (5-13.8)	6 (5-25)	-	-	-	-	-	0.46 [‡]
Peak Finnegan Score*	110	8.0 (6.0-11.0)	8.0 (5.0-11.5)	-	-	-	-	-	0.67 [‡]
Cumulative dose of Morphine treatment (mg)*	29	13.2 (10.5-19.9)	19.3 (16.1-34.4)	-	-	-	-	-	0.03 [‡]
Cumulative dose of Phenobarbitone treatment (mg)*	12	310 (258-701)	215 (181-361)	-	-	-	-	-	0.17 [‡]

* Median (Interquartile Range)

[†] Adjusted for concomitant drug use (Evidence of opiate, benzodiazepine or cocaine use in addition to methadone in maternal urine toxicology testing in the four weeks before delivery or neonatal urine toxicology testing in the first days of life)

[‡] Mann-Whitney U-Test

Table 6-8 Potential Determinants of Medically Treated Neonatal Abstinence Syndrome

		NAS n=29 (25.4%)	No NAS n=85 (74.6%)	OR	95% CI	p	aOR*	95% CI	p
Maternal Smoking During Pregnancy	114 [†]								
None		2 (18.2)	9 (81.8)	1	-	-	1	-	-
1-10 a day		12 (35.3)	22 (64.7)	2.46	0.45-13.2	0.30	2.31	0.41-13.1	0.34
Greater than 10 a day		15 (21.7)	54 (78.3)	1.25	0.24-6.42	0.79	1.29	0.24-6.83	0.77
FTND Score 6 or above	106	11 (27.5)	29 (72.5)	1.09	0.45-2.65	0.84	1.10	0.45-2.70	0.83
Antidepressant use	114	2 (13.3)	13 (86.7)	0.41	0.09-1.94	0.26	0.39	0.08-1.87	0.24
History of NAS in previous neonate	112	6 (25.0)	18 (75.0)	1.06	0.37-3.03	0.91	0.98	0.34-2.83	0.97
Preterm birth < 37 weeks	114	3 (27.3)	8 (72.7)	1.11	0.27-4.50	0.88	1.00	0.24-4.11	1.00
Small for gestational age < 10 th centile	113	12 (25.0)	36 (75.0)	0.94	0.40-2.21	0.89	0.90	0.38-2.16	0.82
Male Sex	114	18 (30.5)	41 (69.5)	1.76	0.74-4.16	0.20	1.85	0.77-4.47	0.17

FTND- Fagerström Test of Nicotine Dependence

[†] Data available for 114 liveborn neonates

*Adjusted for methadone dose at delivery (mg) and concomitant use of opiates, benzodiazepines or cocaine (based on maternal urine toxicology testing in the four weeks before delivery or neonatal urine toxicology testing in the first days of life)

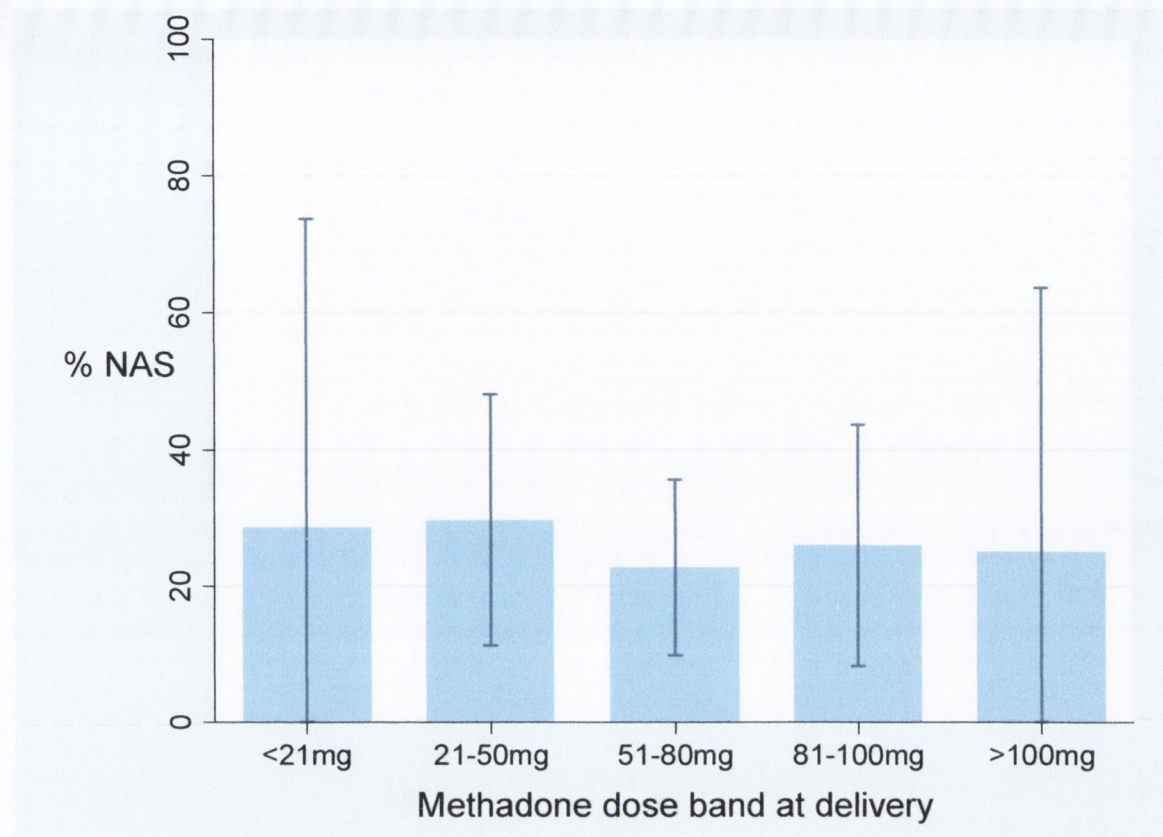


Figure 6-1 Incidence of Medically Treated Neonatal Abstinence Syndrome by Methadone Dose Band at Delivery



Figure 5-1 Incidence of Medically Treated Neonatal Abstinence Syndrome by Morphine Dose Band at Delivery

CHAPTER 7. CONCLUSION

7.1 Summary of Findings

This thesis aimed to address current knowledge deficits relating to the issues of medication use in early pregnancy in an Irish healthcare setting and adverse perinatal outcomes in opioid-dependent pregnant women on methadone maintenance treatment. This chapter summarises the findings of the four elements of the research project designed to address these aims and highlights the clinical and research implications of the thesis as a whole.

The descriptive study of the prevalence and determinants of medication use in early pregnancy found that four in ten women used a medication besides folic acid before booking for antenatal care and that potentially harmful medications were used by approximately 3% of women. Women were more likely to report using medications with potential for fetal harm if they had an unplanned or multiple pregnancy, or if they were unemployed, smokers, single or booked for antenatal care prior to 12 weeks gestation. Methadone was found to be the most commonly reported category D medication (i.e. positive evidence of human fetal risk but the potential benefits may be acceptable despite potential risks).

The systematic review assessed the relationship between maternal methadone dose and the diagnosis or medical treatment of NAS, one of the most commonly occurring adverse perinatal outcomes associated with methadone. Any differences in the incidence of NAS in infants of women on higher compared with lower doses were statistically non-significant in analyses restricted to prospective studies or to those using an objective scoring system to diagnose NAS. Maternal methadone dose did not have a consistent statistically significant effect on the incidence of medically treated NAS.

The retrospective cohort study reported that methadone exposure was associated with an increased risk of adverse perinatal outcomes even when known adverse socio-demographic factors had been accounted for. Methadone exposure was associated with an increased risk of very preterm birth <32 weeks, being small for gestational age <10th centile, admission to the neonatal unit and diagnosis of a major congenital anomaly. There was a significant dose-response relationship between methadone and diagnosis of NAS.

The prospective cohort study suggested that adverse perinatal outcomes such as being small for gestational age and admission to the neonatal unit were common after methadone maintenance treatment in pregnancy. The duration of hospitalisation for the neonate was increased with maternal use of opiates, benzodiazepines or cocaine. The incidence and duration of NAS were not affected by methadone dose, though the severity of NAS, as indicated by the amount of morphine required for treatment, was increased with higher methadone doses.

7.2 Clinical Implications

7.2.1 Medication use in pregnancy

It is important that prescribers and women of childbearing potential are aware of lack of safety data for many medications commonly used in pregnancy. Although use of some potentially harmful medications during pregnancy is not currently amenable to change, pre-conception counselling is important to ensure optimal use of medicines in pregnancy. Women with pre-existing medical disorders may benefit most from pre-conception counselling, allowing an opportunity to review medications, switch to preferable agents if necessary and stabilise management of

the medical disorder before conception. Women should also be counselled to ensure appropriate use of necessary medications during pregnancy.

There is currently no routine provision of pre-conception counselling for all pregnant women in the Irish healthcare system, though some initiatives target specific high-risk groups.^{303 304} Internationally there have been recommendations to target pre-conception counselling at women with certain medical disorders, primarily to reduce the risk of maternal morbidity and mortality e.g. epilepsy, diabetes, auto-immune disorders and severe pre-existing or past mental illness.¹³⁶ Preconception counselling has also been recommended for other groups such as obese women.³⁰⁵ The descriptive study demonstrated that exposure to category D/X medications was more likely in unemployed women, public patients and smokers. Combined with the fact that a significant proportion of pregnancies are unplanned it may be difficult to target pre-conception counselling to the women that need it most.

All women of childbearing potential should be educated about the need to avoid the use of non-essential medications if they may become pregnant. Public health messages regarding avoiding alcohol, smoking cessation and the consumption of at least 400 micrograms of folic acid daily before pregnancy and during the first trimester should also be reinforced. All prescribers should be aware of the danger of prescribing medications with known harmful effects during pregnancy to women of childbearing potential. The use of potentially harmful medications during pregnancy may be reduced by warnings about the use of such medications in women of childbearing potential in prescribing and dispensing software. In light of the rate of unplanned pregnancy, it is important that all pregnant women are

routinely assessed for any use of prescription medications, OTC products, herbal medicines/supplements or illicit drugs at the earliest possible opportunity. This is important to ensure that high-risk exposures such as ACE inhibitors or angiotensin II receptor antagonists are identified as early as possible in pregnancy.

7.2.2 *Methadone use in pregnancy*

The clinical implications of the systematic review and the two cohort studies will be considered together as each study looked at the issue of methadone use in pregnancy using complementary methodologies. Both cohort studies examined a range of perinatal outcomes in addition to NAS. Opioid-dependent pregnant women and their infants require dedicated, well-resourced, multi-disciplinary care as they are at increased risk of a range of adverse perinatal outcomes including preterm and very preterm birth, being small for gestational age, low Apgar scores and admission to the neonatal unit. Although the lower rate of preterm birth in the prospective cohort study may be a chance occurrence, it could also be due to improvements in the delivery of antenatal care between the two study periods. In the interim period opioid-dependent pregnant women started to receive antenatal care from a dedicated specialised antenatal clinic rather than usual care.

It is evident from the prospective study that concomitant drug use is common in these women. Concomitant drug use was associated with a longer duration of hospitalisation for the neonate. Contingency management approaches which incentivise abstinence from concomitant illicit drug use and treatment compliance have been shown to be effective in this setting.³⁰² Such support may also help these women to regularly attend for antenatal care and could potentially impact on neonatal duration of hospitalisation. Concomitant drug use included the use of

benzodiazepines, some of which were prescribed. Reduced benzodiazepine intake during pregnancy should be encouraged if possible as benzodiazepine exposure has been associated with adverse perinatal outcomes including preterm birth and low birth weight.³⁰⁶ Smoking was very common among methadone maintained women in the cohort studies. Interventions to reduce smoking should be incorporated into routine care for these women. Contingency management interventions, which incentivise smoking cessation by the provision of vouchers for evidence of abstinence (breath carbon monoxide levels), have been shown to be effective in pregnant opioid-dependent women.³⁰⁷ Clinicians should be aware of the high rates of unplanned pregnancy reported in the prospective study. High rates of unintended pregnancy have been reported in US opioid-dependent women.³⁰⁸ There have been no reports of interventions to improve contraceptive practices in opioid-dependent women, practical approaches could include regular review of the contraception needs of all opioid-dependent women and provision of easy access to the woman's choice of contraceptive in the postpartum period.

