BUPRENORPHINE AND METHADONE IN PREGNANCY: EFFECTS ON THE MOTHER, FETUS AND NEONATE

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Abstract

The current study aimed to assess the efficacy and safety of buprenorphine maintenance for the treatment of illicit opioid dependence during pregnancy. Parameters investigated assessed pregnancy progression and Neonatal Abstinence Syndrome (NAS) compared to methadone maintenance and non-opioid exposed control pregnancies. This is the first study to present results comparing the two treatment groups to a control population. The trial was a prospective, non-randomised, open-label, flexible dosing study (n=25 for each group). Women were recruited up to a gestational age of 28 weeks and their infants observed postnatally for 4 weeks. Methadone and buprenorphine doses did not change significantly from recruitment to delivery and were 48.40±5.95 $mg.day^{-1}$ and 7.46±0.84 $mg.day^{-1}$, respectively at delivery. Both subjective and objective measures of maternal withdrawal were significantly lower for buprenorphine compared to the methadone group ($p<0.01$ and $p<0.05$, respectively) at the sub-optimal does observed in this study. Direct drug effects were similar between methadone and buprenorphine groups and did not change over the course of pregnancy. Additional substance use during pregnancy was significantly higher for methadone and buprenorphine groups compared to controls but was not significantly different between each other. Patterns of maternal symptom complaints during pregnancy were higher for methadone and buprenorphine compared to controls but were not significantly different to each other and raised several issues regarding maternal health, and re-dosing in the antenatal period. Obstetric complications in the antenatal period and during labour and delivery were similar between the three groups. There was no significant difference between the three groups for infant gestational age at delivery or their Apgar scores. However, methadone exposed infants were significantly smaller than control infants (birth weight $p<0.05$, body length $p<0.05$, head circumference $p<0.05$) while buprenorphine exposed infants did not differ to controls. There was no significant

difference between methadone and buprenorphine exposed infants for the percentage of infants who required pharmacological treatment to control NAS (methadone 60%, buprenorphine 48%). However, significantly less morphine was required to control NAS in buprenorphine compared to methadone exposed infants (methadone: 40.07 ± 3.95 mg, buprenorphine: 22.77 ± 4.29 mg; $p<0.05$) and may have been due to reduced placental transfer of buprenorphine. The current study observed buprenorphine to be at least as efficacious as methadone for the treatment of opioid dependence during pregnancy while minimising NAS.

Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Andrea Louise Gordon, 14th September 2006.

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Publications in support of this thesis

Conference papers

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Abbreviations, prefixes and symbols

AIDS	Acquired immune deficiency syndrome
ANOVA	Analysis of variance
AUC	Area under the curve
AUD	Australian dollar
BF	Breast-fed
BMT	Buprenorphine maintenance treatment
cAMP	Cyclic adenosine monophosphate
CNS	Central nervous system
COWS	Clinical opioid withdrawal scale
CTG	Cardiac tocography
DASSA	Drug and Alcohol Services South Australia
DVT	Deep vein thrombosis
EDDP	2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine
GTP	Guanosine triphosphate
HIV	Human immunodeficiency virus
HQC	High quality control
hr	Hour
l	Litre
LCMS	Liquid chromatography/mass spectrometry
LLOQ	Lowest limit of quantification
LQC	Low quality control
MMT	Methadone maintenance treatment
min	Minute
mg	Milligram
ml	Millilitre
MQC	Medium quality control
ng	Nanogram
NAS	Neonatal abstinence syndrome
NMDA	N-methyl-D-aspartate
OGCT	Oral glucose challenge test
P-gp	P-glycoprotein
QC	Quality control

REC	Research ethics committee
RSD	Residual standard deviation of the mean
SCBU	Special Care Baby Unit
SEM	Standard error of the mean
SOWS	Subjective opioid withdrawal scale
USA	United States of America
UTI	Urinary tract infection
VAS	Visual analogue scale
WCH	Women's and Children's Hospital

1. INTRODUCTION

1.1. General introduction

Women of child bearing age make up a large proportion of the drug using population (Bell & Lau, 1995; Laken et al., 1997). In Australia in 2004, 20% of women interviewed who were pregnant or breast-feeding reported use of tobacco, 47% reported alcohol consumption and 6% reported using at least one illicit drug in the previous 12 months (AIHW, 2005a). In addition, while figures have not been calculated for Australia, in both the United States of America and Europe women of child bearing age make up approximately one third of clients entering treatment for opioid dependence (Johnson et al., 2003b). A complex situation then presents itself when these women become pregnant and continue illicit opioid use or are participating in maintenance therapy programs.

Methadone maintenance treatment (MMT) is currently the treatment of choice during pregnancy to promote abstinence from illicit opioids and has been used in this population of patients since the early 1970's (Kaltenbach et al., 1998). Buprenorphine maintenance is now being increasingly used as an alternative to methadone to promote abstinence from illicit opioids, with approximately 25% of maintenance therapy clients in Australia being maintained on buprenorphine (AIHW, 2005b). As this figure rises, the number of women maintained on buprenorphine who become pregnant will also continue to rise (Johnson et al., 2003b). However, buprenorphine's use as a maintenance therapy during pregnancy is currently restricted. This is due largely to the limited data on the effects of buprenorphine maintenance on pregnancy progression and the newborn as well as the lack of long-term follow up data in these children. However buprenorphine may offer significant advantages

over methadone when used during pregnancy, including reduced withdrawal severity in the opioid dependent newborn.

Withdrawal in the newborn is commonly referred to as Neonatal Abstinence Syndrome (NAS). NAS is not only unpleasant for the infant and distressing for the mother, it also has a large impact on health costs associated with the inpatient care required for these infants. Most importantly, NAS can also be potentially life threatening if left untreated (Coghlan et al., 1999; Finnegan & Kandall, 1997; Fischer et al., 1998). While data are not available for Australia, the most recent figures from the United States of America (USA) estimate that approximately 9,000 infants are born to opioid dependent mothers every year (Bell & Lau, 1995). By comparing buprenorphine to methadone and a non-opioid exposed control population during pregnancy, this study aimed to demonstrate the safety and efficacy of a new pharmacotherapy to be used during pregnancy to promote abstinence from illicit opioids that maintains the mother and fetus, and minimises NAS in the neonate, and therefore extend opioid maintenance therapy treatment options for pregnant women.

1.2. History of opioid use

The term opioid refers to substances, whether they are synthetic or naturally occurring, that are derived from opium or its alkaloids and chemical derivatives. Opium, meaning juice, is an extract of the poppy *Papaver somniferum*. Opioids produce a range of diverse effects including pain relief, decreases in gastrointestinal motility, respiratory depression, sedation, and miosis (Gold & Johnson, 1998). As a result, opioids have been used for medical purposes for thousands of years as agents to produce analgesia, aid with respiratory illness and sleep and in the prevention or treatment of diarrhoea. Opioids have also been used socially over time due to their powerful ability to produce a state of euphoria and well being (Gold & Johnson, 1998; King & Miller, 1998; Rang et al., 1999). These strong reinforcing effects have been suggested to be the reason that opioids in recent times have become the target of abuse and addiction (King & Miller, 1998).

The majority of human experience with opioids has been through eating or smoking of raw opium. During the late 19th century however, several key events changed the human experience with opioids. These events were: (1) the invention of the hypodermic needle; (2) isolation of specific opioids from raw opium; and (3) the synthesis of heroin from morphine. These three key aspects not only meant that man was now able to isolate and synthesise more potent and pure drugs, but now also had the ability to deliver them directly to the brain via the circulation, and thus greatly increased the addiction liability (Gold & Johnson, 1998).

Heroin (diacetylmorphine) was first synthesised in 1874 and was marketed in 1898 as a cough suppressant to aid breathing in patients with severe lung disease (Borg & Kreek, 1998; Sneader, 1998). It has a short half-life of approximately 3 min and is relatively inactive. Following administration heroin is rapidly metabolised to its active metabolites, 6-

monoacetylmorphine and morphine, through which it exerts its effects for approximately 3 hrs (Inturrisi et al., 1984; Rang et al., 1999; Rentsch et al., 2001). In addition, due to heroin's greater lipid solubility and ability to cross the blood brain barrier it is said to be twice as potent, have a more rapid onset of action, and provide a greater "rush" than morphine alone (Inturrisi et al., 1983; Kaiko et al., 1981; Rang et al., 1999). These aspects have contributed significantly to its abuse popularity and give rise to it being the most commonly abused drug of its class (Borg & Kreek, 1998; Gold & Johnson, 1998). Heroin was also found to undergo complete first pass metabolism when administered orally (Inturrisi et al., 1983), hence its popularity for being smoked or snorted. Despite this, along with many other illicit drugs, the most commonly used route of administration remains to be via intravenous injection due to the rapid onset of drug action via this means of administration (Gold & Johnson, 1998).

1.3. Opioid receptors and endogenous ligands

Opioids exert their actions through three major opioid receptor subtypes located on cell membranes in the central nervous system (CNS). These receptors are mu (μ), delta (δ) and kappa (κ) opioid receptors; subtypes may also exist within these classes. Opioids that interact with these receptors are known as opioid agonists, opioid antagonists and partial opioid agonists. Agonists produce a biological effect once bound to the receptor. Antagonists have no effect on their own but will block the effect of an agonist. A partial agonist is a compound that even when the receptor is fully saturated, its effect is still less than the maximal effect obtainable with a full agonist (Ariens, 1983; Zacy & Walker, 1998).

The majority of clinically and illicitly used opioid agonists bind to and exert their actions through μ-opioid receptors. Several opioids interact with more than one type of opioid receptor class even at doses prescribed clinically. Binding of opioids at μ-opioid receptors produces effects such as analgesia (supraspinal), respiratory depression, euphoria and reinforcing effects. Effects observed at κ-opioid receptors include analgesia (spinal) and dysphoria. Those effects observed at δ-opioid receptors include analgesia, respiratory depression and reinforcing effects (Borg & Kreek, 1998; King & Miller, 1998).

Opioids exert their actions by means of mimicking endogenous ligands for opioid receptors (Rang et al., 1999). Each opioid receptor has specific endogenous ligands that bind to them. These are endorphins, endomorphins, dynorphins and enkephalins and bind predominantly to μ-, κ-, and δ-opioid receptors respectively, with some cross-specificity. Endorphins (endogenous morphines) play a role in pathologies such as pain and stress (De Cree, 1989). The most commonly known endorphin is β-endorphin, which has 5-10 times the opioid

activity of morphine and acts mainly via μ-opioid receptors (De Cree, 1989). As well as other areas in the CNS, β-endorphin is produced in the arcuate nucleus within the medial basal hypothalamus (Ferin & Vande Wiele, 1984) and is able to exert an effect on most hypothalamo-pituitary systems, in particular the reproductive physiology of women (De Cree, 1989).

1.3.1. G-protein coupled receptors

Opioid receptors belong to the G-protein coupled class of receptors, which span the cellular membrane and interact with intracellular G-proteins. G-proteins obtain their name through their ability to interact with guanine nucleotides (guanosine triphosphate (GTP) and guanosine diphosphate (GDP)) and consist of three subunits: α β, and γ (Elliott & Elliot, 1997; Rang et al., 1999; Tobin & Morel, 1997).

When inactive, the G-protein itself exists as an unattached αβγ trimer with GDP attached to the α-subunit. Binding of an opioid to its receptor causes a conformational change that in turn causes the receptor to assume a high affinity for the αβγ complex. This association causes the bound GDP to dissociate and be replaced with GTP. This is followed by the dissociation of the trimer to form α-GTP and βγ, the active G-protein forms. These active forms of the G-protein are able to exert their effect via several different mechanisms including interaction with second messengers and regulation of ion channels (Elliott & Elliot, 1997; Rang et al., 1999; Tobin & Morel, 1997). Interaction is either via activation or inactivation and is dependent on the G-protein variant (differences in the α subunit) of which three have been identified: G_s, G_i, and G_o (Cox, 1993; Rang et al., 1999). G_s forms of the protein are so called as they are able to stimulate the production of second messengers such as cyclic adenosine monophosphate (cAMP) and conversely, G_i forms act to inhibit the production of cAMP.

cAMP regulates many aspects of cellular function including cell division and differentiation, contractile proteins in smooth muscle and ion channels (Rang et al., 1999). The majority of opioid agonist actions are mediated through the $G_{i/o}$ variants and a decrease in cAMP concentrations are observed when these are activated. However, it has been suggested that at low concentrations of opioid agonist the G_s variant is activated and consequently an opioid can act in an excitatory manner (Cox, 1993; Varga et al., 2003).