The systematic review and prospective cohort study found that there was no consistent statistically significant dose-response relationship between methadone and the incidence of NAS. The retrospective cohort study reported a significant increase in the diagnosis of NAS with increasing methadone doses. This divergence of results may have several explanations. It could be argued that the retrospective study was sufficiently powered and detected a significant difference that could not be detected by the prospective study because of small sample size, or by the meta-analysis because of the size and power of the included studies. Alternatively, the ascertainment of NAS in the retrospective study, using diagnoses

from electronic records rather than recording the level of medically treated NAS, may have been biased. A diagnosis of NAS may have been recorded for any neonate suspected of having withdrawal symptoms, which could be influenced by knowledge of maternal methadone dose. The differing findings of the retrospective and prospective studies could be viewed in the context of the findings from the meta-analysis, where statistically significant differences, which were present when retrospective studies were included, disappeared when only prospective cohort studies were considered.

Regardless of whether or not the dose-response relationship exists, the desire to prevent NAS should not be viewed as the sole determinant of methadone dose in opioid-dependent pregnant women. Use of appropriate methadone doses to relieve maternal withdrawal and prevent or minimise concomitant illicit drug use is of primary importance. NAS, although distressing, is a short term manageable condition. This should be contrasted with adverse perinatal outcomes such as perinatal death, growth restriction, preterm birth, or vertical transmission of HIV or Hepatitis B which may result from relapse or continued illicit drug use. If women request dose reduction in pregnancy, they should be counselled about the potential risks and the fact that there is no robust evidence to support this approach to reducing the incidence of NAS.

There are no national treatment guidelines for the management of opioid dependence in pregnancy in the Irish healthcare system. As a consequence of the collaborative research group established for the prospective cohort study, a policy on the prescribing and administration of methadone in the Dublin Maternity Hospitals has been developed. This local policy is now being formulated into a

national guideline under the auspices of the Health Service Executive's National Clinical Programme for Obstetric Care. In the absence of evidence-based guidance on the care of opioid-dependent pregnant women there are currently varying approaches to management. A substantial minority of women have their methadone doses decreased during pregnancy, most likely at the mother's request, in the hope of attenuating NAS. This occurs despite the fact that there is no robust evidence supporting this approach to reducing the risk of NAS. There is scope for a broad national guideline that goes beyond the prescribing and administration of methadone and also addresses other relevant issues such as smoking cessation and contraception.

It is important that this research is available to people who care for opioid-dependent pregnant women within the Irish Healthcare system. Copies of publications arising from the project have been disseminated locally within the maternity and addiction services, and in the relevant academic departments. The Health Research Board's National Documentation Centre on Drug Use has indexed each of the published methadone-related studies on their research database, enabling wider dissemination of the results to an important target audience.

7.3 Research Implications

7.3.1 *Medication use in pregnancy*

The descriptive study provides prevalence estimates of the most commonly reported potentially harmful medications in early pregnancy in an Irish context. This allows prioritisation of future research in this area and identification of sizeable cohorts of women exposed to medications of interest. There may be avoidable use of medications with potential for fetal harm during pregnancy. Targeted pre-conception counselling for high-risk women could help ensure optimal use of medications during pregnancy. Further research is required to determine how pre-conception counselling should be targeted and delivered in the Irish healthcare system.

In practical terms, establishing the dataset for the descriptive and retrospective studies involved extracting, cleaning and coding a substantial amount of data from over 60,000 electronic patient records to facilitate analysis of medication exposures and subsequently perinatal outcomes. The resulting dataset contains information on medical and obstetric characteristics, early pregnancy medication exposures and perinatal outcomes for a significant cohort. Ongoing recording of medication exposures has been improved by including a drop-down list of commonly reported medications in the computer-guided antenatal booking interview to simplify recording for midwifery staff and reduce reliance on free text entry of medication names. Future validation studies of recorded maternal characteristics, medication exposures and perinatal outcomes are warranted to ascertain the completeness of electronic record data. There is obvious future

research potential within such a dataset, which, with appropriate ongoing management, will continually grow.

Ancillary research projects carried out using this dataset include studies of optimal folic acid use³⁰⁹ and periconceptional alcohol consumption.³¹⁰ The dataset is also responsive to developing research needs. After the initiation of the H1N1 2009 vaccination programme for pregnant women it was possible to include a question on vaccination status, timing of vaccination and product used for all women admitted to the Delivery Suite in the months following the pandemic. This amended dataset will allow a pharmacoepidemiological study of H1N1 2009 vaccine uptake and perinatal outcomes. The methodologies developed in the course of conducting this research could be used for research utilising the proposed National Maternal and Neonatal Clinical Management System.³¹¹ This national dataset which is currently in development would enable significantly larger pharmacoepidemiological studies which would be representative of the total population of Ireland. In the interim, there is potential for research collaborations to expand the dataset and methodology to include other Irish centres.

7.3.2 *Methadone use in pregnancy*

With regard to adverse perinatal outcomes after methadone exposure in pregnancy, further research is required to elicit the independent risk factors for outcomes such as being small for gestational age and preterm birth. This research could identify potentially modifiable risk factors and may allow further improvement of antenatal care for these women. The findings relating to congenital anomalies from the retrospective cohort study require assessment in other populations, given the limitations of incomplete ascertainment and potential detection bias with more

frequent neonatal unit admission for methadone-exposed neonates. A case-control study would give some indication of whether or not methadone exposure is associated with any specific congenital anomalies or Pierre Robin Sequence. There should be routine assessment and reporting of congenital anomalies in future research examining methadone use in pregnancy.

A pharmacoepidemiological study of perinatal and infant mortality after methadone exposure in pregnancy is required to estimate the potential risk in an Irish setting. Such a study could help determine the aetiology for the increased risk and identify potentially modifiable risk factors. Additionally, further research is required on a potential association between methadone use in pregnancy and prolonged QT interval in the neonate.³¹²

The divergent findings relating to methadone dose and NAS from the three studies demonstrate how results may vary with study design and ascertainment of NAS, highlighting the importance of using complementary methodologies for research in this area. The systematic review demonstrated the heterogeneity of studies in this context with regard to study design, populations, concomitant drug use, ascertainment of outcomes, proportion of neonates treated for NAS, treatment policies for NAS and reporting. The reported findings require verification in an adequately-powered prospective cohort study.

The prospective cohort study demonstrates the feasibility of prospective research examining adverse perinatal outcomes and the determinants of NAS in this setting, with adequate participation rates of a representative group of opioid-dependent pregnant women. Future research should include opioid-dependent

pregnant women treated outside Dublin to improve generalisability. There is potential for international collaboration to prospectively follow up a large cohort of opioid-dependent pregnant women, sufficiently powered to allow detailed assessment of all the determinants of NAS and provide further information on perinatal and long-term outcomes. Such a study should include detailed objective recording of exposures that may affect NAS and standardised follow-up of neonates including assessment of outcomes blinded to methadone dose and concomitant drug use. This study would offer the potential for more long term follow-up to examine neurodevelopmental outcomes. There would also be an opportunity to further investigate inter-patient variations in methadone pharmacokinetic parameters such as metabolic capacity and genetic polymorphisms known to affect placental transfer of methadone.

7.4 Conclusion

This thesis reports on a body of research that addressed the prevalence of medication use in early pregnancy and perinatal outcomes after methadone maintenance treatment in pregnancy. Medication use in early pregnancy was common. Methadone use was associated with a range of adverse perinatal outcomes. Methadone dose did not have a consistent statistically significant effect on the incidence of NAS. Recommendations for clinical practice and future research from this research have been highlighted. Implementation of these recommendations would facilitate optimal use of medicines in pregnancy and help improve outcomes for opioid-dependent pregnant women and their children.

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APPENDICES

APPENDIX I SEARCH STRATEGIES

Pubmed Search Strategy

1. "Pregnancy"[Mesh]
2. Pregnan*
3. "Pregnancy Complications"[Mesh]
4. #1 OR #2 OR #3
5. "Opioid-Related Disorders"[Mesh]
6. (opioid* OR opiate*) AND (abuse* OR addict* OR dependen*)
7. (drug) AND (abuse* OR addict*)
8. "Methadone"[Mesh]
9. Methadone
10. #5 OR #6 OR #7 OR #8 OR #9
11. "Neonatal Abstinence Syndrome"[Mesh]
12. "Infant, Newborn"[Mesh]
13. Neonat* AND Abstinence AND Syndrome
14. Neonat* AND withdraw*
15. #11 OR #12 OR #13 OR #14

16. #4 AND #10 AND #15

17. #16 Limits: Humans

EMBASE Search Strategy

1. 'pregnancy'/exp
2. 'prenatal drug exposure'/exp
3. 'pregnancy outcome'/exp
4. pregnan*
5. #1 OR #2 OR #3 OR #4
6. 'substance abuse'/exp
7. 'drug misuse'/exp
8. 'narcotic dependence'/exp
9. 'opiate'/exp
10. 'methadone treatment'/exp
11. 'methadone'/exp
12. methadone
13. (opioid* OR opiate*) AND (abuse* OR addict* OR dependen*)
14. (drug) AND (abuse* OR addict*)
15. 'withdrawal syndrome'/exp
16. 'drug withdrawal'/exp

17. #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
OR #16
18. 'newborn'/exp
19. 'congenital drug dependence'/exp
20. neonat* AND abstinence AND syndrome
21. neonat* AND withdraw*
22. #18 OR #19 OR #20 OR #21
23. #5 AND #17 AND #22
24. #23 AND [humans]/lim

APPENDIX II QUALITY ASSESSMENT OF INCLUDED STUDIES

Study	Focused	Population	Exposure	Outcomes	Confounding	Measure	Conclusions
Arlettaz 2005	Yes	Not Clear	Yes	Yes	No	Yes	Yes
Bakstad 2009	Yes	Yes	Yes	Yes	No	Yes	Yes
Berghella 2003	Yes	Yes	Yes	Yes	No	Yes	Yes
Blaser 2008*							
Blinick 1975	Yes	Yes	Yes	Not Clear	No	Not Clear	Yes
Brown 1998	Not Clear	Not Clear	No	Not Clear	No	Not Clear	Yes
Brulet 2007*							
Chasnoff 1984	Not Clear	Yes	Yes		Not Clear	Not Clear	Yes
Choo 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dashe 2002	Yes	Yes	Not Clear	Yes	No	Yes	Yes
Davis 1975	Not Clear	Yes	Yes	Not Clear	No	Not Clear	Not Clear
Davis 1973	Yes	Yes	Not Clear	Not Clear	No	Yes	Yes
Dawe 1992	No	Yes	Not Clear	No	No	Not Clear	No
Doberczak 1993	Yes	Yes	Yes	Yes	No	Yes	Yes
Doberczak 1991	Yes	Yes	Yes	Yes	No	Not Clear	Yes
Dryden 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ebner 2007	Yes	Yes	No	Yes	Yes	Yes	Yes
Fajemirokun 2006	Not Clear	Yes	No	Yes	No	Yes	Yes
Finnegan 1978	Not Clear	Not Clear	Yes	Yes	No	Yes	Yes
Fischer 2006	Yes	Yes	Yes	Yes	Not Clear	Yes	Yes
Fundaro 1994*							
Geistlich 1999	Yes	Yes	Yes	Not Clear	No	Not Clear	Yes
Green 1979	Yes	Not Clear	Not Clear	Yes	No	Yes	Not Clear