Ion channels that are directly affected by opioids via G-protein coupled mechanisms include potassium channels (where opioids increase their opening) and voltage operated calcium channels (where opioids decrease their opening). These two mechanisms result in reduced neuronal excitability, therefore inhibiting neurotransmitter release (Reisine & Pasternak, 1996; Williams et al., 2001).

1.3.2. Opioid dependence

Opioid dependence is a collection of symptoms comprised of cognitive, behavioural, and physiological aspects that result in the continuation of opioid use despite significant problems associated with the use of the substance (American Psychiatric Association, 2000). Repeated administration of opioids due to their reinforcing effects can often lead to tolerance, withdrawal and compulsive drug taking behaviour (American Psychiatric Association, 2000).

Tolerance occurs when an increase in the dose of a drug is required to achieve a given pharmacological effect, or a diminished effect is observed with continual use of the same amount (American Psychiatric Association, 2000). When blood or tissue concentrations of a substance decline in an individual who has continued heavy use of a substance for an extended period of time, the individual may experience withdrawal. Withdrawal can be separated into two components; physical and psychological withdrawal. Symptoms of

physical withdrawal are often the opposite of symptoms observed from acute drug administration (American Psychiatric Association, 2000; Cox, 1993). In the case of opioids, these symptoms include, but are not limited to, nausea, diarrhoea, influenza type symptoms, yawning and pupillary dilation. Psychological withdrawal is associated with a strong craving or desire to continue drug administration and also includes negative affects, such as dysphoria and irritability and is often far more complex and difficult to treat than physical withdrawal (Rang et al., 1999).

While neither tolerance nor withdrawal is necessary to diagnose substance dependence, a past history of the two is often associated with a more severe course of dependence. The following describe several patterns of compulsive substance use that are characteristic of dependence. Firstly, the individual may take larger amounts of the substance and/or for longer periods than intended. This is followed by a persistent desire to cut down or cease substance administration, often with many failed attempts to do so. Secondly, the individual may spend increasing periods of time obtaining, using or recovering from the effects of the substance. Finally, the individual may continue to use the substance despite known detrimental physical and/or psychological effects (American Psychiatric Association, 2000).

1.3.2.1. Neurobiology of tolerance and dependence and withdrawal

Chronic administration of opioids results in a number of neurobiological adaptations, both at the individual neuronal cell level, the synaptic level and also at neuronal network and pathway levels that may underlie the development of tolerance, dependence and withdrawal. A review by Williams and colleagues (2001) discusses three main mechanisms that may work together and produce neurobiological adaptations as a result of chronic opioid exposure that contribute to tolerance, dependence and withdrawal. This review focuses mainly on mechanisms that are

associated with μ-opioid receptor adaptations, as this is believed to be the primary receptor involved with mechanisms of tolerance and dependence (Williams et al., 2001).

1.3.2.1.1. Desensitisation, internalisation and down-regulation of opioid receptors

The first type of adaptation is that of desensitisation, internalisation and down-regulation of μ-opioid receptors (Williams et al., 2001). Desensitisation of μ-opioid receptors (a decrease of receptor signalling) following acute administration of opioids is quite often the result of receptor phosphorylation. The cytoplasmic protein arrestin has high affinity for the phosphorylated receptor and binds to it preventing the coupling of the inactive G-protein and the receptor, and initiates internalisation/endocytosis of the receptors. Once the receptor is no longer on the cell surface, this prevents an agonist from binding to the cell and causing an effect, therefore the cell is desensitised to the agonist. Following internalisation, fully functional receptors can be recycled to the cell surface and pushed through the cell membrane thereby resensitising the cell to agonists (Whistler et al., 1999). Unlike methadone and buprenorphine, morphine and heroin do not promote receptor internalisation (Whistler et al., 1999). As a result it has been suggested that differing abilities of different opioid agonists to induce receptor internalisation may be related to their potential for addiction or their ability to be used therapeutically for the treatment of opioid dependence (Whistler et al., 1999), although this has not yet been fully established.

Despite short-term response to opioids, such as acute tolerance, potentially being mediated by desensitisation and internalisation of opioid receptors, it is not clear if these short-term changes contribute to long-term changes associated with chronic opioid use such as receptor down-regulation, or a reduction in the actual number of opioid receptors (Williams et al.,

2001). Down-regulation of opioid receptors as a result of chronic opioid administration has been observed (Bernstein & Welch, 1998), although it is not fully understood as to whether this reflects a reduced number of receptors on the cell surface or a disruption in the coupling of G-proteins to opioid receptors.

1.3.2.1.2. Counteradaptation

The second type of adaptation related to tolerance is that of counteradaptation where the opioid is required to maintain normal function. On removal of the drug, adaptive changes that have occurred as a result of chronic opioid administration at multiple levels of the signal transduction pathway result in a withdrawal syndrome (Bernstein & Welch, 1998). At the cellular level, the most commonly studied adaptation is that of upregulation of adenylate cyclase. Under acute circumstances opioids act to inhibit adenylate cyclase activity. After chronic exposure to opioids cells become tolerant to agonist activity as increases in adenylate cyclase activity, due to positive regulation, compensate for the inhibition of the enzyme activity caused by the presence of the agonist. Cells also become dependent upon agonists for their functioning, as withdrawal of the agonist or displacement by an antagonist results in a rebound effect and a sharp increase in adenylate cyclase activity can be observed, thereby representing withdrawal at the cellular level (Sharma et al., 1975). These increases in adenylate cyclase activity have been related to changes in neurotransmitter activity and cause an increase in release of the inhibitory neurotransmitter GABA at synaptic terminals. This increase in release of GABA can be inhibited by opioid administration (Williams et al., 2001).

The mesolimbic dopaminergic pathway, the main reward pathway in the brain, is also continuously activated during chronic administration of opioids where large amounts of dopamine, an excitatory neurotransmitter, are released. Following withdrawal of the agonist a depression of mesolimbic dopamine release is observed which may account for the negative

mood states observed as a result of opioid withdrawal (Maldonado, 1997; Rang et al., 1999; Unnithan et al., 1992). More recent research suggests a role for the mesolimbic dopamine pathway in mediating the motivational effects of opioids in states of dependency and withdrawal in that inhibition of dopamine transmission alone does not seem to be sufficient for the induction of the motivational and somatic opioid withdrawal syndrome (Caille et al., 2003; Laviolette et al., 2002).

1.3.2.1.3. Synaptic plasticity

The third type of neuronal adaptation contributing to opioid dependence is related to synaptic plasticity and the changes between neuronal synapses in the CNS. As craving and relapse to opioid use can occur long after the acute withdrawal phase, this is indicative of long-term changes to the function of neural pathways and brain plasticity (Koob, 2000). It is likely that synaptic adaptations caused by drugs of abuse such as heroin share common mechanisms with other normal activity dependent plasticity such as long-term potentiation and long-term depression of synaptic transmission, which are thought to form the cellular basis of learning and memory. Activity dependent plasticity observed may be a direct result of opioid action on releasing excitatory neurotransmitters through direct interactions with cells that express opioid receptors or may be indirect. Understanding disruptions to synaptic plasticity in conjunction with reward pathways such as the mesolimbic dopaminergic pathway, may become one of the key components to understanding the induction of compulsive self-administration of substances of abuse (Williams et al., 2001).

1.3.3. Consequences of opioid use

1.3.3.1. Health

Illicit opioid addiction is a chronic relapsing brain disorder with considerable associated morbidity and mortality that requires extended therapy (Gold & Johnson, 1998; Koob, 2000; Ling et al., 2003). Substance users are more likely to suffer from psychiatric illness and depression, at least some of which may be caused by the substance use itself. Substance use via the intravenous route also exposes the user to diseases such as Hepatitis C and Human Immunodeficiency Virus (HIV). Furthermore, substance use is also associated with overdoses whether they are lethal or non-lethal (Goldstein & Herrera, 1995; Havard et al., 2006).

A recent Australian Household Survey (AIHW, 2005a) observed that 1.4% of the Australian population had used heroin at least once in their lifetime with 0.2% of the population having used it within the previous year. While figures are not available for opioid use alone, in 2004 it was reported that 32% of injecting drug users had attended a health professional for a psychiatric illness other than substance use (AIHW, 2005b). The prevalence of Hepatitis C was also shown to be high among injecting drug users and increases in relation to the number of years of injecting drug use, with 73% of those who had been injecting drugs for 10 or more years testing positive for Hepatitis C (AIHW, 2005b). In 2003 approximately 5% of Acquired immune deficiency syndrome (AIDS) diagnoses were directly related to injecting drug use alone (AIHW, 2005b). In 2004, 55% of injecting drug users reported a non-fatal heroin overdose at some stage in their life, and one quarter of those interviewed reported this occurrence in the previous year (AIHW, 2005b). Latest figures from a 2003 report stated that fatal opioid overdoses occurred in 31.5 people per million (AIHW, 2005b).

1.3.3.2. Crime

Heroin use is also associated with high crime rates as a result of the high cost associated with continuous use of opioids required to suppress withdrawal symptoms (Gold & Johnson, 1998; Goldstein & Herrera, 1995; Ward et al., 1999). While individual statistics are not available for illicit opioid users alone, in 2004 48% of injecting drug users reported that they had committed a crime and 42% admitted to being arrested (AIHW, 2005b). In the period between 2003 and 2004, heroin accounted for 5% of arrests made on dealers or traffickers of illicit drugs and for the same period accounted for 63% of arrests of illicit drug consumers (AIHW, 2005b). Twenty percent of all prisoners tested for illicit drug use on admission to prison also tested positive to opioids (AIHW, 2005b). Once again individual statistics are not available for heroin, however for those individuals sentenced to prison in 2004, 10% were sentenced for offences directly related to drugs such as dealing or trafficking, use or possession and manufacture (AIHW, 2005b). This does not take into account crimes related to drug use such as theft in order to obtain goods to barter or sell in exchange for drugs.

1.3.3.3. Cessation of illicit opioid use

As a result of the above-mentioned consequences associated with continued illicit opioid use, it is vital that individuals cease use of illicit opioids for not only their own health and well-being, but also that of the broader community. There are several options available to assist the user to cease illicit opioid use and aid in rehabilitation. While other methods such as residential treatment facilities and psychological treatment alone are employed to combat illicit opioid use, the three most common methods currently in practice include detoxification, opioid antagonist pharmacotherapies and substitution maintenance pharmacotherapies in conjunction with psychotherapy.

Substitution maintenance pharmacotherapies provided on a long-term basis in conjunction with psychotherapy and social support, have advantages over other forms of illicit opioid treatment such as antagonist therapies and immediate total abstinence approaches. Individuals maintained on antagonist therapies often experience high rates of dysphoria and hence return to illicit opioid use. Immediate total abstinence approaches by means of rapid detoxification (often employing short-term antagonist administration), show disproportionately high rates of relapse to illicit opioid use (Gold & Johnson, 1998; Ling et al., 1994; 2003). For the purposes and scope of the current research only substitution maintenance pharmacotherapies will be discussed in further detail below.

1.4. Substitution maintenance pharmacotherapies

The overall primary aim of substitution maintenance pharmacotherapy is the discontinuation of illicit drug use and removal of the user from the drug seeking environment and the associated harms and risks. The outcomes include improvement to the health of individuals, reducing the spread of blood borne viruses associated with injecting drug use, reducing the risk of overdose, minimising crime associated with the high cost of obtaining illicit opioids and also the return of the individual to normal social functioning (Havard et al., 2006; Henry-Edwards et al., 2003). Both the individual and maintenance therapy prescriber should view substitution maintenance therapy as a long-term commitment, with relapse rates significantly reduced when opioid substitution therapy is provided on a long-term basis as distinct from short-term detoxification (Ling et al., 1994).

The aims of substitution maintenance therapy are achieved by suppression of withdrawal symptoms over individual dosing intervals, whilst also minimising opioid side effects. This can be achieved by substituting intravenously administered shorter acting opioid agonists such as heroin, for orally administered long acting opioid agonists or partial agonists. If withdrawal is not suppressed or undesirable side effects occur, there is the risk a patient will relapse back to illicit opioid use and discontinue maintenance therapy (Ling et al., 2003; Ward et al., 1999). Several studies have highlighted the importance of adequate maintenance therapy dosing as a crucial factor in retention of the individual in maintenance therapy programs, with inadequate dosing observed to be one of the primary reasons for patient non-compliance and treatment retention failure. Higher doses of maintenance therapies result in reduced illicit opioid use as observed by fewer urines positive for illicit opioids, and a generally higher rate of retention in maintenance therapy programs (Farre et al., 2002; Joseph et al., 2000; Ling et al., 1994).

Maintenance pharmacotherapies such as methadone and buprenorphine when administered in adequate doses, and in conjunction with psychotherapy and social support networks, have been shown to reduce the use of illicit opioids. This results in a reduction in mortality and morbidity in this population by reducing the spread of infectious diseases such as HIV/AIDS and Hepatitis C. This is achieved by reducing risk taking associated with needle sharing, and also through the reduction of illicit opioid overdoses. Crime as a result of obtaining opioids has also been observed to decrease as a result of maintenance pharmacotherapy treatment (Goldstein & Herrera, 1995; Joseph et al., 2000; Mattick et al., 2003a; Strain et al., 1993; Ward et al., 1999).

In 2004 approximately 34,000 Australians were registered as participating in opioid maintenance therapy programs. Approximately 75% of these were registered as participating in MMT programs with the remainder being registered as participating in buprenorphine maintenance treatment (BMT) (AIHW, 2005b).

1.4.1. Methadone

Methadone was first found to prevent the development of opioid withdrawal symptoms in 1948 and was first investigated as an ongoing maintenance treatment in 1965 (Dole & Nyswander, 1965; Isbell & Eisenman, 1948). Given in adequate doses, methadone has been shown to reduce opioid withdrawal symptoms and craving (Ling et al., 2003; Ward et al., 1999). It was first introduced in Australia to treat heroin dependence in 1969 and in conjunction with adjunctive psychotherapy has become the gold standard used to treat illicit opioid dependence (Henry-Edwards et al., 2003).

1.4.1.1. Chemistry

Methadone [(±)-6-dimethylamino-4,4-diphenylheptan-3-1] is a synthetic opioid that is administered as a racemate consisting of equal proportions of the two enantiomers, R(-)-methadone and S(+)-methadone.

The molecular weight of methadone is 309 with a pKa of 9.0. Methadone is a highly soluble lipid molecule with an octanol/water partition coefficient of 116.33 at 37°C (Kaufman et al., 1975).

1.4.1.2. Pharmacokinetics

1.4.1.2.1. Absorption

Methadone is reported as having a high oral bioavailability of 79 to 95% (Meresaar et al., 1981; Nilsson et al., 1982a) and is therefore administered orally as a hydrochloride salt in a 5 $mg.ml^{-1}$ solution (Henry-Edwards et al., 2003; Somogyi, 1998). Following oral administration of methadone the time taken to reach peak plasma concentration is between 2-4 hrs (de Vos et al., 1995; Meresaar et al., 1981; Nilsson et al., 1982a).

1.4.1.2.2. Metabolism

The major metabolic pathway involved in methadone biotransformation is N-demethylation by hepatic microsomal enzymes. This results in the formation of a highly unstable compound which undergoes spontaneous dehydration and cyclization to form the major inactive metabolite 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) (Figure 1) (Sullivan & Due, 1973). Methadone is N-demethylated by the cytochrome P450 3A4 isoform (CYP3A4) (Iribarne et al., 1996). Variations in CYP3A4 expression have been observed between

individuals (Forrester et al., 1992) and are due to environmental as well as genetic factors (Birkett, 1998) resulting in inter-individual variations in methadone metabolism. Cytochromes 2B6, 2C18, 2C19 and 2D6 have also been shown to contribute to a lesser extent than CYP3A4 in the metabolism of methadone, although controversy exists as to the degree of their contribution (Crettol et al., 2005; Foster et al., 1999; Gerber et al., 2004; Iribarne et al., 1996; Moody et al., 1997; Wang & DeVane, 2003).

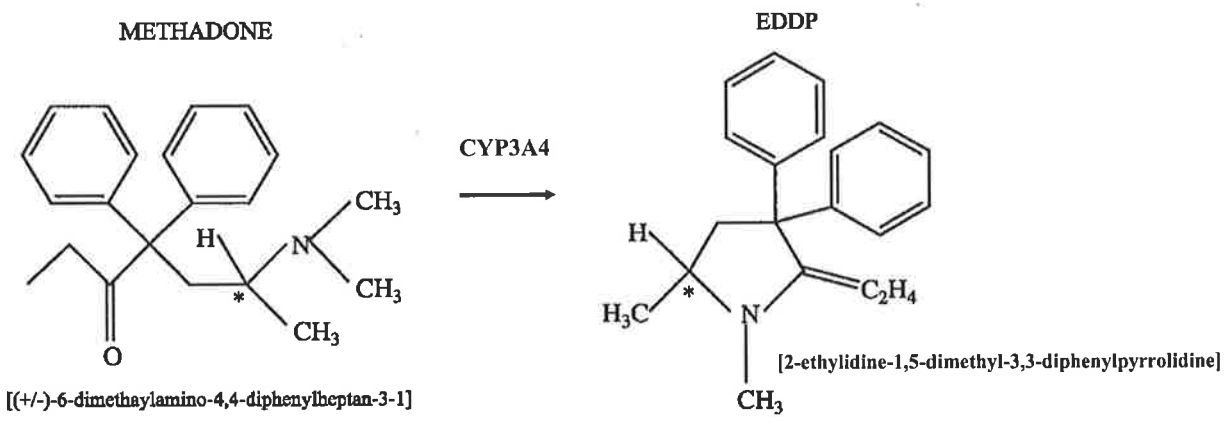

Figure 1-1 Methadone metabolism (*denotes chiral carbon).

1.4.1.2.3. Plasma protein binding and half-life

Methadone is highly bound in plasma with approximately 90% bound, of which most is bound to α_1-acid glycoprotein. In addition, albumin and other proteins such as lipoproteins do play a small role in the binding of methadone in plasma (Eap et al., 1990). Methadone has a relatively large volume of distribution ranging between 3 and 5.5 $l.kg^{-1}$ (de Vos et al., 1995; Meresaar et al., 1981; Nilsson et al., 1982a). The absorption half-life of methadone has been reported to be between 0.7 and 2.95 hrs (Meresaar et al., 1981; Wolff et al., 1997), whilst it has a much longer elimination half-life (approximately 30 hrs) and duration of action between 19 and 48 hrs and is therefore administered on a once daily basis (Meresaar et al., 1981; Nilsson et al., 1982a; Verebely et al., 1975; Wolff et al., 1997).

1.4.1.2.4. Clearance and excretion

Under normal physiologic conditions methadone is primarily cleared via hepatic metabolism with only small amounts of methadone detected in the urine and faeces (Nilsson et al., 1982b). However, alterations in urinary pH as a result of renal disease and other factors can greatly affect the renal clearance of methadone (Nilsson et al., 1982c; Wolff et al., 2000). When urine pH falls below 6, renal clearance accounts for 20-35% of total body clearance at 150ml.min^{-1}. When urine pH exceeds 6, renal elimination of methadone decreases to 90 ml.min^{-1} and therefore becomes less important, resulting in metabolism becoming the main route of elimination. Metabolism under this circumstance accounts for 95% of the body's clearance, with only small amounts of methadone detected in the urine, indicating complete reabsorption by the kidneys (Nilsson et al., 1982a; Nilsson et al., 1982b; Nilsson et al., 1982c; Wolff et al., 2000). The elimination of methadone via the faeces results in the recovery of between 3-20% of daily doses with mostly EDDP excreted via this route (Verebely et al., 1975).

1.4.1.2.5. Stereoselectivity

Foster and colleagues (2000) examined the steady-state pharmacokinetics of unbound R(-)- and S(+)- methadone and found substantial stereoselectivity for the majority of the methadone pharmacokinetic parameters previously discussed. Examples of this are lower intrinsic clearance of unbound pharmacologically active R(-)- methadone than S(+)- methadone (4611 and 7845 ml.min^{-1}, respectively) and also significantly greater fractions of unbound R(-)- than S(+)- methadone (3.84 ± 0.86% and 2.11 ± 0.52%, respectively), which may give rise to differences in volume of distribution. Peak plasma R(-)- and S(-)-methadone concentrations were observed to be 251 ng.ml^{-1} and 303 ng.ml^{-1}, respectively. Peak to trough plasma R(-)-methadone concentrations were significantly lower than peak to trough plasma S(-)-methadone concentrations (1.81 and 2.30, respectively).

1.4.1.3. Neuropharmacology

1.4.1.3.1. Opioid receptor actions

Pasternak and Wood (1986) isolated two subtypes of the μ-opioid receptor. These were a high affinity but low capacity μ_1-receptor, and a low affinity but high capacity μ_2-receptor. The μ_1-receptor is reported to mediate supraspinal analgesia while the μ_2-receptor is reported to mediate spinal analgesia. R(-)-methadone has approximately 10 times higher affinity for binding at both μ-opioid receptors (K_i=0.945 nM) than S(+)-methadone (K_i=19.7 nM) and twice that of racemic methadone (K_i=1.7 nM). However, as indicated by displacement of known opioid ligands from the receptor, R(-)-methadone binds with greater affinity at the μ_1-receptor compared with the μ_2-receptor ($IC_{50}\mu_1$: 3.01 nM, $IC_{50}\mu_2$:6.94 nM) (Codd et al., 1995; Kristensen et al., 1995). Both enantiomers have low affinity for δ- and κ-opioid receptors: for the δ-receptor, S(+)-methadone has 20 times less affinity than that of R(-)-methadone (K_i=960 nM and 360 nM, respectively) and both enantiomers possess an equally low affinity for the κ-receptor (S(+)-methadone K_i=1370nM; R(-)-methadone K_i=1860nM) (Kristensen et al., 1995). Therefore, methadone can be said to be a full agonist at the μ-opioid receptor.

1.4.1.3.2. Non-opioid receptor actions

Opioids also act at sites other than opioid receptors. Codd and colleagues (1995) reported that drugs such as morphine and methadone inhibited the synaptosomal re-uptake of the neurotransmitters noradrenaline and serotonin. Of the two enantiomers of methadone, Codd and colleagues (1995) found that R(-)-methadone was a much more potent inhibitor of serotonin and noradrenaline reuptake than S(+)-methadone.

Gorman and colleagues (1997) discovered that both enantiomers of methadone acted as non-competitive antagonists at the n-methyl-d-aspartic acid (NMDA) receptor. This receptor is

normally activated by excitatory amino acids such as glutamate and R(-)-methadone was found to be a slightly more potent antagonist than S(+)-methadone.

1.4.1.4. Pharmacodynamics

The majority of opioid effects produced by methadone are a result of the actions of R(-)-methadone with S(+)-methadone thought to produce little or no effect (Isbell & Eisenman, 1948; Scott et al., 1948). This may be due to the limited ability of opioid receptors to bind enantiomers of the (+)-conformation (Goldstein, 1976). However, recent reports have suggested that S(+)-methadone may be responsible for producing adverse subjective and physiological responses (Mitchell et al., 2004).