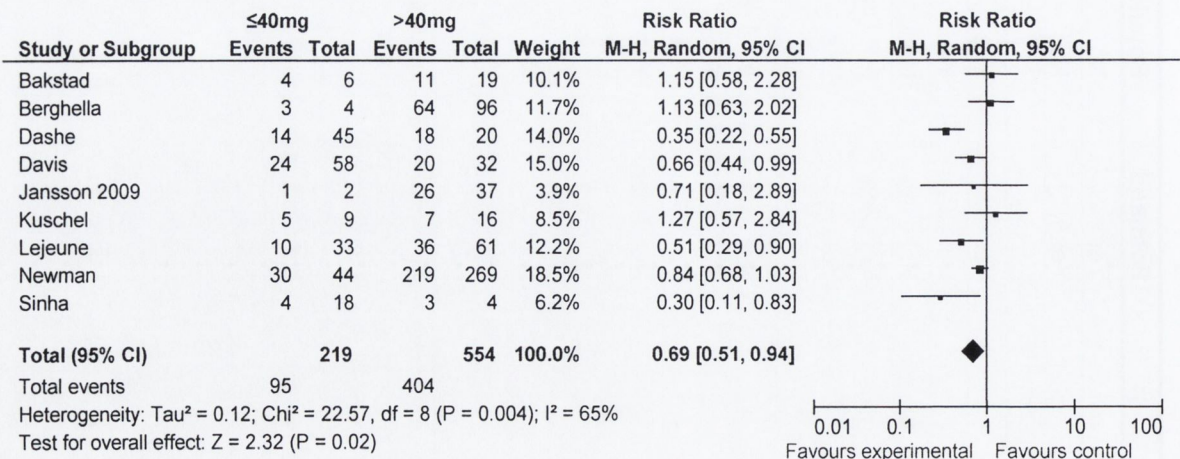
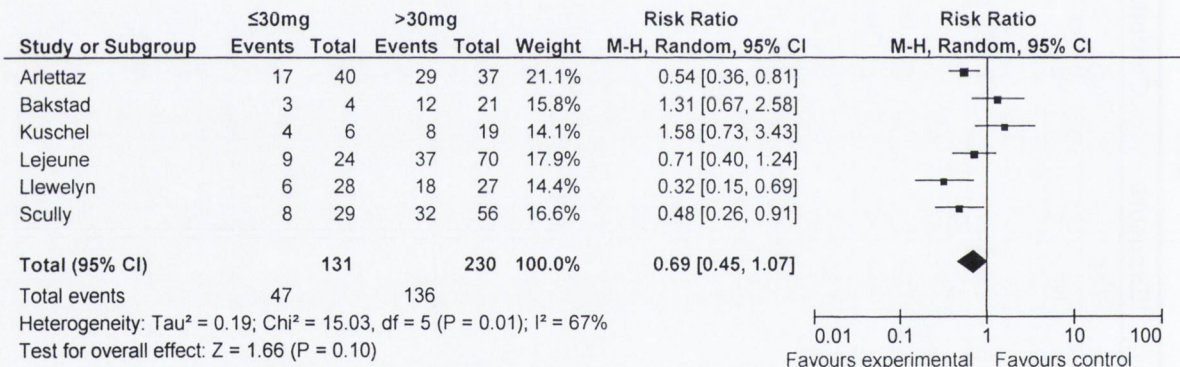
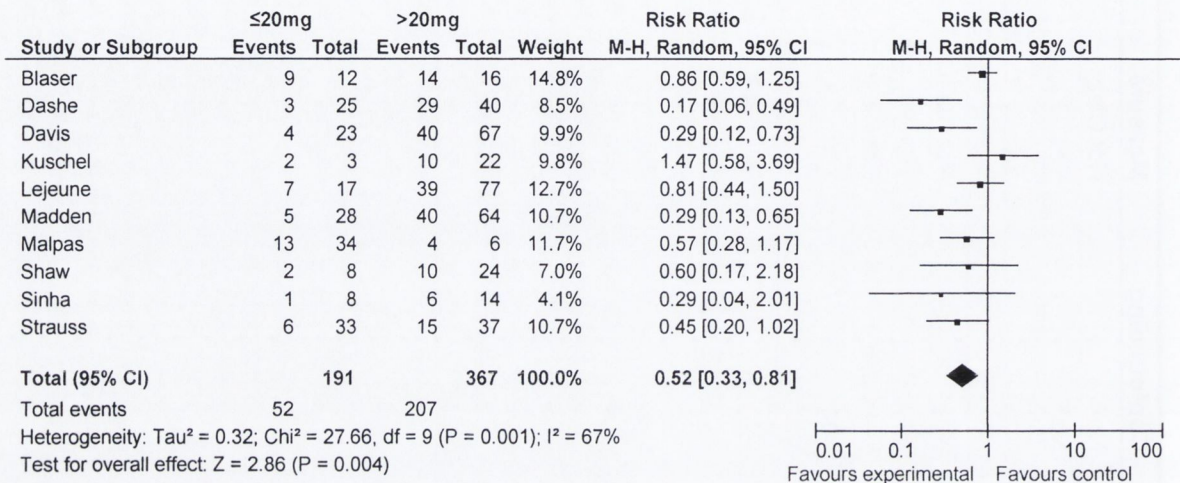
Study	Focused	Population	Exposure	Outcomes	Confounding	Measure	Conclusions
Hagopian 1996	Yes	Yes	Yes	Not Clear	Yes	Not Clear	Yes
Harper 1977	Yes	Yes	Yes	Yes	No	Yes	Yes
Harper 1974	Not Clear	Yes	Not Clear	Not Clear	No	Yes	Yes
Heimann 2006*							
Jansson 2009	Yes	Yes	Yes	Yes	Not Clear	Yes	Yes
Jansson 2007	Not Clear	Yes	Yes	Yes	Not Clear	Yes	Yes
Jansson 2008	Yes	Yes	Yes	Yes	No	Yes	Yes
Johnson 2003	Yes	Yes	No	Yes	No	Yes	Yes
Jones 2005	Yes	Yes	Yes	Yes	No	Yes	Yes
Jones 2008	Yes	Yes	Yes	Yes	No	Yes	Yes
Kakko 2008	Yes	Yes	Yes	Yes	No	Yes	Yes
Kandall 1977	Not Clear	Yes	No	Yes	No	Yes	Not Clear
Kandall 1983	Yes	Yes	Yes	Yes	No	Yes	Yes
Kuschel 2004	Yes	Yes	Yes	Yes	No	Yes	Yes
Lejeune 2006	Not Clear	Yes	Yes	No	No	Yes	Yes
Lim 2009	Yes	Yes	Yes	Yes	Not Clear	Yes	Yes
Llewelyn 1997	Not Clear	Not Clear	Yes	Not Clear	No	No	Not Clear
Mack 1991	Yes	Yes	Yes	Yes	No	Yes	Yes
Madden 1977	Yes	Not Clear	Not Clear	Yes	No	Yes	Yes
Malpas 1995	Yes	Yes	Yes	Yes	No	Yes	Yes
Mayes 1996	Yes	Yes	Yes	Yes	No	Yes	Yes
Mayet 2008	Not Clear	No	No	No	No	No	No
McCarthy 2005	Yes	Yes	Yes	Yes	No	Not Clear	Not Clear
Miles 2007	Yes	Yes	Yes	No	Yes	Yes	No
Morrison 1995	Not Clear	No	Yes	No	No	Not Clear	Yes
Newman 1975	Not Clear	Yes	Not Clear	No	No	No	Yes

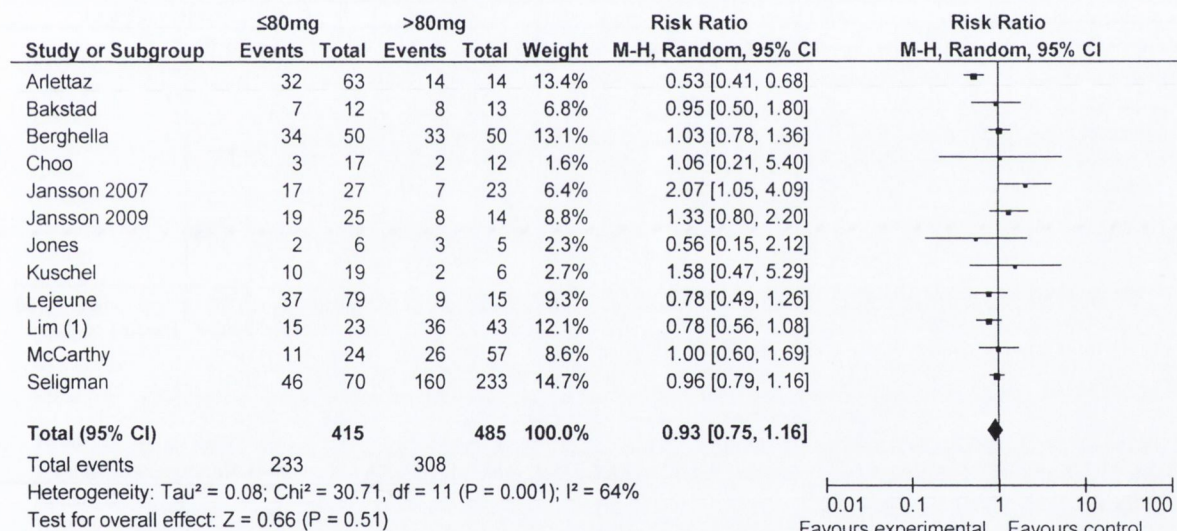
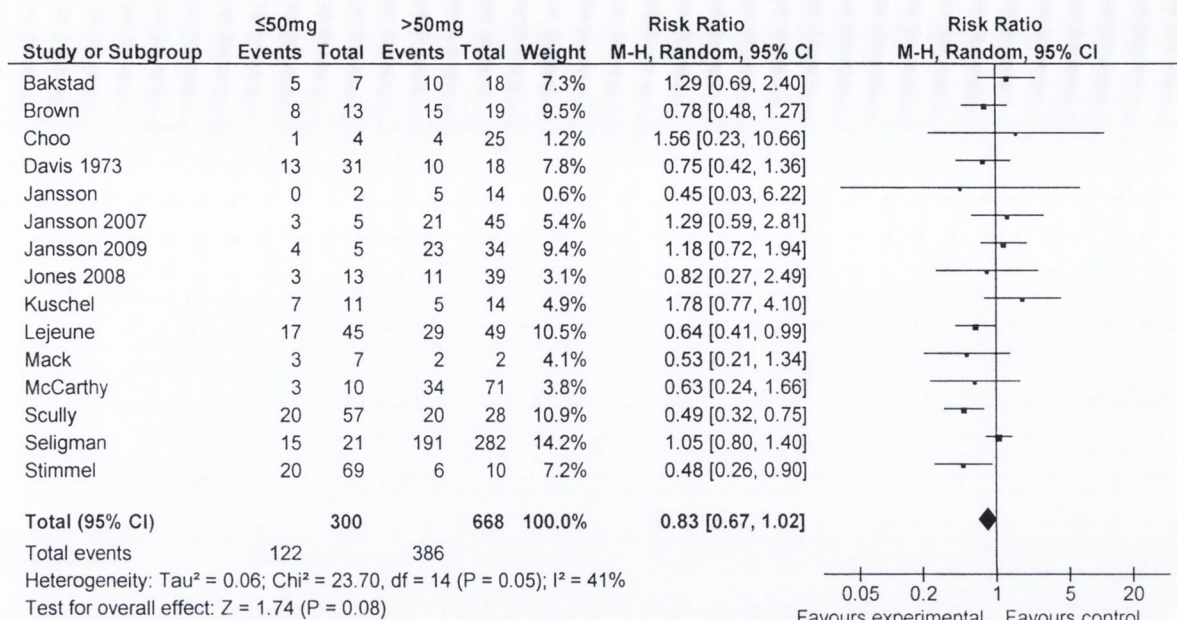
Study	Focused	Population	Exposure	Outcomes	Confounding	Measure	Conclusions
Offidani 1986	Yes	No	Yes	No	No	Not Clear	Yes
Ostrea 1976	Yes	No	No	Yes	No	Yes	No
Rohrmeister2001*							
Rosen 1975	Yes	Yes	Yes	Not Clear	No	Yes	Not Clear
Rosen 1985	Not Clear	Yes	Yes	No	No	Not Clear	Yes
Scott 1973	Not Clear	Not Clear	Yes	Not Clear	No	Yes	Yes
Scully 2004	Not Clear	Not Clear	Yes	Not Clear	Not Clear	Not Clear	Yes
Seligman 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Serane 2008	No	No	No	Yes	No	Yes	No
Shaw 1994	Yes	Not Clear	Yes	Not Clear	No	Not Clear	Yes
Sinha 2001	Not Clear	Yes	Yes	Yes	No	Yes	Yes
Statzer 1972	Not Clear	Not Clear	Not Clear	Not Clear	No	Not Clear	Yes
Stimmel 1982	Not Clear	Yes	Not Clear	No	No	Not Clear	Not Clear
Strauss 1976	Yes	Not Clear	Not Clear	Yes	No	Yes	Yes
Suffet 1984	Yes	Yes	Not Clear	Not Clear	No	Yes	Yes
Vucinovic 2008	No	Not Clear	No	No	No	No	Yes
Wilson 1981	Yes	Yes	Not Clear	Yes	No	Yes	Yes
Wolff 2005	Yes	Yes	Yes	Not Clear	No	No	Yes

Focused	Clearly focused and appropriate question
Population	Clear description of study populations
Exposures	Clear definition of exposure
Outcomes	Primary/secondary outcomes clearly defined
Confounding	Assessment of confounding in statistical analysis
Measure	Measure of effect for outcomes and appropriate measure of precision
Conclusions	Conclusions supported by results with biases and limitations taken into consideration

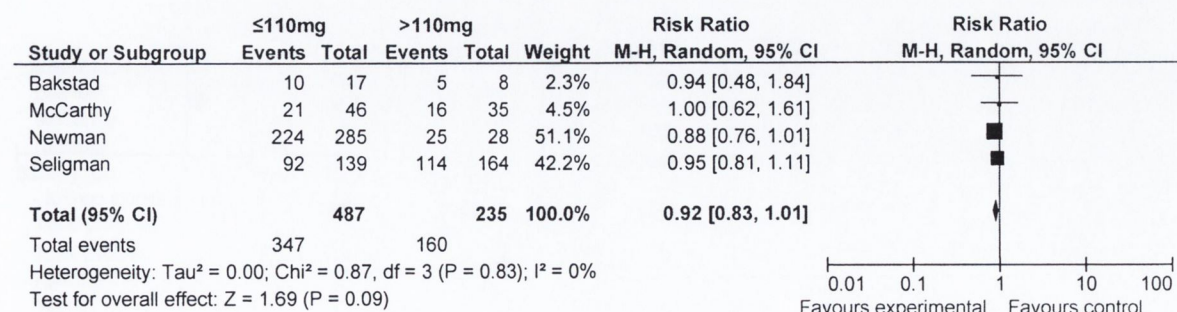
APPENDIX III FOREST PLOTS

All Studies

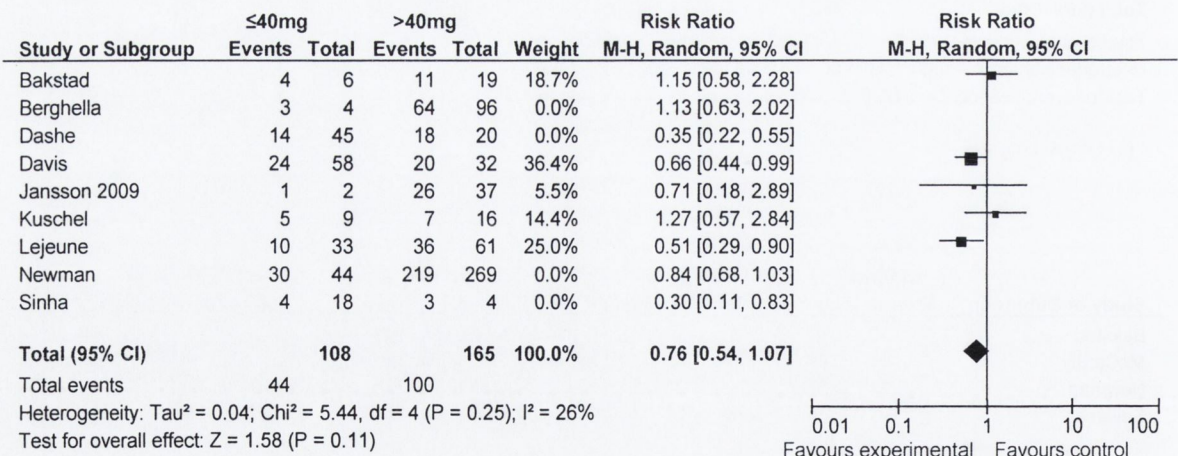
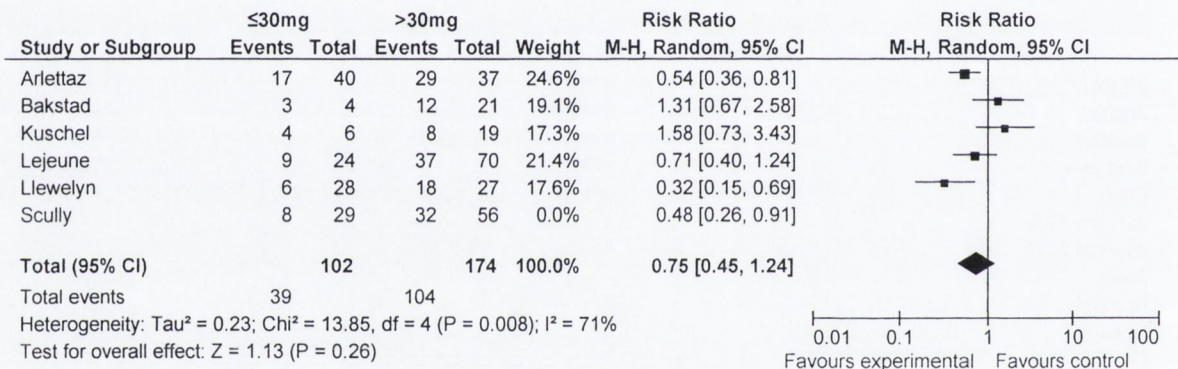
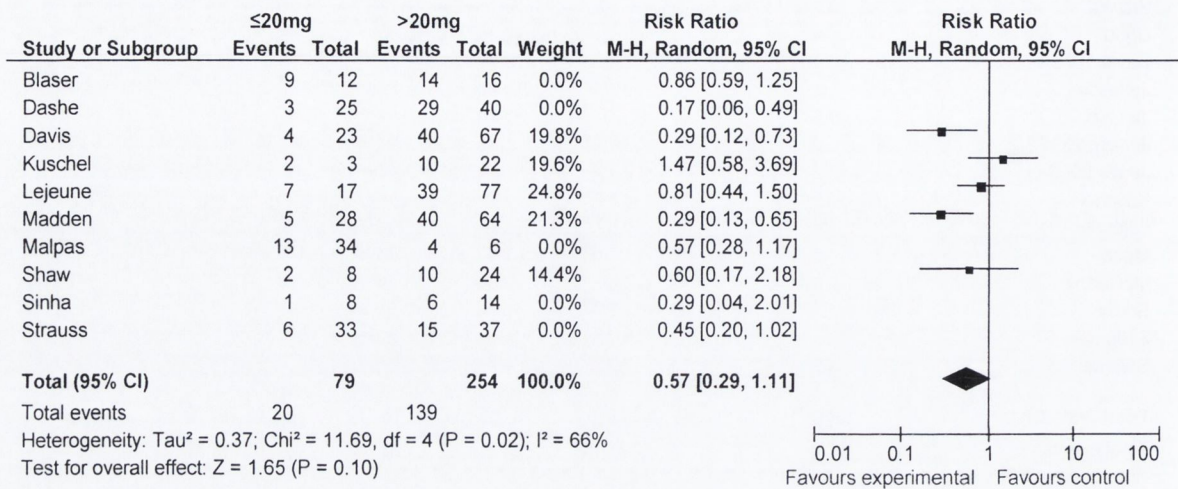


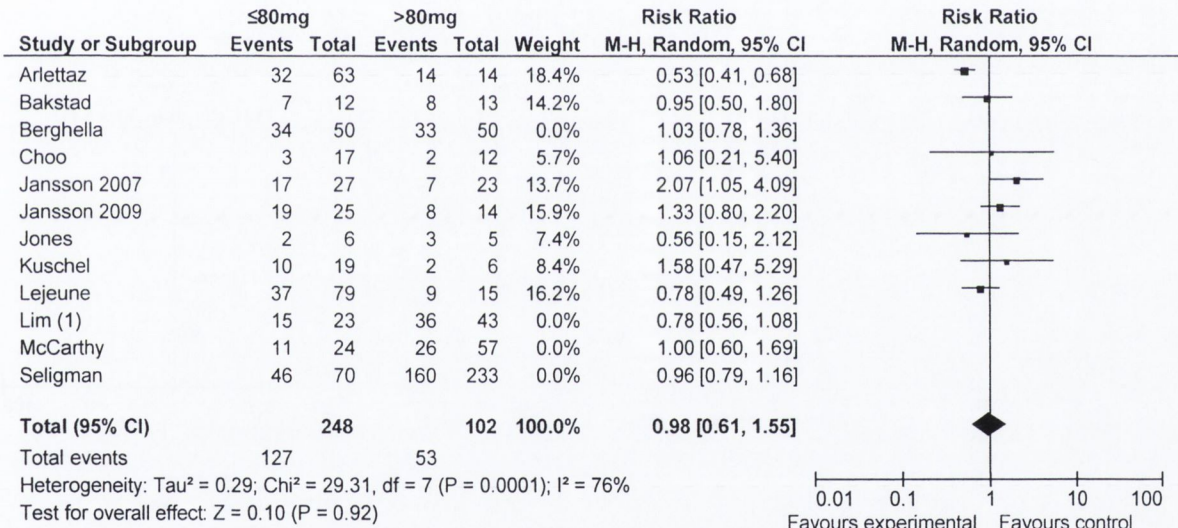
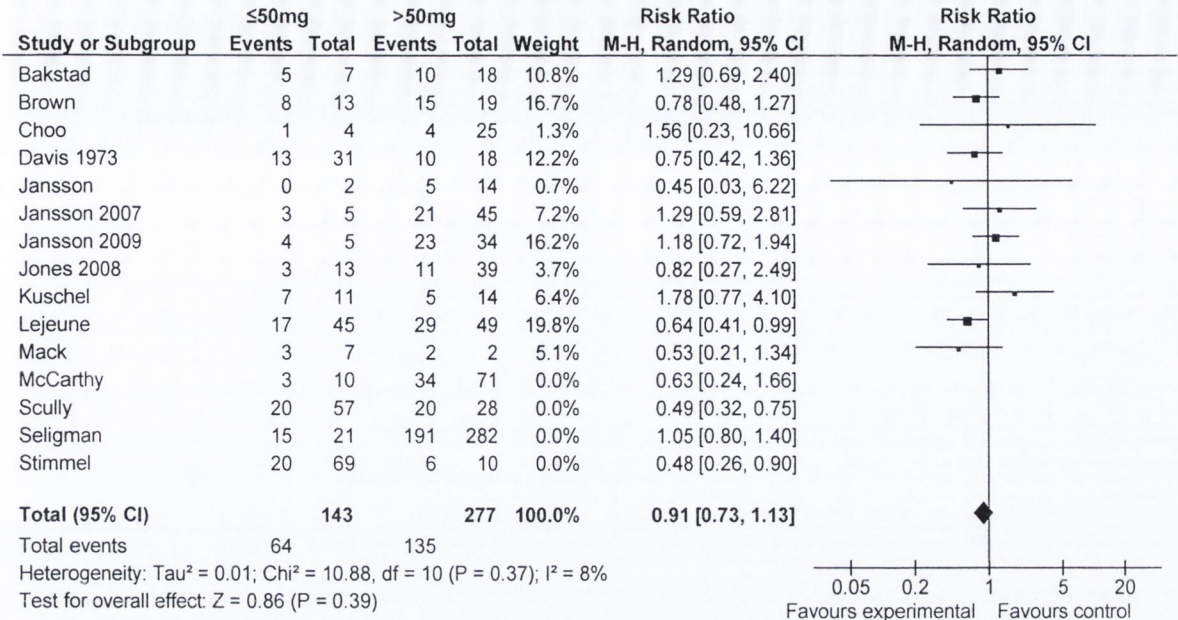