As a full opioid agonist showing high μ-opioid receptor selectivity, methadone produces effects similar to other opioid agonists. Acute administration of methadone in non-tolerant individuals can cause nausea and sedation, however under chronic administration conditions, tolerance develops rapidly to these effects and they are rarely seen (King & Miller, 1998). Pharmacodynamic effects of methadone over 24 hr dosing intervals are related to methadone plasma concentrations. For example, pupil diameter and respiratory rate both decrease following methadone administration with the maximal opioid effect occurring 2-4 hrs after administration (Dyer et al., 1999; Dyer et al., 2001).

Over 24 hr dosing intervals methadone withdrawal symptoms show an inverse relationship to plasma methadone concentrations, with withdrawal scores peaking in the period immediately prior to each dose. In addition, small changes in plasma methadone concentrations can translate into relatively large changes in withdrawal severity (Dyer et al., 1999; Dyer & White, 1997). A similar pattern was observed with mood states in methadone maintained individuals

where total mood disturbances were at a maximum prior to methadone dosing (Dyer et al., 2001).

Other symptoms of complaint in methadone maintained individuals include constipation, dry mouth, increased sweats, insomnia and reduced libido (Dyer & White, 1997; Kreek, 1979).

Upon cessation of methadone treatment, following gradual tapering of methadone dose, there is a rapid increase in withdrawal symptoms that gradually subside. However, total withdrawal does not appear to be ameliorated in some cases until 40 days after methadone cessation (Gossop et al., 1987).

1.4.2. Buprenorphine

Buprenorphine was first introduced into medical practice as an intramuscular analgesic in 1976 (Rolly & Versichelen, 1976). A study by Jasinski and colleagues (1978) was the first to suggest that buprenorphine could be used for the treatment of opioid dependence. Since that time, buprenorphine has been shown to be more effective than a placebo control for the treatment of opioid dependence by suppressing heroin self-administration (Johnson et al., 1995; Mattick et al., 2006; Mello & Mendelson, 1980; Mello et al., 1982). It was first registered for use as a maintenance pharmacotherapy in Australia in 2001 (Lintzeris et al., 2001).

1.4.2.1. Chemistry

Buprenorphine [21-cyclopropyl-7α-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-*endo*-ethano-6,7,8,14-tetrahydrooripavine] is a derivative of the morphine alkaloid thebaine (Cowan et al.,

1977; Lewis, 1973) and has been shown to be up to 25-50% more potent and longer acting than morphine (Cowan et al., 1977; Jasinski et al., 1978).

The molecular weight of buprenorphine is 467 with a pKa of 8.24 (Mendelson et al., 1997). Buprenorphine is a highly lipid soluble molecule. Limited research has been performed observing the octanol/water partition coefficient of buprenorphine, although one study reports it to be 1943 at 37°C (Ohtani et al., 1995).

1.4.2.2. Pharmacokinetics

1.4.2.2.1. Absorption

Buprenorphine has a low oral bioavailability of approximately 14% (Mendelson et al., 2001) due to extensive first pass metabolism (Brewster et al., 1981). For this and other reasons it is administered sublingually in tablet form as a hydrochloride salt and has a bioavailability of 28 to 60% (Everhart et al., 1997; Kuhlman et al., 1996; Mendelson et al., 1997; Nath et al., 1999). The time taken to reach peak plasma buprenorphine concentrations is 0.5-3 hrs (Everhart et al., 1997; McAleer et al., 2003; Mendelson et al., 1997; Nath et al., 1999; Schuh & Johanson, 1999; Walsh et al., 1994).

1.4.2.2.2. Metabolism

Buprenorphine is metabolised by a combination of phase I and phase II enzymes. The major metabolic pathway involved in buprenorphine biotransformation is N-dealkylation to form the pharmacologically active, major metabolite norbuprenorphine (Figure 2) (Cone et al., 1984; Huang et al., 2001). CYP3A4 is responsible for up to 75% of norbuprenorphine formation (Iribarne et al., 1997).

Buprenorphine also undergoes glucuronidation to buprenorphine-3-glucuronide. As much as 75% of buprenorphine glucuronidation activity can be attributed to UGT1A1 (King et al., 1996) with UGT1A3 playing a minor role (Green et al., 1998).

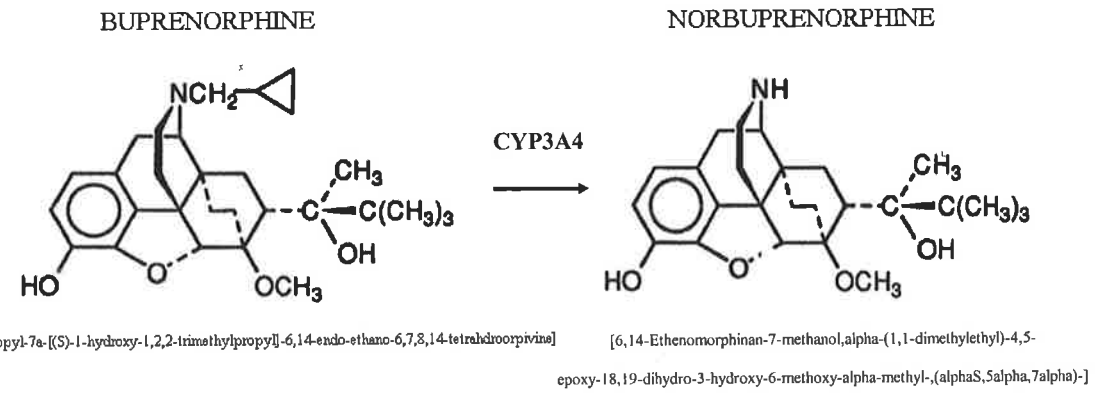

Figure 1-2 Buprenorphine metabolism.

1.4.2.2.3. Plasma protein binding and half-life

Buprenorphine is highly bound to plasma proteins, predominantly α- and β-globulin fractions (approximately 96%) (Walter & Inturrisi, 1995) and has a large volume of distribution (90-190 $l.kg^{-1}$) (Bullingham et al., 1980; Bullingham et al., 1983). The intravenous absorption half-life of buprenorphine is very short at around 1.5 to 2 mins due to its high lipophilicity (Bullingham et al., 1980; Ho et al., 1991). In contrast, the terminal half-life is highly variable ranging between 16.2 ± 20 hrs following intravenous administration (Mendelson et al., 1997). Similarly, the terminal half-life of buprenorphine when administered sublingually is highly variable (approximately 26 hrs, range 9-69 hrs, (McAleer et al., 2003)). However, reports have shown that when administered sublingually, its duration of action is at least as long as that of methadone, if not longer (24-69 hrs) (Kuhlman et al., 1998; Walsh et al., 1994). This may be due to the slow dissociation of buprenorphine from its binding sites (see below) (Hambrook & Rance, 1976; Iribarne et al., 1997) or contribution from norbuprenorphine to the pharmacological effect (Huang et al., 2001).

1.4.2.2.4. Clearance and excretion

The clearance of buprenorphine has been found to be between 900-1300 $ml.min^{-1}$ when administered intravenously (Bullingham et al., 1980; Mendelson et al., 1997). Buprenorphine is primarily excreted via faeces, with little buprenorphine detected in the urine (approximately 30% faecal recovery and less than 10% urinary recovery as total buprenorphine conjugate). Norbuprenorphine is also excreted via faeces (about 20% of the dose) with low total urinary recovery of norbuprenorphine (about 10% of the dose) and it is excreted over the course of 4 days (Cone et al., 1984).

1.4.2.3. Neuropharmacology

Buprenorphine is a potent partial agonist at the μ-opioid receptor with low intrinsic activity; that is, it does not activate the receptor to the same extent as a full μ-opioid agonist, but it has high affinity for the μ-opioid receptor (K_i=0.08 nM) (Ariens, 1983; Huang et al., 2001; Jasinski et al., 1978; Johnson et al., 2003c). Buprenorphine is also a partial agonist at κ-opioid receptors with low efficacy, but shows potent antagonist activity (K_i=0.11 nM) (Huang et al., 2001). Buprenorphine has high affinity at δ-opioid receptors (K_i=0.42 nM), displaying no agonistic activity but, acts as a competitive antagonist at this receptor (Huang et al., 2001).

Norbuprenorphine exhibits high affinities for μ-, δ- and κ-opioid receptors (K_i=0.07 nM, K_i=3.14 nM and K_i=0.91 nM, respectively). Earlier research suggested that similarly to buprenorphine, norbuprenorphine is also a partial agonist at μ- and κ-opioid receptors, however it acts as a full agonist at δ-opioid receptors. However, more recent research observing the acute toxicity and respiratory effects of norbuprenorphine in rats has suggested that it may in fact be a full agonist at μ-opioid receptors (Megarbane et al., 2006). Norbuprenorphine has also been shown to be a relatively potent dose-dependent analgesic (Huang et al., 2001).

An inverse correlation between lipophilicity and the rate of dissociation from opioid binding sites has previously been suggested. Considering buprenorphine's high lipophilicity, it dissociates exceedingly slowly from opioid receptor binding sites. This has been proposed to be a major contributing factor to the drug's long duration of action (Hambrook & Rance, 1976).

1.4.2.4. Pharmacodynamics

A partial agonist on an empty receptor system will act as an agonist and produce an effect (Ariens, 1983). In terms of reported subjective responses and physiological actions, agonist effects produced by buprenorphine resemble those of morphine and methadone and include sedation, euphoria, pupillary constriction and respiratory depression (Pickworth et al., 1990; Walsh & Eissenberg, 2003). As a partial agonist, buprenorphine has ceiling effects and for some actions (such as respiratory depression but not analgesia) there appears to be an inverted U–shaped dose-response curve. That is, there are dose-related increases in efficacy and opioid effect in the lower dose range, with higher doses producing no greater or even decreased effects (Jasinski et al., 1978; Walsh et al., 1994). During chronic dosing in maintenance subjects, physiological and subjective changes over the dosing interval are relatively small (Lopatko et al., 2003).

In subjects who have had experience with opioids but were not physically dependent, sublingual doses of 32 mg of buprenorphine have been shown to cause a decrease in respiratory rate of 4 breaths.min^{-1}. However, this dose of buprenorphine is said to be equivalent to 530 mg of intramuscular morphine and 1060 mg of oral methadone (Walsh et al., 1994) based on analgesic dose equivalents. While these doses of morphine and methadone are in the lethal range, the equivalent dose of buprenorphine only shows marginal effects on respiratory function relative to these other opioid agonists (Walsh et al., 1994; Ward et al.,

1998a). Chronic daily dosing with 16 mg of buprenorphine has also produced insignificant effects on respiration (Lopatko et al., 2003).

A partial agonist is also able to displace a full agonist from an opioid receptor, reducing the effect of the agonist and, therefore, behaving as an antagonist. In someone physically dependent on opioids it can produce a precipitated withdrawal in the same manner as an antagonist (Ariens, 1983; Jacobs & Bickel, 1999). Buprenorphine has been shown to produce a dose-related blockade of opioid agonist effects (Bickel et al., 1988a; Mello & Mendelson, 1980). In terms of antagonist effects, buprenorphine is similar to naltrexone in regard to its duration of action of 29.5 hrs (Jasinski et al., 1978). For this reason, when beginning buprenorphine treatment, caution must be taken in order to prevent precipitated withdrawal. The probability of precipitated withdrawal due to buprenorphine administration is dependent on the type and dose of opioid previously administered, the length of time it was administered, and the dose of buprenorphine to be administered (Schuh et al., 1996; Strain et al., 1992; Walsh et al., 1995). Therefore, an appropriate time period is required between the last opioid administration and the first buprenorphine dose (Ling et al., 1994).

The abrupt termination of buprenorphine has produced subjective reports of a mild to moderate withdrawal syndrome that occurs within the first three days, peaking between days three and five and gradually diminishing over days 8 to 10 (Fudala et al., 1990; Kuhlman et al., 1998). On the basis of this evidence it has been suggested that buprenorphine produces a relatively low level of physical dependence (Bickel et al., 1988b; Jasinski et al., 1978; Mello & Mendelson, 1980; Mello et al., 1982).