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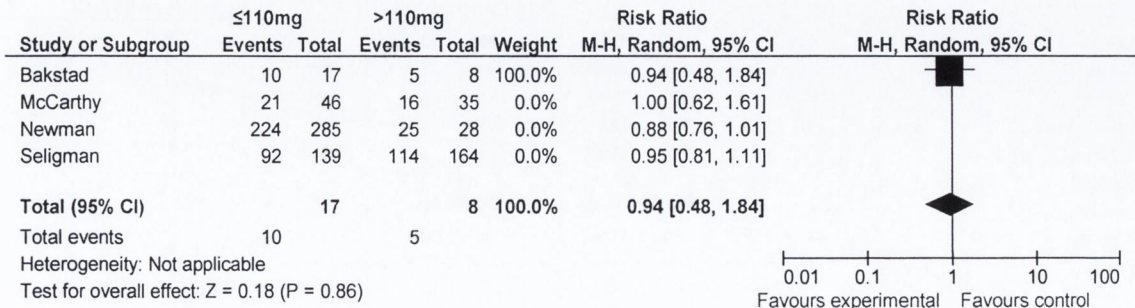


Prospective Studies Only

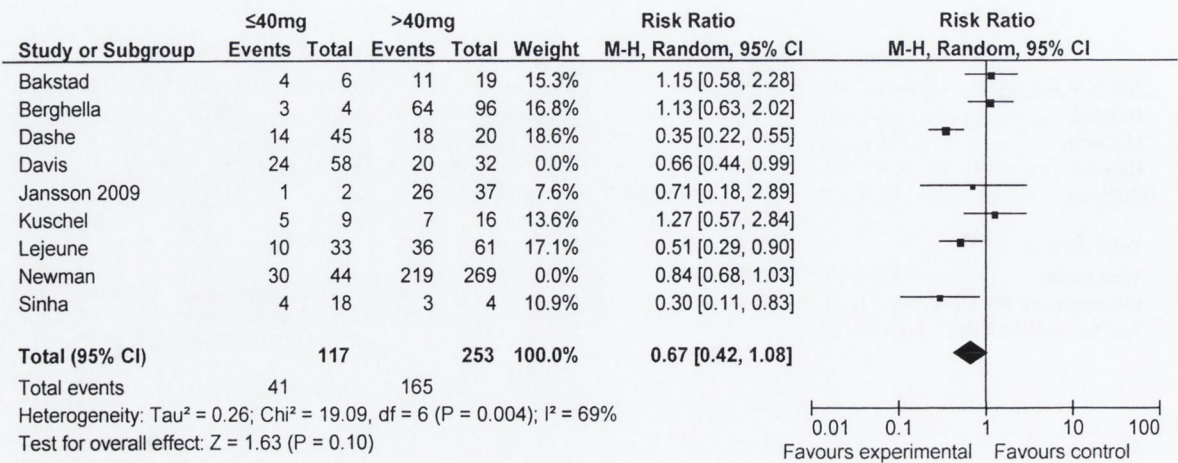
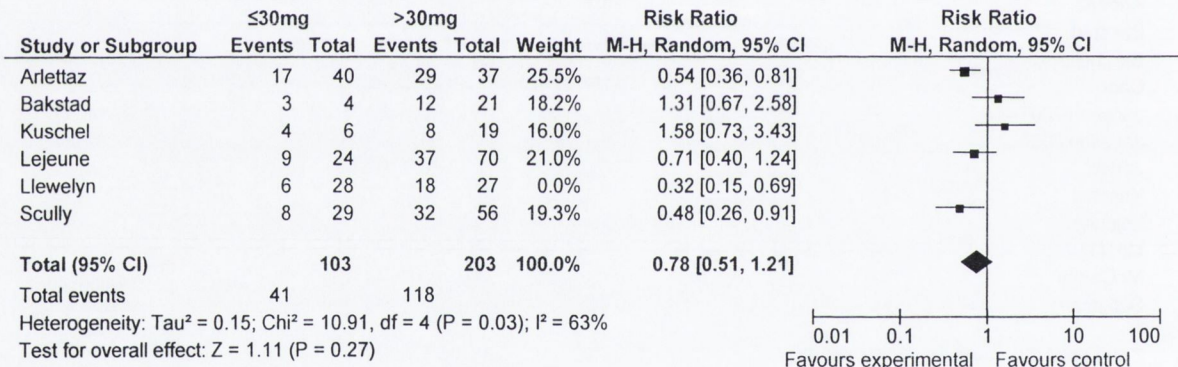
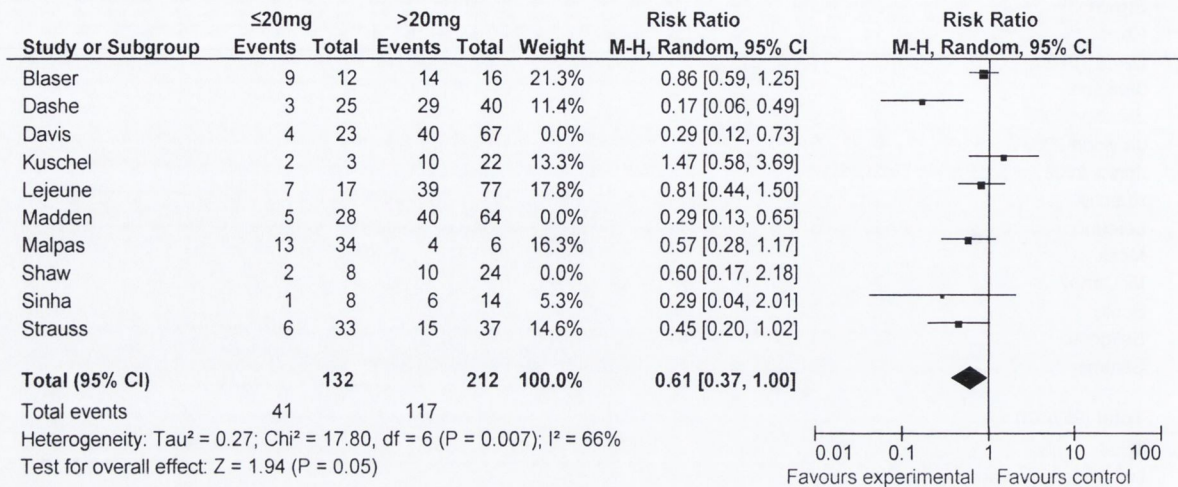


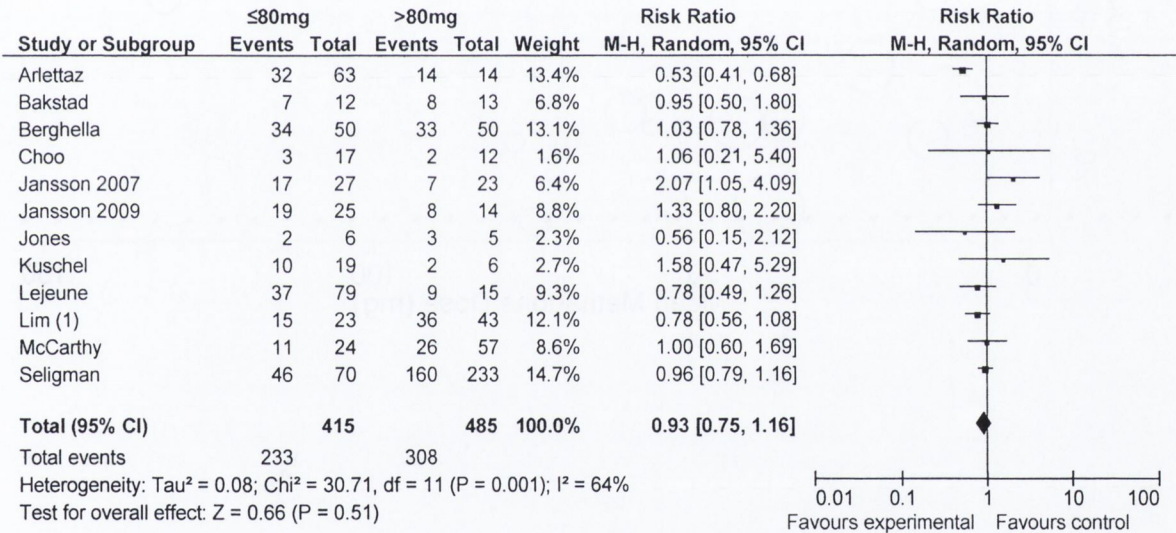
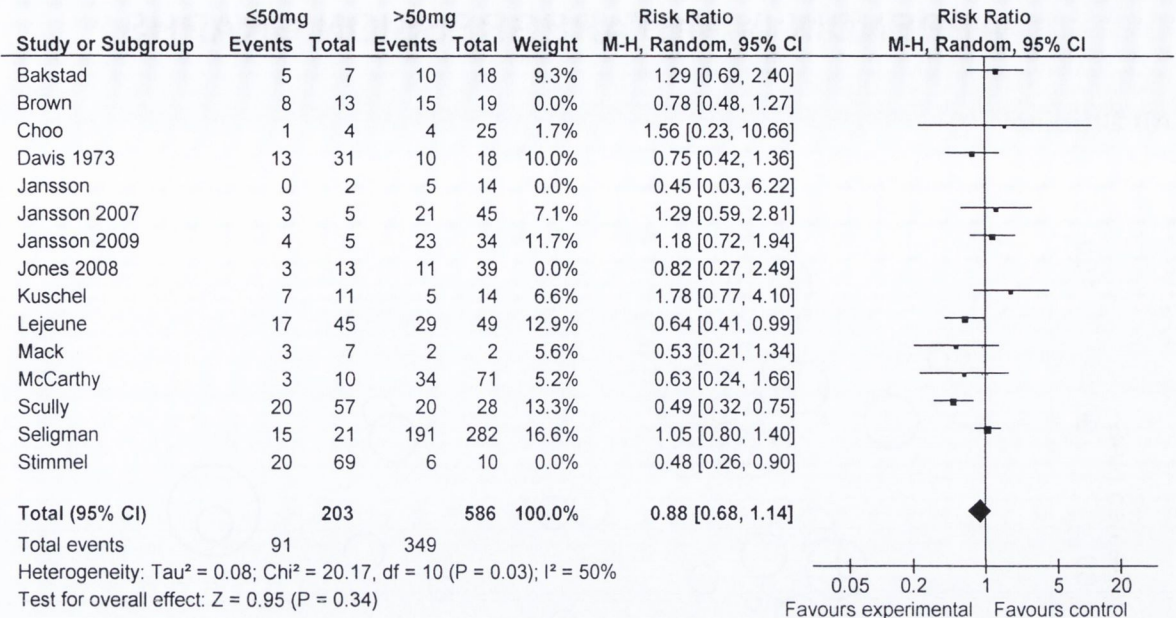


(1) Lim- ≤70mg

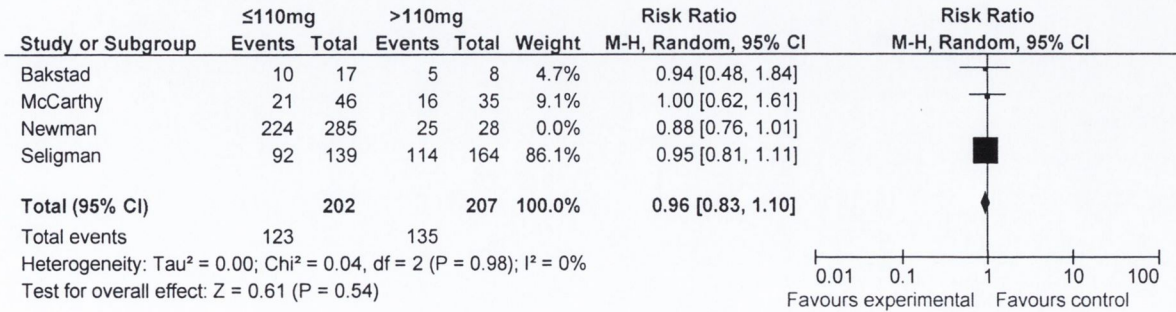


Studies Using an Objective Scoring System Only



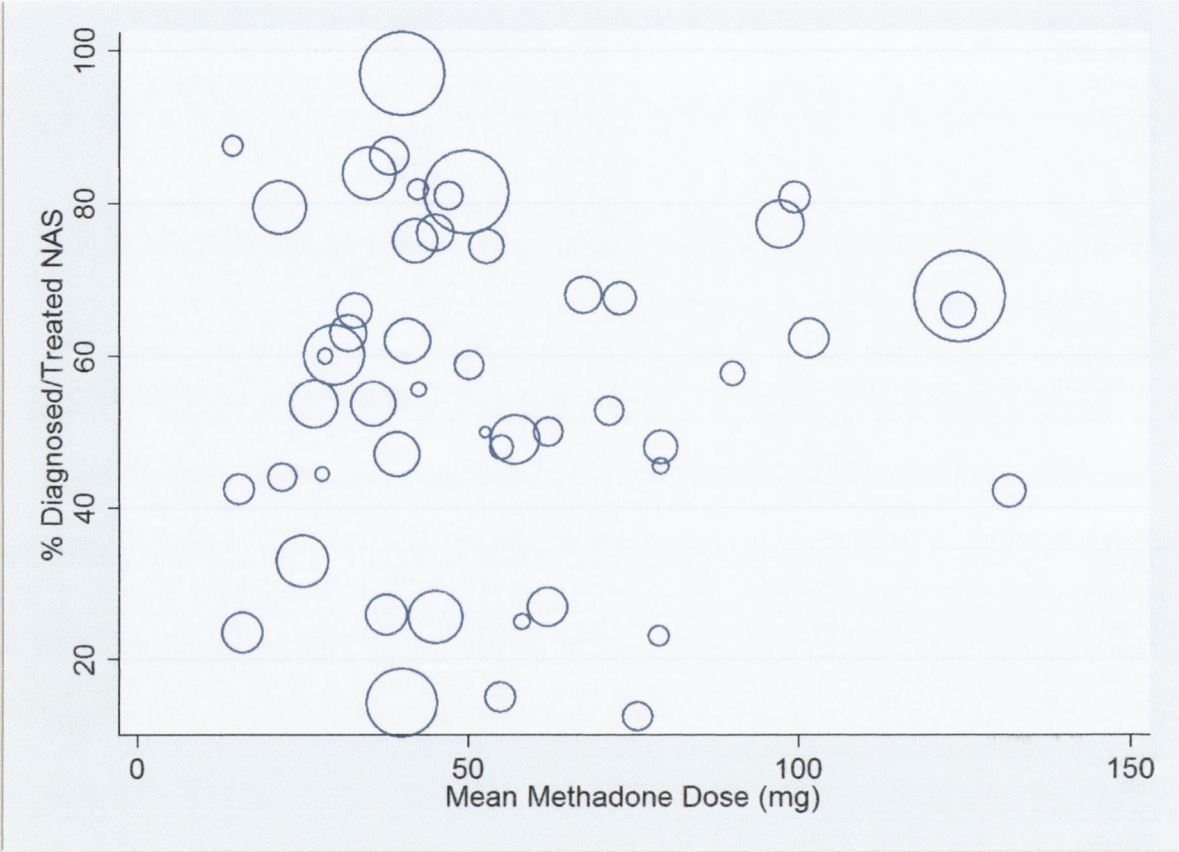


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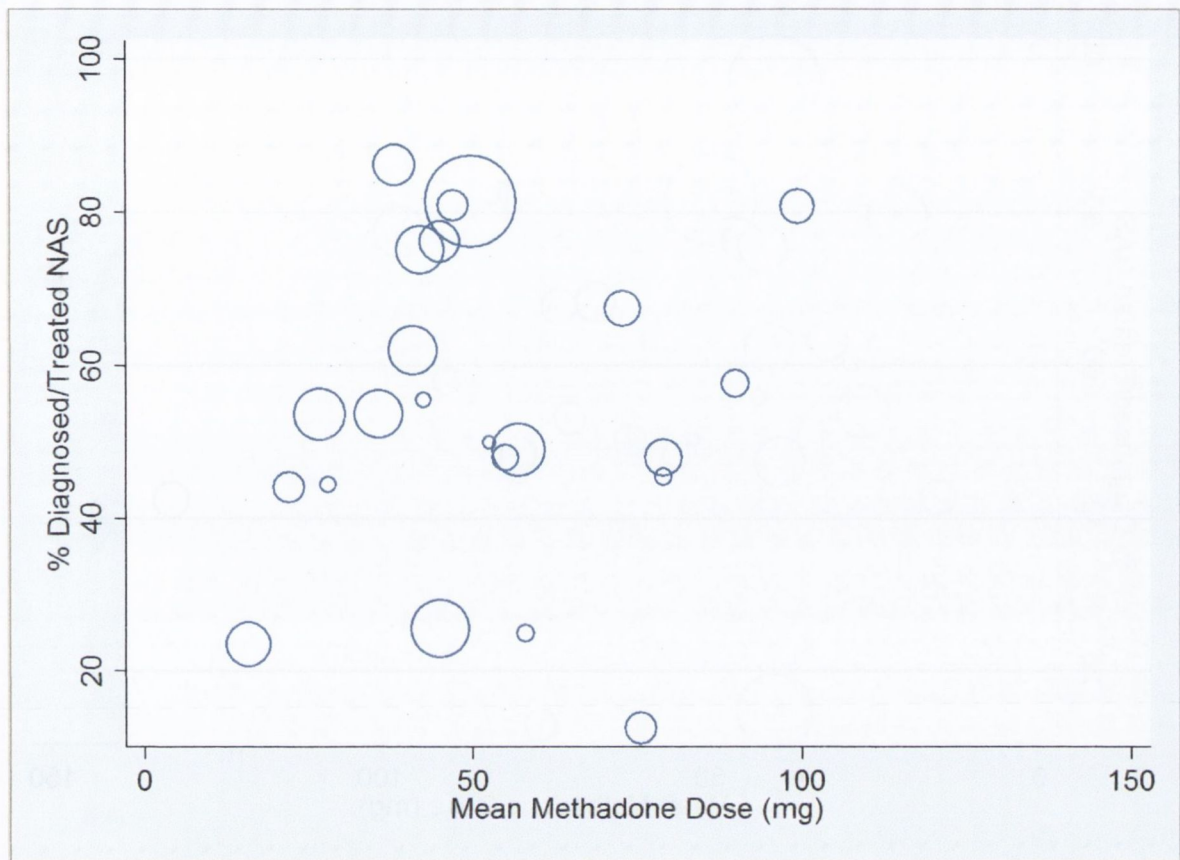


APPENDIX IV METAREGRESSION GRAPHS

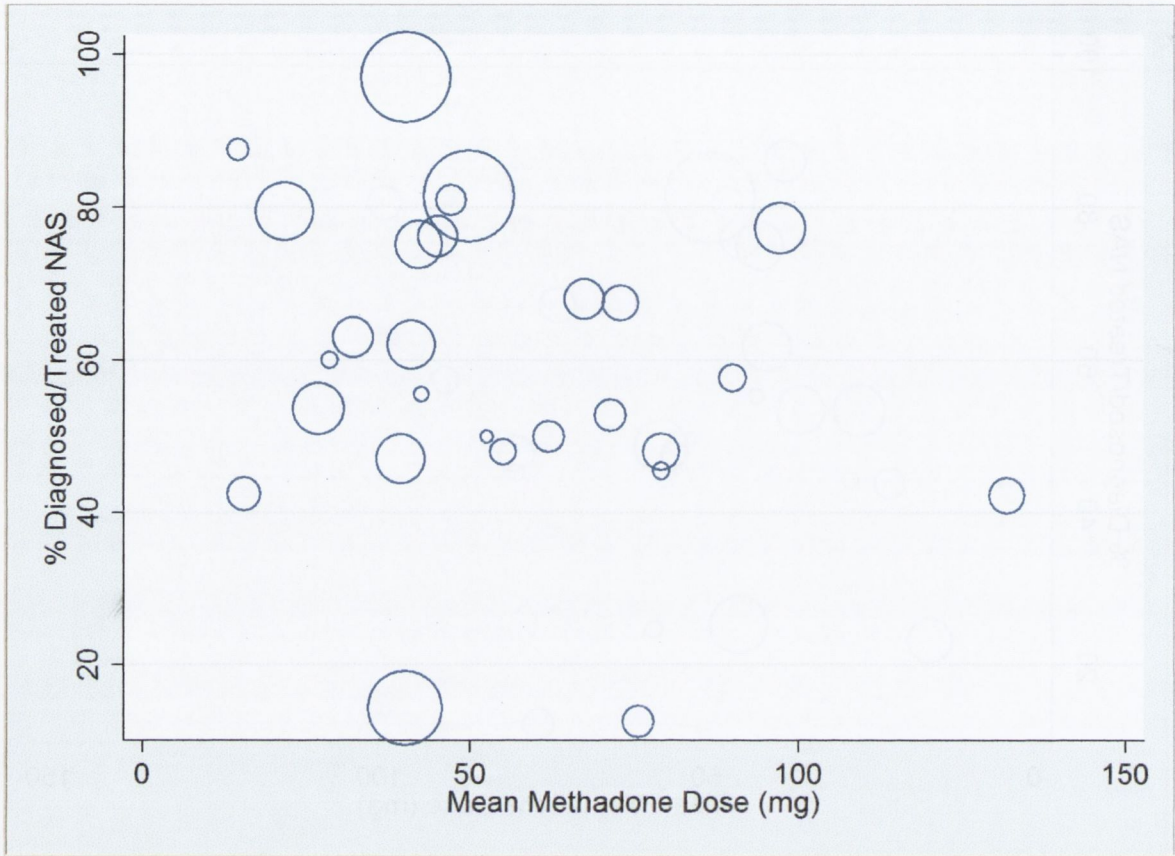
All Studies



Prospective Studies Only

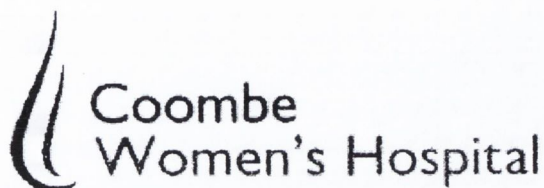


Studies Using an Objective Scoring System Only



APPENDIX V ETHICS COMMITTEE APPROVAL LETTERS

Descriptive Study



MC/MJ

26 October 2007

Prof. Deirdre Murphy
Consultant
Coombe Women's Hospital

Re.: Study No. 2007: 27 – A retrospective cohort study of medication use during pregnancy and pregnancy outcomes

Dear Prof Murphy

This project was discussed at the Research Ethics Committee meeting held on the 17th October 2007, and was approved.

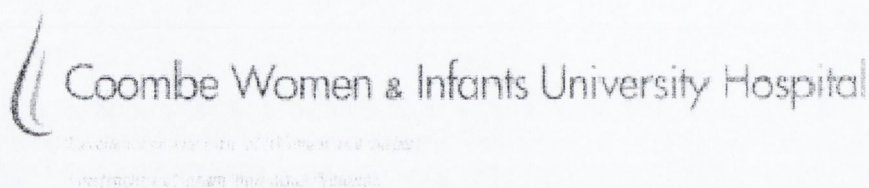
Yours sincerely

A handwritten signature in black ink, appearing to read "Michael Carey", is written over a horizontal line.

Dr Michael Carey
Chairman

Cop: Mr Brian Cleary, Pharmacist, Coombe Women's Hospital

Retrospective Cohort Study



MC/MM

17th February 2009.