1.4.2.4.1. Factors affecting methadone and buprenorphine disposition

1.4.2.4.1.1. Other substances

As previously mentioned, illicit opioid users are more likely to suffer from psychiatric illness. These psychiatric illnesses often require pharmacological treatment with drugs that may interfere with the pharmacological properties of both methadone and buprenorphine, causing adverse events. Poly-drug use is also more common among illicit opioid users than the general population and these other substances may also interfere with the pharmacological properties of methadone and buprenorphine. The most common mechanism by which drug interactions occur with methadone and buprenorphine is by induction or inhibition of CYP450 enzymes. This may be due to inhibited or induced metabolism of methadone or buprenorphine by other drugs. Conversely, methadone or buprenorphine may cause inhibition or induction of metabolism of other drugs, leading to serious adverse events (Zhang et al., 2003).

In opioid dependent individuals, methadone and buprenorphine are often administered in conjunction with other drugs such as benzodiazepines (Zhang et al., 2003). These may be administered for therapeutic purposes within normal therapeutic ranges or in much higher illicitly consumed doses. Methadone and buprenorphine themselves have been shown to inhibit CYP3A4, which also metabolises many benzodiazepines, therefore resulting in the potential for enhanced plasma concentrations of benzodiazepines and an increase in sedative effects (Thummel & Wilkinson, 1998; Zhang et al., 2003). Several deaths have been reported due to benzodiazepine misuse in conjunction with high dose buprenorphine and may be a result of pharmacodynamic interactions (Reynaud et al., 1998).

In addition, methadone inhibition of CYP3A4 should be taken into consideration during the induction phase of maintenance. Methadone inhibits CYP3A4 activity following single dose

administration (Boulton et al., 2001) and, therefore, during induction, dose increases should be carefully monitored as greater than expected toxicity may occur due to decreased methadone clearance. Methadone has also been shown to inhibit CYP2D6 activity resulting in differing abilities to metabolise methadone. Inhibition of CYP2D6 may result in poor metabolism of methadone in methadone maintained patients that may lead to toxicity and undesirable effects (Shiran et al., 2003; Wu et al., 1993).

Inhibition of CYP450 enzymes by drugs such as fluconazole, ketoconazole, fluoxetine, paroxetine, sertraline, ciprofloxacin, and fluvoxamine have been shown to increase plasma methadone and buprenorphine concentrations and if not monitored closely may result in overdose (Davis & Walsh, 2001; Eap et al., 2002; Iribarne et al., 1998). In contrast, decreased methadone and buprenorphine plasma concentrations have been observed as a result of induction of CYP450 enzymes due to St John's wort, rifampicin, phenobarbitone, amylobarbitone, phenytoin, carbamazepine, spironolactone, fusidic acid, nevirapine, efavirenz, amprenavir, nelfinavir and ritonavir (Davis & Walsh, 2001; Eap et al., 2002; Eich-Hochli et al., 2003). This may result in reduced efficacy of methadone and buprenorphine if doses are not adjusted appropriately.

As previously mentioned, fluctuating levels of plasma binding proteins (Eap et al., 1990), and differing expressions of CYP3A4 (Forrester et al., 1992) can affect the disposition of both methadone and buprenorphine, and urine pH has also been shown to affect the disposition of methadone (Nilsson et al., 1982c).

1.4.2.4.1.2. Pregnancy

Pregnancy has also been shown to affect the disposition of methadone with significant changes in the pharmacokinetic parameters of methadone being observed. Several studies

have observed a decrease in trough methadone concentrations as well as increased total (bound and unbound) plasma methadone clearance (170-300 $ml.min^{-1}$) during late pregnancy compared with post-partum observations (Jarvis et al., 1999; Kreek, 1979; Pond et al., 1985). This may contribute to the decreased half-life of methadone during pregnancy, which has been observed to be between 8.1 and 19 hrs (Jarvis et al., 1999; Swift et al., 1989). A recent study observed decreases in mean plasma methadone concentrations from 0.12 $mg.l^{-1}$ in the first trimester to 0.07 $mg.l^{-1}$ in the third trimester, and, similarly, the mean area under the plasma concentration time curve for the interdosing interval was reduced from 4.5 to 2.9 $mg.h.l^{-1}$, respectively. An increase in methadone clearance was observed from 0.17 $l.h.kg^{-1}$ in the first trimester to 0.21 $l.h.kg^{-1}$ in the third trimester (Wolff et al., 2005).

There are several reasons as to why these changes in pharmacokinetic parameters of methadone may occur, with the main reason focussed on increases in methadone metabolism. Increases in CYP2D6 and 3A4 activity have been observed as a result of pregnancy and may account for changes in methadone metabolism. CYP2D6 activity has been shown to increase in a temporal fashion with the largest increase of 50% observed in the third trimester. In contrast, CYP3A4 activity is significantly increased (35-38%) throughout pregnancy compared to postpartum. As a result of these changes it has been suggested that dosing regimes of drugs that are metabolised by these enzymes may need to be altered during pregnancy (Tracy et al., 2005).

The pharmacokinetics of buprenorphine during pregnancy are not as clearly understood, as buprenorphine has not been approved for use during pregnancy. However, considering both methadone and buprenorphine are metabolised by similar enzymes, pharmacokinetic changes observed with methadone during pregnancy may also occur with buprenorphine during pregnancy.

1.4.3. Comparison of buprenorphine and methadone

The obvious and major comparison to be made between buprenorphine and methadone is that methadone is a full μ-opioid receptor agonist whereas buprenorphine is a partial μ-opioid receptor agonist. These differences in opioid receptor action give rise to differences in a number of properties or measures including overdose and abuse potential, dose scheduling, induction processes, patient acceptance and duration of withdrawal.

1.4.3.1. Overdose and abuse potential

Buprenorphine is a relatively safe drug when compared with methadone. As previously mentioned, very high sublingual doses of 32 mg of buprenorphine have been shown to cause a relatively small decrease in respiratory rate of only 4 breaths.min^{-1}. This demonstrates the previously mentioned ceiling effects of buprenorphine at high doses beyond which no greater effects are observed (Walsh et al., 1994). It has also been observed that there are no additive effects on respiratory depression when buprenorphine is administered along with another pure μ-opioid receptor agonist and that buprenorphine has also been shown to produce a dose related blockade of opioid agonist effects due to its opioid antagonist properties (Bickel et al., 1988a; Mello & Mendelson, 1980). These factors suggest that the possibility of lethal overdose due to respiratory depression in subjects maintained on buprenorphine is limited in comparison to methadone (Johnson et al., 1989; Walsh et al., 1994). Therefore, should buprenorphine abuse occur, it would have far less serious medical consequences than would methadone abuse (Mello et al., 1982). It is also thought that a ceiling on the euphoric effects of buprenorphine may also limit its abuse potential (Walsh et al., 1994). However, if significant respiratory depression does occur as a result of buprenorphine abuse, it becomes difficult to reverse with traditional opioid antagonists. This is because buprenorphine has a

higher affinity for μ-opioid receptors than antagonists such as naloxone (K_i= 2.3 nM (Poisnel et al., 2006)) that are used in the reversal of opioid agonist overdose.

1.4.3.2. Induction and maintenance

Too slow an induction process has been blamed for poor treatment retention within the first week of maintenance therapy dosing, as patients experience dysphoria, withdrawal discomfort, and often revert back to illicit opioid use (Fischer et al., 1999; Mattick et al., 2003a; Petitjean et al., 2001). Despite this, there are several safety aspects that need to be taken in to consideration when inducting individuals on to maintenance therapy programs.

An increase in overdose mortality has been observed in methadone maintained individuals during the induction period. In some studies the overdose mortality rate during the methadone induction period is elevated relative to the overdose rate from continued use of illicit opioids. Several factors that are thought to contribute to these deaths are the excessive accumulation of methadone during the induction period, inadequate assessment of opioid tolerance prior to induction and a compounding effect of increased stress and irritability that usually occur around the time of entry into treatment (Ballesteros et al., 2003; Buster et al., 2002; Caplehorn & Drummer, 1999; Williamson et al., 1997; Zador & Sunjic, 2000). The major cause of overdose deaths during the induction period is thought to be hypoxia due to respiratory depression (White & Irvine, 1999). Therefore patients are observed daily during the first 2 weeks of induction. Maintenance dose is gradually achieved during this period and further adjusted if necessary (Henry-Edwards et al., 2003).

Once issues relating to buprenorphine precipitated withdrawal have been resolved, given the safety profile of buprenorphine, it has been suggested that individuals may undergo relatively rapid induction on to buprenorphine when compared to methadone. Doses between 2-6 mg of

buprenorphine have been associated with reduced patient compliance during the induction period and it has been suggested that doses up to 12-16 mg should be achieved by the third day of induction to maximise treatment retention in the first week, with few clinical management issues or adverse events (Mattick et al., 2003a; Petitjean et al., 2001). Patients are again reviewed daily and doses adjusted until stabilisation occurs which is typically by the end of the first week (Lintzeris et al., 2001).

Once the induction process has been successfully completed, as previously mentioned, it is imperative to ensure that individuals be maintained on adequate doses of medication to continue with maintenance therapy. For methadone, doses exceeding 50 mg have been shown to be effective and recommended for adequately maintaining individuals on a methadone maintenance therapy program (Ward et al., 1998b). Doses exceeding 12 mg of buprenorphine are recommended for maintenance in order to ensure patient comfort and therefore continuation in maintenance therapy (Lintzeris et al., 2001).

1.4.3.3. Dose scheduling

Attending a clinic on a daily basis for supervised medication administration, as is the case with methadone, is inconvenient and burdensome on the patient, and works against the patient's ability to become involved in employment, education, child care and other activities associated with a non-drug dependent lifestyle (Ling et al., 1994). In an attempt to combat this shortcoming, take away doses are often provided to enable the individual to take doses at home on certain days. However, this has resulted in the diversion of methadone and the creation of street methadone as well as accidental overdose deaths in children (Ling et al., 1994). The advantage of buprenorphine is that in highly motivated, clinically stable individuals, buprenorphine can be administered on an alternate-day dosing regimen without inducing a physiologically measurable withdrawal syndrome (Fudala et al., 1990). This can be

successfully achieved by doubling the dose of buprenorphine and administering it every 48 hrs, or even tripling the dose and administering every 72 hrs, without any additional opioid effect, withdrawal or detriment to retention rates (Bickel et al., 1999; Johnson et al., 2000; Schottenfeld et al., 2000).

The advantages of maintaining opioid dependent individuals in a treatment that does not require the daily administration of medication include decreased perception of the inconvenience associated with visiting a clinic on a daily basis and more time and opportunity for patients to re-establish themselves into society. It may also eliminate the need for take home doses and therefore minimise illegal diversion of maintenance therapy medications. It also provides the possibility of increasing treatment capacity at the same time as reducing the overall cost per patient (Bickel et al., 1999; Fudala et al., 1990).

1.4.3.4. Patient acceptance

Methadone in some cases has been perceived as "just another addicting drug" that is more dependence producing and a less desirable alternative to remaining on heroin (Resnick et al., 1992). In addition, significant numbers of those maintained on methadone report inadequate suppression of withdrawal and the occurrence of side effects over the interdosing interval (Dyer & White, 1997), and is a reflection of the continual cycling in and out of MMT that typically occurs (Bell et al., 2006). It has been shown that heroin addicts who remain outside health-care systems for this reason will accept treatment with buprenorphine even if daily attendance is required (Resnick et al., 1992). Subjects have reported that buprenorphine therapy makes them feel more "normal" or "reality orientated" compared to the typical opioid "drugged" or "intoxication" feeling experienced with methadone (Eder et al., 1998; Fischer et al., 1999). However, this may work in the reverse in that buprenorphine's partial agonist

properties may be less attractive to some patients who prefer to have a full agonist effect and be consistent with buprenorphine's reported lower "buzz" rating (Mattick et al., 2003a).

1.4.3.5. Withdrawal

As previously mentioned in Section 1.4.2.4, the abrupt termination of buprenorphine has produced subjective reports of a mild to moderate withdrawal syndrome (Fudala et al., 1990; Kuhlman et al., 1998). However, following the slow reduction of buprenorphine dose, withdrawal symptoms, if present at all (Mello & Mendelson, 1980; Mello et al., 1982), are relatively mild in contrast to the pure opioid agonist methadone, where moderate to severe withdrawal symptoms can last up to 40 days (Bickel et al., 1988b; Gossop et al., 1987; Martin et al., 1973). Therefore, buprenorphine produces a low level of physical dependence compared to the protracted withdrawal observed as a result of methadone use (Bickel et al., 1988b; Jasinski et al., 1978; Mello & Mendelson, 1980; Mello et al., 1982), making complete detoxification from opioids a much more achievable task (Bickel et al., 1988b; Ward et al., 1998a).

1.4.3.6. Summary

From research to date it is apparent that methadone and buprenorphine are effective in suppresson of illicit opioid use (Mattick et al., 2003b; 2006; Strain et al., 1994; Ward et al., 1998a). It should be noted that with both methadone and buprenorphine if induction processes are not undertaken appropriately and doses are not adequate during the maintenance phase, this may result in patient non-compliance and discontinuation of the maintenance therapy (Farre et al., 2002; Joseph et al., 2000; Ling et al., 1994; Petitjean et al., 2001).

1.5. Substance use and pregnancy

As previously mentioned, women of child bearing age are prevalent in the drug using population. A complex situation then presents itself when these women become pregnant and continue their substance use.

It has been shown that pregnant illicit opioid dependent women often experience a high incidence of obstetric complications that include premature labour, premature rupture of membranes and antepartum haemorrhage (Kennare et al., 2005; Silver et al., 1987). These complications usually result from inadequate or the complete lack of antenatal care (Stone et al., 1971). In addition, the continual cycling from intoxication to withdrawal as a result of illicit opioid use can often lead to fetal stress. Removal of the mother from a drug-seeking environment prevents these continual fluctuations in drug plasma concentrations, therefore minimising maternal but most importantly, fetal stress (Brown & Zuckerman, 1991).

1.5.1. Development of NAS

NAS develops in response to the sudden cut off from the supply of the drug that the mother used during pregnancy (Ghodse, 1989). NAS is a "generalised disorder characterised by signs and symptoms of CNS hyperirritability, gastrointestinal dysfunction, respiratory distress and vague autonomic symptoms that include yawning, sneezing, mottling and fever" (Kaltenbach et al., 1998). Many manifestations of NAS are non-specific and occur regardless of the drug used. Onset, severity and duration of symptoms may differ depending on the drug class used by the mother, the timing of her last substance use prior to delivery and the rate of drug elimination by the newborn (Finnegan & Kandall, 1997).

The Finnegan Scale is one of the most common methods currently used in the identification and rating of NAS severity and is a 21-item scale separated into three sub-sections according to withdrawal symptoms shown by the infant (CNS Disturbances, Metabolic Vasomotor and Respiratory Disturbances and Gastrointestinal Disturbances). A maximum score of 46 can be obtained which indicates severe NAS and a minimum score of 0 indicates the absence of NAS. Modifications of the Finnegan Scale are often used with maximum score ranging from 42 to 44. The Finnegan scale is administered at 2 hourly intervals for the first 48 hrs of life and then every 4 hrs thereafter. If at any time the infant's score is observed to be 8 or greater, 2 hr scoring is again initiated and continued for 24 hrs from the last total score of 8 or greater. If 2 hr scores continue to be 7 or less for 24 hrs, scoring is returned to 4 hourly intervals (Finnegan & Kandall, 1997).

1.5.2. Treatment of NAS

It is recommended that pharmacological intervention for the treatment of NAS begin when a Finnegan score of 8 is observed on 3 consecutive scoring sessions or when the average of any 3 consecutive scores is 8 or greater. The Finnegan score also determines the dose of pharmacotherapy to be used in treating the infant (Finnegan & Kandall, 1997).

There are two main pharmacological methods used in the treatment of NAS. These include treatment with a substitution therapy (an appropriate agonist) or a non-specific CNS depressant such as phenobarbitone (Finnegan & Kandall, 1997; Kandall, 1999). NAS arising as a result of opioid exposure is best treated with a substitution therapy such as morphine sulphate. Where it is suspected that infants have been exposed to multiple substances through maternal poly-drug use (whether they be a combination of opioid or non-opioid) is best treated with a sedative such as phenobarbitone. However, phenobarbitone does not appear to prevent abstinence-associated seizures (Kandall et al., 1983). It is important to note that unrecognised

and untreated NAS may result in death due to excess fluid losses (as a result of excessive vomiting and diarrhoea), hyperpyrexia, seizures, respiratory instability, aspiration and apnoea (Finnegan & Kandall, 1997).

Infants born with NAS experience longer hospitals stays (often spending this time in intensive care units) than non-drug exposed infants due to the severity of symptoms and the associated treatment. Other factors may influence the length of hospital stay in these infants including social factors concerning the suitability of mothers to care for their infants (Johnson et al., 2003a). If the mother is found to be unsuitable and there are concerns for the infant's safety, there is a requirement to find adequate foster care for these infants to be housed in. This can often take considerable time resulting in an increased length of infant hospital stay.

1.5.3. Abstinence during pregnancy

Taking into account the above mentioned pregnancy complications and the likely development of NAS if substance use continues, the ideal situation during pregnancy would be for complete opioid abstinence in the mother (Fischer, 2000). However, due to the short period of time in which the pregnant woman would be expected to reach total abstinence, this is often unachievable as significant maternal and fetal withdrawal may develop, and place the mother and fetus under a great deal of stress (Fischer, 2000). Opioid detoxification attempts during pregnancy have produced increased levels of adrenaline and noradrenaline in amniotic fluid, indicating fetal stress due to increased activity of the adrenal gland and the sympathetic nervous system (Zuspan et al., 1975). There is also a high failure rate with the majority of mothers attempting detoxification returning to methadone programs (Finnegan, 1991; Kashiwagi et al., 2005).

As a result, detoxification is not recommended in the first trimester due to an increased risk of spontaneous abortion or in the third trimester due to an increased risk of premature labour (Keenan et al., 1993). Similarly, non-medicated withdrawal ("cold turkey") from opioids has even been shown to result in an increased percentage of still born children (Bashore et al., 1981). There is also a very high rate of relapse to heroin use associated with non-medicated withdrawal due to significant maternal discomfort (Blinick et al., 1973; Finnegan, 1991; Kaltenbach et al., 1998; Kandall, 1995). Therefore, only a small number of highly motivated women may be candidates for medical withdrawal (Finnegan & Kandall, 1997) and they must be closely, clinically and biochemically, monitored (Zuspan et al., 1975).

1.5.4. MMT during pregnancy

MMT has been shown to improve attendance at antenatal care (Johnson et al., 2003a) and therefore reduce obstetric complications in opioid dependent women. Connaughton and colleagues (1977) observed that women who delivered infants while still actively using heroin attended on average 1.8 antenatal appointments. This was in comparison to women participating in MMT who attended at least 4 antenatal appointments, with an average 8.2 appointments recorded. Similarly Doberczak and colleagues (1993) observed the average number of antenatal appointments attended by 18 of 21 women receiving methadone to be 7±4.

It has been shown that complications during pregnancy in women maintained on methadone tend to be similar to those of the general obstetric population (Blinick et al., 1976). Strauss and colleagues (1974) noted that low dose methadone in conjunction with prenatal care reduced obstetric risk to a level that was comparable to that of non-addicted women. Silver and colleagues (1987) noted that in 112 drug dependent women, of which 72 were participating in MMT, the average duration of the first, second and third stages of labour were

comparable to those women who were not drug dependent and with a normal course of labour. The incidence of labour abnormalities and Caesarean sections were also no higher than in controls matched for gravidity, parity and socioeconomic background. Doberczak and colleagues (1993) observed unremarkable obstetric courses in 19 women enrolled in approved MMT programs except for one mild case of pre-eclampsia that did not require pharmacotherapy.

MMT is also associated with more normal fetal growth and reduced fetal mortality (Kandall et al., 1977). Fetal stress has been shown to be attenuated when maternal methadone dose is increased (Zuspan et al., 1975) and may be a reflection of minimising maternal withdrawal distress. Hagopian and colleagues (1996) observed that higher methadone doses in the third trimester of pregnancy are associated with increased head circumference, which was thought to reflect both increased gestational duration and improved overall fetal growth. This could also be a reflection of improved maternal nutrition associated with MMT, as heroin dependent women often develop a range of nutritional deficiencies as a result of preoccupation with drug seeking (Finnegan & Kandall, 1997).

Most importantly, MMT provides the pregnant heroin dependent mother with an opportunity to restructure her life and enhance her ability to prepare for the birth of her infant by removing her from a drug-seeking environment (Finnegan & Kandall, 1997; Kandall et al., 1977). This is vital as continuous intravenous heroin use throughout pregnancy increases the risk of contracting HIV/AIDS and Hepatitis, resulting in adverse effects for both the mother and fetus (Brown & Zuckerman, 1991).

1.5.4.1. Disadvantages of methadone during pregnancy

While the same principles of maintenance therapy (as discussed in Section 1.4) still apply during pregnancy, there are additional factors such as NAS to be taken into consideration when a maintenance therapy is used in this population. Despite the considerable advantages of MMT during pregnancy, its use is not without debate as several side effects have been observed (Kaltenbach et al., 1998)

1.5.4.1.1. Fetal disadvantages

Methadone has been shown to cause highly significant changes to all aspects of fetal neurobehavioral functioning that appears to be dependent on trough and peak methadone concentrations. An early study by Wittman and Segal (1991), observed significant decreases compared to normal controls in both fetal body movements and breathing episodes and a significant increase in the longest period of inactivity following single daily methadone dosing regimes. A similar trend was observed before and after a split daily methadone dosing regime, although outcomes in this instance were more similar to normal control fetal behaviour. This finding may provide additional support for the split dosing of methadone during pregnancy in order to minimise fluctuations in drug concentrations and minimise fetal sedation.

In a more recent study Wouldes and colleagues (Wouldes et al., 2004) observed suppression of fetal breathing movements 1 hr post maternal daily methadone dose that was not observed in a control population. Reductions in fetal breaths per minute, fetal body movements per breathing episode and total fetal activity were also observed with the conclusion that maternal methadone dose has an effect on total fetal activity within 1 hr of dose consumption. This may affect fetal lung growth and maturation.

Following on from this, Jansson and colleagues (2005) observed significantly slower fetal heart rate, reduced variability and fewer heart rate accelerations at times of assumed peak plasma methadone concentrations. Peak and trough plasma methadone concentrations were not actually measured in this study and therefore fetal monitoring was observed at times when peak and trough methadone concentrations were thought to occur based on previous research. The number of movement bouts was unchanged at times of assumed peak methadone concentrations. However, the duration of each movement and the resultant total amount of fetal motor activity were both reduced significantly by approximately half at times of assumed peak maternal plasma methadone concentrations. In addition, the degree of coupling between fetal movements and fetal heart rate was significantly lower at assumed peak maternal plasma methadone concentrations. The overall reduction of fetal activity, including body movements, breathing and heart rate, may be indicative of delayed maturation of the CNS.

1.5.4.1.2. Anaesthetic challenges

Several studies have observed increases in the percentage of opioid dependent women who require analgesia and anaesthesia during labour and delivery, and also increases in the amount of analgesia and anaesthesia administered. Silver and colleagues (1987) observed a 40% increase in use of epidural analgesia in opioid dependent women. This coincided with almost double the number of forceps deliveries in this group of women. In addition, the quantity of both analgesia and anaesthesia administered in opioid dependent women was in excess of quantities administered to the non-opioid dependent population.