*Mr. Brian Cleary
Pharmacy Department
Coombe Women & Infants University Hospital
Cork Street
Dublin 2.*

Re: Study No. 5 – 2009 - Methadone Use During Pregnancy and Neonatal Abstinence Syndrome- a Retrospective Cohort Study

Dear Brian

This study was considered at the recent Research Ethics Committee meeting held on the 11th February 2009.

The study was approved in principle. The Committee strongly felt that all data leaving the hospital would be encrypted and once linked with the data from the Primary Care Reimbursement Service the entire data set should be deleted from the computer of the trusted third party after it has been handed back to the Coombe.

The Committee felt that if it was possible the data linkage should be carried out on site at the Coombe Women & Infants University Hospital to minimise any misplacement of data that might occur during transfer to any outside agency. With regard to perinatal outcomes it was felt that "attempt to breastfeed" should be included in the breastfeeding status.

Yours sincerely

A handwritten signature in dark ink, appearing to read 'Michael Carey', is written over a horizontal line. Below the line, the text 'Michael Carey' and 'Chairman.' is printed in a serif font.

*Michael Carey
Chairman.*

Prospective Cohort Study



Coombe Women & Infants University Hospital

*For women, babies and families
with a history of drug and alcohol use*

MC/MJ

23 April 2009

Prof. Deirdre Murphy
Consultant Obstetrician/Gynaecologist

**Re.: Study No.: 7 – 2009 – Methadone use and Pregnancy Outcomes in a
Prospective Cohort of women.**

Dear Prof. Murphy

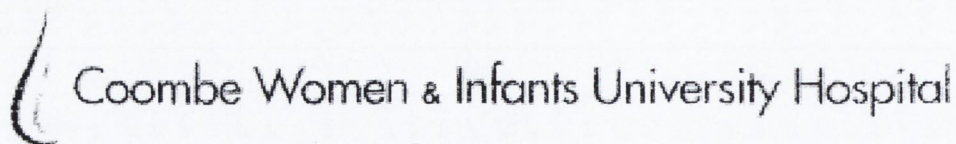
This study was considered at the recent Research Ethics Committee meeting. Concerns were raised around the issues of child protection. In this respect the opinion of Rosemary Grant, Head Social Worker, will be sought. The Committee also felt that the 'Addiction Services Policy on Confidentiality' should be clearly spelt out in the 'Patient Information Leaflet' and the questionnaire used by researcher should be submitted to the Committee. Hopefully the study will be approved when these outstanding issues are resolved.

Yours sincerely

Dr Michael Carey
Chairman

Copy: Mr Brian Cleary, Research Pharmacist

Prospective Cohort Study



MC/MJ

03 June 2009

Mr Brian Cleary
Pharmacist

Re.: Study No. 7 – 2009 – Methadone use and Pregnancy Outcomes in a Prospective Cohort of women.

Dear Brian

The questionnaires to be used in this study were reviewed along with the amended Patient Information document. In the paragraph entitled 'Will my information be kept confidential?' the sentence, which states that the information provided to the researcher at the interview will not be entered into your medical records, should be deleted and the words 'for example, Child Protection Concerns' should also be deleted from the second last sentence.

In the criteria for exclusion from the study, the statement 'Unable to Give Consent' should be extended to say 'Unable to Give Consent for this Study'.

This project was approved.

Yours sincerely

A handwritten signature in black ink, appearing to read "Michael Carey".

Dr Michael Carey
Chairman

Prospective Cohort Study



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April 28, 2009.

Mr. Brian Cleary
Research Pharmacist
Coombe Womens' and
Infants University Hospital
Dublin 8.

Re: Methodone use and pregnancy outcomes in a prospective cohort of women

Dear Mr. Cleary,

Thank you for presenting your proposed study at the Research Ethics Meeting on 28 April.

As noted at the meeting the information leaflet should be transparent and refer specifically to, for example, serology results, lifetime drug use during the lifetime and that other sources of information will be accessed, for example, addiction services. We understand that you will use a paper based record and that no identifying information will be removed from the Rotunda Hospital. We understand that you personally will be responsible for the data. We would also be grateful if you would specify the researchers in addition to yourself who will have access to the database. We understand that Christine McDermott will assist you in obtaining infant details in the Rotunda.

We note in your information sheet that you address the need to breach confidentiality to protect the welfare of the child. We suggest that this should be broadened as outlined in the letter to me from Ms. Cliona Christle, Hospital Solicitor. If there are items in her letter that may be particularly difficult to address, these can be discussed further. As discussed, a confidentiality agreement will be required to allow you to access hospital documents relevant to this study and this could be arranged by Dr. Eoghan through the Master's Office.

We look forward to receiving the revised documentation.

We plan to have your proposal on the agenda of the Committee meeting on Tuesday 26th May and recommend that you attend to address any outstanding issues.

Yours sincerely,

Prof. T. Clarke
Chairman
Research Ethics Committee
Rotunda Hospital

Cc Dr. Maeve Eoghan, Consultant Obstetrician & Gynaecologist,
Prof. D. Murphy, Prof. of Obstetrics, Coombe Womens' and Infants University Hospital



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The Rotunda Hospital, Dublin 1. Tel 01 873 0700 Fax 01 872 6523
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Prospective Cohort Study

From:
Sent: 30 April 2009 14:40
To:
Subject: FW: Rotunda Research Ethics Committee [ALG.01307284]

Follow Up Flag: Follow up
Flag Status: Green

Categories: Filed

From:
Sent: 29 April 2009 12:33
To: y
Subject: Rotunda Research Ethics Committee [ALG.01307284]

Dear Prof Clarke,

Methadone Use and Pregnancy Outcomes in a Prospective Cohort of Women

Arising from yesterday's meeting I said that I would e mail the issues which required follow up before this study can be approved.

1 The patient information leaflet needs to be amended to set out the detail of the information that will be collected from patients records e.g. the obstetric and paediatric records as well as the drug addiction services and the prescription databases. As drafted a person reading the information leaflet would have no idea of the extent of the data being collected from these sources and therefore their consent would not be informed. Therefore this must be addressed.

2 Where data is being sourced from external agencies HSE addiction services and medical card data bases the researchers must seek the consent of the agencies responsible for these data bases to the information being used for the purpose of the study. The fact that the individuals concerned will have given informed consent will meet a key requirement of these agencies.

3. It is acknowledged by all that this is a vulnerable patient group and the information being disclosed to Brian Cleary in unredacted form is highly sensitive personal data. As he is an external researcher it is felt that in addition to having the patients' informed consent to disclosure additional safeguards in terms of confidentiality are required and it is proposed to offer him an honorary contract of employment for the specified purpose of this research. I would like to see the format that is intended so that I can review the confidentiality provisions and ensure that they are appropriate having regard to this study and data protection requirements.

4 We have been told that for the purpose of the study a study number will be used which is a version of the patients hospital number see page 17 of the application. This is the number that will appear on the data base and on the paper study records and not the name, hospital number or other identifying personal information. The specific key should be kept confidential and only disclosed strictly on a need to know basis. The current drug use history document refers to both hospital number and study number this needs to be amended to delete hospital number.

We were told yesterday that there will be a master list which links patient identity with the study number. In addition the current version of the consent form has the individuals name as well as their study id number. This list and identifying documentation is to be held securely by Dr Eogan at the Rotunda and is not to leave the hospital. The study protocol and consent form state that personal information will be held for 5 years. The ability to link the identities of individuals to the study data should be destroyed after 5 years and this is the responsibility of Dr Eogan.

5 The patient information leaflet states that the interview will ask the participant questions about drug use during pregnancy. The interview document at p 27 is more extensive than this and it seeks a life time history. The patient information leaflet needs to be amended so that it is not misleading.

Prospective Cohort Study

6 At yesterday's meeting we discussed the issue of disclosure of confidential information in the absence of consent. I expressed the opinion that the patient information leaflet is more restrictive than needs be. The circumstance that would justify disclosure under data protection law in the absence of consent is set out in Section 8 (d) of the Data Protection Acts 1988- 2003 and states under the heading

Disclosure of personal data in certain cases

" 8 Any restrictions in this act on processing of personal data do not apply if the processing is

(d) required urgently to prevent injury or other damage to the health of a person or serious loss of or damage to property "

I would suggest that the patient information leaflet would be amended to read " Only in circumstances where from the interview disclosure is needed urgently to prevent injury or damage to the health of a person, for example child protection concerns, would there be disclosure to the appropriate agency . Any such concern would be discussed fully with you. "

This language is broader and would enable disclosure in an appropriate circumstances of concerns in relation to the patient, any child or in respect of the unborn. As reflected in our discussions yesterday the circumstances in which disclosure would be appropriate requires the exercise of judgement in any individual case. The Rotunda will need to identify for the researcher to whom in the Rotunda he should communicate his concerns so that the appropriate action may be taken at Hospital level.

7 This study proposal is for a period of 1 year and the committees approval should be for this period.

I look forward to hearing from you. I am happy to review the revised documentation . If you send me the standard for of honorary employment contract I will review and amend it as required.

Prospective Cohort Study

Dr Sam Coulter-Smith
Master



Rotunda Hospital
DUBLIN

Founded in 1745

26th May, 2009.

Mr. Brian Cleary,
Coombe Women & Infants University Hospital,
Cork Street,
Dublin 8.

Re: Methadone use and pregnancy outcomes in a prospective cohort of women

Dear Mr. Cleary,

Thank you for your letter and enclosures of 12th May 2009.

As the issues raised at the meeting of 28th April have now been addressed the Committee are happy to give approval to your research proposal.

Yours sincerely,

Professor T. Clarke.
Chairman.
Research Ethics Committee.

c.c. Dr. Maeve Eogan



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Rotunda Hospital, Dublin 1. Tel 01 872 9005 Fax 01 873 0932
email: masterssecretary@rotunda.ie www.rotunda.ie



Prospective Cohort Study

DRUG TREATMENT CENTRE BOARD 40 YEARS ON

**PRIVATE & CONFIDENTIAL
STRICTLY ADDRESSEE ONLY**

Mr. Brian Cleary,
Research Pharmacist,
Coombe Women and Infants University Hospital,
Pharmacy Dept.,
Dublin 8.

15th May, 2009

**Re: Methadone use and pregnancy outcomes in a prospective
Cohort of Women"**

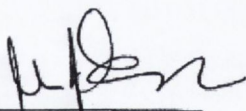
Dear Mr. Cleary,

The Ethics Committee have approved the above proposal.

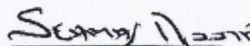
We would ask that you inform us regarding the outcome of the research with a summary of the conclusions and if it is published could you send us the reference of same.

Can you please clarify the commencement date? We would like to wish you the best of luck with your study.

Yours sincerely,



Dr. John O'Connor
Consultant Psychiatrist/Clinical Director



Seamas Noone
Vice Chairman

BORD AN LÁRIONAID COIREÁLA DRUGAÍ
Cúirt na Tríonóide, 30-31 Sráid an Phiarsaigh, Baile Átha Cliath 2
Teileafón: +353 1 6488600 Facs: +353 1 6488700
Riomhphost: info@dtcb.ie Láithreán: www.addictionireland.ie

DRUG TREATMENT CENTRE BOARD
Trinity Court, 30-31 Pearse Street, Dublin 2.
Telephone: +353 1 648 8600 Fax: +353 1 648 8700
E-mail: info@dtcb.ie Website: www.addictionireland.ie

APPENDIX VI PATIENT INFORMATION SHEETS

Prospective Cohort Study- Patient Information Sheet CWIUH



Coombe Women & Infants University Hospital

Coventry, Warwickshire, CV4 7PL

Telephone: 02476 860000 Fax: 02476 860001

Patient Information Sheet:

Dear Patient,

My name is Brian Cleary. I am a Pharmacist conducting a study on methadone use in pregnancy with a team of Doctors, Midwives and University staff. We would like your help to find out more about why some babies get withdrawal signs from methadone. This leaflet gives some information about the study.

Study Title:

Methadone use and pregnancy outcomes

Introduction:

You are being asked to take part in a research study. This study aims to improve the information available about taking methadone during pregnancy. Before you decide to take part or not, you need to understand what the research is about and what will happen during the study. It is important that you read this information sheet in order to make an informed decision. Make sure that everything is clear to you before you decide to take part or not. Please ask if you have any questions.

Why is this study being done?

We want to improve the information available about taking methadone during pregnancy. We want to see what affects the baby's chances of getting withdrawal signs from methadone. The study will also look at the effect of methadone dose on premature birth, low birthweight and being admitted to the special care baby unit.

Why have I been asked to take part in this study?

We want to contact all women who take methadone during pregnancy in the Coombe and Rotunda hospitals. Over one year we hope to recruit about 170 women for the study.

Do I have to take part?

Taking part in this research study is entirely up to you. If you do decide to take part you will need to sign a consent form. You will be given this information leaflet to take with you. If you do not take part it will not affect your care, or the care of your baby, in any way. You can withdraw from the study at any time, without having to give a reason, and without affecting your care, or the care of your baby, in any way.

What will happen during the study?

If you decide to take part in this study, the researcher (Brian Cleary) will require access to your medical records and those of your baby, including those held by the addiction services and the medical card scheme. Information on medical history, blood test results, antenatal care, methadone doses, drug use and pregnancy outcomes will be collected from medical records in the hospital. Information on

methadone dose and urine screens will be collected from addiction services records. Information on medical card prescriptions will be collected from the medical card scheme. You will also be asked to take part in a short interview (roughly 10 minutes) with the researcher. The interview will take place before one of your clinic visits near the end of your pregnancy. The researcher will ask you questions about smoking and your previous and current use of drugs and prescribed medicines. Any withdrawal symptoms that you have will be recorded. A paper record will be kept of the interview and anonymised details of the interview will be kept on computer. We would ask you to be completely honest in your responses.

Will my information be kept confidential?

Your identity will remain confidential. Neither your name, nor the name of your baby will be published. Your details will be used to find medical records held outside the hospital (addiction services/medical card records). Any study records held on a computer will not have your name, date of birth, address or other details that could identify you. The computer file will be password protected and only accessible to the researchers. The information collected will at all times be kept in a secure location. Any information that you tell the researcher will remain confidential. Only in circumstances where from the interview disclosure is needed urgently to prevent injury or damage to the health of a person would there be disclosure to the appropriate agency. Any such concern would be discussed fully with you.

What are the risks and benefits of taking part in the study?

This study will not change the care of you or your baby in any way. This research will have no direct benefit for you, but it will improve the information available for women who take methadone during pregnancy in the future.

What will happen to the results of the study?

Your information will remain anonymous. We plan to publish the information in medical journals to inform others about taking methadone during pregnancy. We can give you a copy of any publications. It can take up to a year after the end of the study to publish the findings.

Who is funding the research?

This project is funded by the charity Friends of the Coombe and the School of Pharmacy, Royal College of Surgeons in Ireland.

Contact Details:

If you have any questions about the study you can contact the researchers:

Brian Cleary
Research Pharmacist
Coombe Women and Infants
University Hospital

Dr. Michael O'Connell
Consultant Obstetrician
Coombe Women and Infants
University Hospital

(01) 4085200.

(01) 4085200.

Thank you for your time

Prospective Cohort Study- Patient Information Sheet Rotunda



The
Rotunda Hospital
DUBLIN

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Patient Information Sheet:

Dear Patient,

My name is Brian Cleary. I am a Pharmacist conducting a study on methadone use in pregnancy with a team of Doctors, Midwives and University staff. We would like your help to find out more about why some babies get withdrawal signs from methadone. This leaflet gives some information about the study.

Study Title:

Methadone use and pregnancy outcomes

Introduction:

You are being asked to take part in a research study. This study aims to improve the information available about taking methadone during pregnancy. Before you decide to take part or not, you need to understand what the research is about and what will happen during the study. It is important that you read this information sheet in order to make an informed decision. Make sure that everything is clear to you before you decide to take part or not. Please ask if you have any questions.

Why is this study being done?

We want to improve the information available about taking methadone during pregnancy. We want to see what affects the baby's chances of getting withdrawal signs from methadone. The study will also look at the effect of methadone dose on premature birth, low birthweight and being admitted to the special care baby unit.

Why have I been asked to take part in this study?

We want to contact all women who take methadone during pregnancy in the Coombe and Rotunda hospitals. Over one year we hope to recruit about 170 women for the study.

Do I have to take part?

Taking part in this research study is entirely up to you. If you do decide to take part you will need to sign a consent form. You will be given this information leaflet to take with you. If you do not take part it will not affect your care, or the care of your baby, in any way. You can withdraw from the study at any time, without having to give a reason, and without affecting your care, or the care of your baby, in any way.

What will happen during the study?

If you decide to take part in this study, the researcher (Brian Cleary) will require access to your medical records and those of your baby, including those held by the addiction services and the medical card scheme. Information on medical



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history, blood test results, antenatal care, methadone doses, drug use and pregnancy outcomes will be collected from medical records in the hospital. Information on methadone dose and urine screens will be collected from addiction services records. Information on medical card prescriptions will be collected from the medical card scheme. You will also be asked to take part in a short interview (roughly 10 minutes) with the researcher. The interview will take place before one of your clinic visits near the end of your pregnancy. The researcher will ask you questions about smoking and your previous and current use of drugs and prescribed medicines. Any withdrawal symptoms that you have will be recorded. A paper record will be kept of the interview and anonymised details of the interview will be kept on computer. We would ask you to be completely honest in your responses.

Will my information be kept confidential?

Your identity will remain confidential. Neither your name, nor the name of your baby will be published. Your details will be used to find medical records held outside the hospital (addiction services/medical card records). Any study records held on a computer will not have your name, date of birth, address or other details that could identify you. The computer file will be password protected and only accessible to the researchers. The information collected will at all times be kept in a secure location. The information that you give to the researcher at the interview will not be entered into your medical records. Any information that you tell the researcher will remain confidential. Only in circumstances where from the interview disclosure is needed urgently to prevent injury or damage to the health of a person, for example child protection concerns, would there be disclosure to the appropriate agency. Any such concern would be discussed fully with you.

What are the risks and benefits of taking part in the study?

This study will not change the care of you or your baby in any way. This research will have no direct benefit for you, but it will improve the information available for women who take methadone during pregnancy in the future.

What will happen to the results of the study?

Your information will remain anonymous. We plan to publish the information in medical journals to inform others about taking methadone during pregnancy. We can give you a copy of any publications. It can take up to a year after the end of the study to publish the findings.

Who is funding the research?

This project is funded by the charity Friends of the Coombe and the School of Pharmacy, Royal College of Surgeons in Ireland.

Contact Details:

If you have any questions about the study you can contact the researchers:

Brian Cleary	Dr. Maeve Eogan
Research Pharmacist	Consultant Obstetrician
Coombe Women and Infants University	Rotunda Hospital
Hospital	
(01) 4085200.	(01) 873 0700.

Thank you for your time

APPENDIX VII CONSENT FORMS

Prospective Cohort Study- Consent Form CWIUH

COOMBE WOMEN'S HOSPITAL

Title of research study: Methadone use and pregnancy outcomes

This study and this consent form have been explained to me. My doctor has answered all my questions to my satisfaction. I believe I understand what will happen if I agree to be part of this study.

I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights. I have received a copy of this agreement.

PARTICIPANT'S NAME:

PARTICIPANT'S SIGNATURE:

Date:

Date on which the participant was first furnished with this form:

Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Investigator's signature:

Date:

(Keep the original of this form in the participant's medical record, give one copy to the participant and keep one copy in the investigator's records)

Prospective Cohort Study- Consent Form Rotunda

Ver 1
16/04/09

Consent Form

Respondent / Participant Number /I.D.

Title of Project: Methadone use and pregnancy outcomes

Principal Investigator: Brian Cleary

I confirm that I have read and fully understood all the information provided in the accompanying Information Sheet and each of my inquiries about the study has been answered.

YES [] NO [] Initials []

I fully understand that my participation is completely voluntary and that I am free to withdraw at any given time without providing a reason and it will not affect my care in any way.

YES [] NO [] Initials []

I agree to take part in the research interview and allow the Research Team to access my medical records and those of my baby, including those held by the addiction services and the medical card scheme.

YES [] NO [] Initials []

I understand that the Researchers involved in this Research Study will hold in confidence and securely all collected data and other relevant information, and that data will be anonymised and kept in a password protected computer.

Additionally, I understand that I will not be identified as a participant/respondent in this study and that the Researchers may hold my personal information for 5 years duration.

YES [] NO [] Initials []

I agree to participate in the above Research Study.

YES [] NO [] Initials []

Name of Respondent/Participant:

Printed _____ Signature _____ Date _____

Name of Person Taking Consent:

Printed _____ Signature _____ Date _____

Name of Researcher:

Printed _____ Signature _____ Date _____

APPENDIX VIII STUDY INSTRUMENTS

Prospective Cohort Study-Drug Use History Questionnaire

Modified from the European Addiction Severity Index (ASI-X)

Study ID Number _____

Date of Interview _____

Apart from methadone, are you taking any prescribed medication on a regular basis?

0=No, 1=Yes _____

Medication 1 _____

Medication 2 _____

Medication 3 _____

Medication 4 _____

Medication 5 _____

At what age did you regularly start using...?

How did you take When you first used...?

Did you ever inject?

What age were you when you first injected.....?

How many days in the past 30 have you used...?

What is your usual or most recent way of taking...?

How many years in your life have you regularly used.? By regularly, I mean 3 or more times a week.

Age Now _____	Age first use	Route first use	Ever Inj/Age	Past 30 days	Lifetime Yrs.	Route of admin.	Comments (quantity/amount spent/usage pattern)
Heroin							
Methadone							
Cocaine							
Benzodiazepines							
Night Sedation							
Cannabis							
Alcohol							
Other							

Route of administration: 1=Oral 2=Nasal 3=Smoking 4=Non-IV Inj. 5= IV Inj. 6=Other
Previous Infants NAS

Prospective Cohort Study-Fagerström Test for Nicotine Dependence

Questions	Answers	Points
1. How soon after you wake up do you smoke your first cigarette	Within 5 minutes	3
	6-30 minutes	2
	31-60 minutes	1
	After 60 minutes	0
2. Do you find it difficult to refrain from smoking in places where it is forbidden e.g. in church, at the library, in cinema, etc.?	Yes	1
	No	0
3. Which cigarette would you hate most to give up?	The first one in the morning	1
	All others	0
4. How many cigarettes/day do you smoke?	10 or less	0
	11-20	1
	21-30	2
	31 or more	3
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
	No	0
6. Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

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Prospective Cohort Study-Objective Opiate Withdrawal Scale

Date: _____ Time: _____

Observe the patient during a 5 minute observation period then indicate a score for each of the opioid withdrawal signs listed below (items 1-13). Add the scores for each item to obtain the total score

	Sign	Measures		Score
1	Yawning	0 = no yawns	1 = ≥ 1 yawn	
2	Rhinorrhoea	0 = < 3 sniffs	1 = ≥ 3 sniffs	
3	Piloerection (observe client's arm)	0 = absent	1 = present	
4	Perspiration	0 = absent	1 = present	
5	Lacrimation	0 = absent	1 = present	
6	Tremor (hands)	0 = absent	1 = present	
7	Mydriasis (pupil dilation)	0 = absent	1 = ≥ 3 mm	
8	Hot and Cold flushes	0 = absent	1 = shivering / huddling for warmth	
9	Restlessness	0 = absent	1 = frequent shifts of position	
10	Vomiting	0 = absent	1 = present	
11	Muscle twitches	0 = absent	1 = present	
12	Abdominal cramps (Holding stomach)	0 = absent	1 = Holding stomach	
13	Anxiety	0 = absent	1 = mild - severe	
	TOTAL SCORE			

Total score range 0-13

Handelsman L, Cochrane K, Aronson M, Ness R, Rubinstein K, Kanof P 1987 'Two new rating scales for opiate withdrawal' *American Journal of Drug and Alcohol Abuse* 13 (3), p. 293-308.
Source: Women's Alcohol and Drug Service (WADS), Royal Women's Hospital, Melbourne Victoria.