In a retrospective study performed at the WCH (Cassidy & Cyna, 2004), 7,449 deliveries were assessed over a 24 month period of which 85 women were taking regular opioids such as methadone and/or heroin. Of these women, 47% received epidural analgesia in labour compared with the overall hospital rate of 38%. Twenty three and a half percent had

documented problems related to analgesia during labour and 74% of those who had a Caesarean section reported problems related to analgesia following the procedure. Most commonly reported problems were incomplete or inadequate analgesia. This increase in the percentage of women who require analgesia and anaesthesia and the reported increase in the amount of analgesia and anaesthesia administered during delivery, may be a reflection of the recent discovery that chronic opioid use results in hyperalgesia or diminished tolerance to pain (Doverty et al., 2001).

1.5.4.1.3. Birth weight

The birth weights of infants born to mothers maintained on methadone during pregnancy, while significantly higher than those of infants born to mothers using heroin, are usually significantly lower than those of controls, with up to one third of methadone exposed infants being premature by weight (Blinick et al., 1973; Kaltenbach & Finnegan, 1987). In an early study Kandall and colleagues (1976) observed methadone exposed infant birth weights to be approximately 2961 g, heroin exposed infants approximately 2490 g and control infants to weigh approximately 3176 g. More recently, Wouldes and colleagues (2004) also observed significantly lower birth weights in methadone exposed infants than control infants (3033±464 g and 3657±410 g, respectively). The issue of low birth weight is important, as decreased infant birth weight has been associated with increased infant morbidity and cognitive deficits later in the child's life (Connaughton et al., 1977; Hack, 2006; Peterson et al., 2006).

1.5.4.1.4. Apgar scores

Methadone exposure has also been shown to be responsible for decreased Apgar scores at birth. Apgar stands for Activity Pulse Grimace Appearance and Respiration and is administered 1 and 5 mins after birth to assess infant appearance. The score ranges from 0-10

with a score between 7-10 considered normal. A score of 4-7 indicates that the infant may require some resuscitative measures, with a score of 3 or below indicating immediate resuscitation is required (Apgar, 1953). Some studies have observed up to 10% of methadone exposed infants to have depressed Apgar scores at birth (Blinick et al., 1973). However, others have shown median scores to be within the normal range at birth (Doberczak et al., 1993). This area therefore requires further investigation of the effect of fetal methadone exposure.

1.5.4.1.5. NAS

Most importantly, methadone fails to prevent NAS, resulting in extensive treatment and long hospital stays (Johnson et al., 2001). The severity of NAS as a result of methadone exposure is also positively correlated with gestational age, with more term infants suffering severe NAS and requiring pharmacotherapy than pre-term infants (Doberczak et al., 1991). Several reasons are thought to contribute to this, including immaturity of the CNS (Volpe, 1987) and also immature hepatic functioning of the enzymes that metabolise methadone (Lacroix et al., 1997; Shimada et al., 1994; Sonnier & Cresteil, 1998; Tateishi et al., 1997; Yang et al., 1994). The latter may result in accumulation of methadone and subsequent late presentation of withdrawal that is not detected during the hospital stay (Doberczak et al., 1991).

A preliminary study (Blinick et al., 1973) observing 61 infants exposed to methadone during pregnancy showed 32% of infants to experience mild twitching and irritability that did not require treatment. However, irritability and non-infectious diarrhoea were severe enough in 26% of infants to require the administration of phenobarbitone or tincture of opium to control withdrawal. NAS symptoms were absent in the remaining 42% of infants. The average length of infant hospital stay was 15 days with a range between 7 and 30 days.

A much later study (Doberczak et al., 1993) observed 21 infants of which 19 of their mothers were enrolled in registered MMT programs and the remaining 2 were using street methadone during pregnancy. Seventeen of the 21 infants showed moderate to severe signs of withdrawal and required pharmacotherapy. Twelve infants received paregoric alone, 1 phenobarbital alone and the remaining 4 required both paregoric and phenobarbital. The remaining infants did not require treatment. The median maximum withdrawal score was 7 (range 4-11) according to the Lipsitz scale (Lipsitz, 1975; Lipsitz & Blatman, 1974) (a less commonly used method of identifying NAS than the Finnegan scale with a maximum score of 20) and was reached on day 3-4.

In a large scale study (Grimmer et al., 1999) 132 infants whose mothers had been taking heroin prior to pregnancy were observed. At the time of delivery 105 of the infants' mothers were enrolled in MMT programs. Although results did not distinguish between infants exposed to either methadone or heroin alone, using the Finnegan scale, NAS was observed in 114 out of the 132 infants. Of these, 94 infants received pharmacological treatment in the form of phenobarbital for the duration of severe abstinence symptoms which ranged between 2-36 days (median=10 days). The median peak Finnegan score was 15, ranging between 8 and 24.

The incidence of NAS in infants exposed to methadone during pregnancy is even higher compared to infants exposed to heroin (63-85% and 42-68%, respectively) (Bell & Lau, 1995). Similarly, the severity (as can be measured by the amount and duration of medication administered to control withdrawal symptoms) of NAS is higher in methadone compared to heroin exposed infants (Kandall et al., 1977). Kandall and colleagues (1977) observed that infants exposed to heroin during pregnancy required 10 days of treatment for NAS compared with infants exposed to methadone who required 29 days of treatment for NAS. An increase in

neonatal seizures (one of the most severe signs of NAS) in infants exposed to methadone (10%) during pregnancy compared to those exposed to heroin (1.5%) (Kandall et al., 1977) has also been observed.

The increased incidence and severity of NAS in infants exposed to methadone compared to heroin is thought to be due to the fact that heroin has a shorter half-life than methadone and is not stored by the fetus to any appreciable degree. If the mother has been taking heroin alone, the infant will present with signs of withdrawal within the first 4-24 hrs of life (Bell & Lau, 1995; Finnegan & Kandall, 1997). Methadone, however, has a longer half-life than heroin and accumulates in fetal tissue (mainly in the lung, liver and spleen) (Finnegan & Kandall, 1997). The rate of methadone tissue clearance and excretion postnatally is also highly variable, making the time of onset and severity of NAS in methadone exposed infants highly unpredictable (Kandall, 1999). If the mother has been taking methadone alone, the infant may not display withdrawal symptoms until 24-72 hrs after birth. Some infants do not present withdrawal symptoms until the end of the first week or even the second week of life (Finnegan & Kandall, 1997). The duration of the withdrawal syndrome in methadone dependent neonates ranges from 6 days to 8 weeks, however some withdrawal symptoms and general irritability may last for up to 4 months (Finnegan & Kandall, 1997).

The most detrimental infant outcomes occur when the infant has been exposed to a combination of methadone and heroin (often as a result of inadequate methadone dose to attenuate withdrawal symptoms and an attempt to self-medicate with heroin) (Fajemirokun-Odudeyi et al., 2006). In a recent study by Fajemirokun-Odudeyi and colleagues (2006), 1 min Apgar scores were significantly lower in infants exposed to both heroin and methadone compared to heroin alone. The number of infants requiring morphine treatment and the maximum morphine dose used was also significantly greater in infants exposed to both heroin

and methadone compared to methadone alone (heroin/methadone 40%, methadone 19%; heroin/methadone 584.3 $\mu g.day^{-1}$, methadone 502 $\mu g.day^{-1}$, respectively). The duration of hospital stay was also significantly longer in infants exposed to both heroin and methadone (17.2 days) compared to methadone alone (11.8 days). This again highlights the importance of ensuring that mothers are maintained on adequate maintenance therapy doses throughout their pregnancy.

1.5.4.1.5.1. Maternal methadone dose and severity of NAS

There are inconsistent data in the literature with regard to the relationship between maternal methadone dose at delivery and the severity of NAS. A relationship has been difficult to establish as some studies have reported correlations between maternal dose and severity of NAS whereas others have not (Kaltenbach et al., 1998).

Doberczak and colleagues (Doberczak et al., 1993; Doberczak et al., 1991) observed a positive correlation between maternal methadone dosage and the severity of NAS across a wide range of gestational ages. Higher maternal methadone concentrations were associated with an increase in severity of CNS signs of withdrawal.

Malpas and colleagues (1995) did not observe a significant correlation between maternal methadone dose at delivery and NAS score. However, a significant dose-response relationship was observed between maternal methadone dose at delivery and outcome measures such as mean duration of hospital stay (also used as an indicator of the severity of NAS), the proportion of infants receiving treatment for symptoms of NAS and the duration of treatment. All of these outcome measures markedly increased with increasing maternal methadone dose. However mean maternal methadone doses were relatively low in this population at 15.4 $mg.day^{-1}$.

Ostrea and colleagues (1976) observed that, when compared to infants of drug addicted mothers who were not on a methadone program, a significantly higher incidence of moderate to severe NAS was noted among the infants whose mothers participated in a methadone program, but only if the mothers were on a methadone dose of greater than 20 $mg.day^{-1}$. The same effect was not observed if the mothers were on less than 20 $mg.day^{-1}$. Moderate to severe NAS was also experienced by significantly more infants whose mothers were maintained on 20 $mg.day^{-1}$ or more of methadone compared to those whose mothers were on less than 20 $mg.day^{-1}$ of methadone.

Therefore, early research led to the recommendation that mothers participating in MMT during pregnancy should decrease their methadone dose to 20 $mg.day^{-1}$ of methadone before delivery (Ostrea et al., 1976), with the understanding that the neonate is more likely to show significant withdrawal signs if the maternal methadone dose is greater than 30 $mg.day^{-1}$. This target dose however, is often difficult to achieve and maintain, especially in the third trimester, due to previously discussed changes in methadone pharmacokinetics, which often result in the occurrence of significant withdrawal symptoms in the mother (Pond et al., 1985). As maternal opioid withdrawal during pregnancy is associated with fetal distress (Zuspan et al., 1975), in many cases maternal methadone dose has to be increased above the 20 mg target dose and/or given as a split dosing regimen in order to prevent significant withdrawal and to maximise patient compliance (DePetrillo & Rice, 1995; Jarvis et al., 1999; Pond et al., 1985; Swift et al., 1989; Wittmann & Segal, 1991).

However, more recent research has not observed a correlation between maternal methadone dose and severity of NAS. Berghella and colleagues (2003) compared infants exposed to maternal methadone doses of 80 mg or greater to infants exposed to maternal methadone doses of less than 80 $mg.day^{-1}$. There were no significant differences between the two groups

for the presence of NAS (≥80 mg 62%; <80 mg 74%), highest score received using the Finnegan scale (≥80 mg 11.2; <80 mg 11.5) or mean duration of treatment (≥80 mg 12.9 days; <80 mg 14.2 days).

In a study assessing 81 infants McCarthy and colleagues (McCarthy et al., 2005) compared infants exposed to maternal methadone doses of 100 mg or greater to infants exposed to maternal methadone doses of less than 100 $mg.day^{-1}$. No significant differences were observed between the two groups for incidence of treated NAS (≥100 mg 51%; <100 mg 49%). There was also no significant correlation observed between maternal methadone dose and number of days of infant hospitalisation.

Kuschel and colleagues (2004) also did not observe a correlation between maternal methadone dose and the requirement for infant NAS treatment. Mean maternal methadone doses of mothers of treated infants were not significantly different to those of maternal methadone doses of untreated infants (treated 47.5 mg; untreated 65 mg).

This area therefore remains controversial and is based around attempts to avoid or reduce the incidence of NAS, at the same time as achieving an effective therapeutic methadone dose (Berghella et al., 2003).

1.5.4.2. Summary

Selection of optimal methadone dosage during pregnancy is a complex problem. The favourable outcome of maintaining maternal functioning and alleviating withdrawal throughout pregnancy must be weighed against the controversial risk associated with increased severity of NAS (Hagopian et al., 1996). It has been proposed that "methadone is

good for the pregnant mother and fetus but bad for the newborn baby" (Blinick et al., 1976). Therefore, there is a need for an alternative pharmacotherapy that improves or maintains maternal functioning during pregnancy, while decreasing the incidence and severity of NAS. One medication with this potential is buprenorphine due to the mild withdrawal symptoms observed upon termination of its use in opioid abusers (Johnson et al., 2001).

1.5.5. Buprenorphine during pregnancy

There is an increasing amount of research being performed observing the effects of buprenorphine both during and after pregnancy and the effects that it may have on the mother, fetus and neonate. Following is an overview of some of the more notable studies that have been performed in this area.

In a single case study, Marquet and colleagues (1997) observed an infant born to a mother maintained on 4 $mg.day^{-1}$ of buprenorphine. While receiving buprenorphine the mother rapidly withdrew from heroin, which was confirmed by toxicological investigations that showed she was negative for opioids other than buprenorphine. A weak withdrawal syndrome in the infant occurred approximately 48 hrs after birth with symptoms such as agitation, poor sleeping and yawning recorded. An adapted peak Finnegan score (range 0 to 40) of 12 was reported and despite this no sedative treatment was found necessary. Apgar scores of 10 were recorded at both 1 and 10 mins after birth.

In a more detailed preliminary study, Johnson and colleagues (2001) studied 3 opioid dependent women, one of whom was maintained on 12 $mg.day^{-1}$ of buprenorphine, while the remaining 2 were maintained on 8 $mg.day^{-1}$ of buprenorphine. All 3 women reported positively on the medication and minimal levels of heroin craving, indicating that buprenorphine is effective for maintaining the mother during pregnancy. All infants showed

signs associated with an opioid withdrawal syndrome according to a modified Finnegan scale. Onset of symptoms occurred in the first 12 hrs after birth with the 3 main symptoms being disturbed tremors, hyperactive Moro reflex and less than 2 hrs sleep after feeding. Symptoms peaked by 72 hrs and returned to the onset levels by 120 hrs. Maximum Finnegan scores reported for the three infants were 10, 6 and 13. Pharmacological intervention was to be instituted when a Finnegan score of 11 or higher was obtained on 3 consecutive occasions or if an average score of 11 or higher was obtained over three consecutive occasions. As a result, none of the infants required pharmacological intervention for withdrawal. Of the 3 infants, 2 were delivered in hospital and both presented with normal Apgar scores. In addition, 2 infants were discharged from hospital on the fourth day post delivery, which was the minimum length of stay specified by the hospital involved.

In a retrospective study, Kayemba-Kays and colleagues (2003) observed 13 infants exposed to buprenorphine during pregnancy. Infants were born at an average gestational age of 39 weeks and had a mean birth weight of 3000 g, although 4 infants were found to be small for gestational age. Out of 9 infants tested, urinalysis was positive for additional opioids in 4 infants. NAS occurred in 11 newborns (85%) and pharmacological treatment was required in 10 of these infants. It should be noted that of the 3 infants that did not require treatment, 1 mother ceased buprenorphine treatment 5 days before delivery and the other 2 were on low doses of 0.4 $mg.day^{-1}$ buprenorphine for a week prior to delivery. Maternal doses ranged from 0.4 up to 8 $mg.day^{-1}$ at delivery. Infants were treated with a variety of medications due to changes in hospital policy over the data collection period and these included paregoric alone, paregoric in combination with diazepam and oral morphine chlorhydrate. The time interval for development of NAS ranged from day 1-5 with highest Finnegan scores ranging from 4-13. Treatment duration ranged from 14-40 days and length of hospital stay from 6-48 days.

In a prospective study Lacroix and colleagues (2004) assessed 34 women maintained on buprenorphine during pregnancy. In the early stages of pregnancy mothers were maintained on 6.6 ± 4.9 $mg.day^{-1}$ buprenorphine (0.4-32 $mg.day^{-1}$) and towards the end of pregnancy were maintained on 3.9 ± 4.6 $mg.day^{-1}$ buprenorphine (0.1-32 $mg.day^{-1}$). Two women tested positive for additional opioids. Ten women experienced obstetric complications during pregnancy. Of the 34 pregnancies, 31 ended as live births, one still birth, one spontaneous abortion and one voluntary termination. Average gestational age at birth was 38.4 ± 2.5 weeks with a mean birth weight of 2796 ± 558 g and body length of 47.4 ± 2.1 cm. NAS was observed in 13 cases (41.9%) and 8 infants required pharmacological treatment. Maximum Finnegan scores were 11.0 ± 3.6 and NAS occurred between day 1 and 8. Maternal buprenorphine doses for infants suffering from NAS and infants not suffering from NAS were 2.9 ± 2.5 and 4.6 ± 6.8 $mg.day^{-1}$, respectively, suggesting that there is no significant correlation between buprenorphine dose and severity of NAS.

Jones and colleagues (2005) published the first results from an ongoing double-blind randomised study comparing 11 methadone exposed infants and 9 buprenorphine exposed infants following delivery. In terms of maternal outcome, average maternal methadone dose was 79.1 $mg.day^{-1}$ and 18.7 $mg.day^{-1}$ buprenorphine. Low rates of illicit drug use prior to delivery were observed during the study in both groups. Percentages of urine samples that were positive for opioids (15.6, 16.7), benzodiazepines (0.4, 2.5), and marijuana (7.5, 0), for methadone and buprenorphine, respectively, were not significantly different. Eight of 11 methadone and 7 of 9 buprenorphine maintained women were negative from all illicit drugs for 4 weeks or more prior to delivery. All but one birth in each group were vaginal with normal presentations and use of anaesthesia and maternal length of stay were also similar in each group.

For infant parameters, there was no significant differences between methadone and buprenorphine exposed infants for gestational age at delivery (methadone 38.8 ± 0.56 weeks; buprenorphine 38.8 ± 0.76 weeks), birth weight (methadone 3002 ± 121 g; buprenorphine 3530 ± 163 g), body length (methadone 49.6 ± 0.76 cm; buprenorphine 52.8 ± 1.05 cm), head circumference (methadone 33.2 ± 0.48 cm; buprenorphine 34.9 ± 6.4 cm) or Apgar scores at 1 (methadone 8.3 ± 0.24; buprenorphine 8.1 ± 0.18) or 5 mins post-delivery (methadone 8.9 ± 0.09; buprenorphine 8.7 ± 0.15). When observing NAS, there was no significant difference between the two groups for the percentage of infants requiring treatment for NAS (methadone 20%; buprenorphine 45.5%) or total morphine drops administered to control NAS (methadone 93.1 ± 23.5 drops; buprenorphine 23.6 ± 19.3 drops). However, buprenorphine exposed infants remained in hospital for a statistically significant shorter period of time than methadone exposed infants (methadone 8.1±0.78 days; buprenorphine 6.8±0.86 days). Finally, daily peak NAS total scores over all observations days were not significantly different between the two groups. This most recent study by Jones and colleagues (2005) shows that buprenorphine is at least as safe and effective as methadone to be used in the treatment of illicit opioid use during pregnancy. Observed trends show that buprenorphine may even result in a decrease in the severity of NAS as can be indicated by fewer infants requiring treatment for NAS and less morphine administered to control NAS.

Fischer and colleagues have undertaken three studies observing the effect of buprenorphine administration during pregnancy (Fischer et al., 1998; Fischer et al., 2000; Fischer et al., 2006). The first study (Fischer et al., 1998) observed 9 pregnant women who were transferred from slow-release oral morphine (n=3) or methadone (n=6) during an average of the 28th week of pregnancy to buprenorphine. Induction was relatively trouble-free, with only 2 women experiencing transient dysphoric mood status. Ultrasounds performed on the fetus during this

induction period did not show any alterations. Subjects were maintained on buprenorphine doses ranging from 1-10 mg.day^{-1}and did not report withdrawal symptoms during the course of the pregnancy. No illicit opioid use was discovered when assessing urinalysis. Six women experienced natural births with no additional analgesics required. The remaining 3 infants were delivered by Caesarean section. All 9 infants had normal birth weights (2290-3700 g) and Apgar scores were 9 at 1 min, and 10 at 5 and 10 mins post-delivery. Most importantly, neonates showed no indication of NAS.

In the second larger study Fischer and colleagues (2000) examined 15 opioid dependent women who were maintained on doses of buprenorphine ranging from 1-10 mg.day^{-1} with a mean dose at delivery of 7.4 ± 3.3 mg.day^{-1}. A total of 259 urine samples were collected from the 15 women, of which 24 were positive for opioids. Ten women delivered vaginally and 5 women required Caesarean deliveries. Infants were delivered at an average gestational age of 39.6 weeks with a mean birth weight of 3049 g. Of the infants born to these women, withdrawal symptoms (according to the Finnegan scale) were absent in 8 infants, mild (not requiring treatment) in 4 infants and moderate (requiring treatment with oral morphine) in 3 infants with the main symptoms being tremor and hyperreflexia. The mean duration of NAS was approximately 2 days. There was no correlation between maternal buprenorphine dose at delivery and severity of NAS.

The third and most recent study published by Fischer and colleagues (Fischer et al., 2006) reported results from another ongoing double-blind, double-dummy study comparing 9 women randomised to methadone and 9 to buprenorphine following transfer from slow release oral morphine. Over the course of the study there were 3 non-completions in the methadone group: one still birth due to sudden intrauterine death, one voluntary termination

and one withdrawal for study non-compliance. One woman in the buprenorphine group was also withdrawn for study non-compliance.

Mean maternal daily methadone and buprenorphine doses at the end of the titration period were 47.5 and 13.5 $mg.day^{-1}$ respectively and had risen to 52.5 $mg.day^{-1}$ methadone and 14 $mg.day^{-1}$ buprenorphine during the last trimester. There was no significant difference in maternal withdrawal scores throughout the course of pregnancy between the two groups. Urine toxicology data indicated that additional opioid use was greater in the buprenorphine compared to the methadone group, but this may have been a reflection of the greater number of urine samples supplied by the buprenorphine group. There was no significant difference in additional benzodiazepine use between the two groups. Eleven women had a vaginal delivery with 1 woman in the methadone group requiring a ventouse delivery and there were 2 planned Caesarean deliveries in the buprenorphine group. Three infants in the methadone group were delivered prematurely and 2 in the buprenorphine group. There was no significant difference between the two groups for mean birth weight or Apgar scores. Fifty percent of infants in the methadone group required treatment to control NAS and 62% in the buprenorphine group. Time to treatment initiation from the last maternal medication administration before delivery did not significantly differ between the two groups (methadone: 60 ± 11 hrs, buprenorphine: 72 ± 35 hrs). The duration of treatment or the cumulative dose of morphine administered to control NAS were also not significantly different between the two groups (methadone: 5.3 ± 1.5 days, buprenorphine: 4.8 ± 2.9 days; methadone: 2.71 ± 1.68 mg, buprenorphine: 2.00 ± 2.00 mg). There was no correlation between maternal maintenance therapy dose and severity of NAS. Fifty percent of infants in each group were breast-fed and this did also not appear to affect the severity of NAS.

1.5.5.1. Summary

From these studies we can observe that buprenorphine appears to at least as beneficial as methadone when used as a maintenance pharmacotherapy during pregnancy in terms of preventing maternal withdrawal and continued illicit substance use. Most importantly from this research it is apparent that buprenorphine has the potential to minimise NAS in exposed infants, with trends observed in some studies towards fewer infants requiring pharmacological treatment to control NAS, and those infants that are treated requiring less treatment than methadone exposed infants.

1.5.6. Placental transfer of substances

Substances administered to the mother during pregnancy may have direct or indirect effects on the fetus. Indirect effects on the fetus are usually the result of adverse effects of the drug on placental functions responsible for normal fetal growth and development. However, direct effects of the drug are related to its concentration in the fetal circulation, which depends largely on the transfer and metabolism of the drug by placental tissue (Nanovskaya et al., 2002).

There is no direct exchange of blood between the mother and the fetus. Within the placenta all that exists between maternal blood and the fetal blood vessel is a thin layer of trophoblast cells. This area between the maternal and fetal circulations forms the exchange surface between the two compartments. The placenta undergoes considerable changes throughout pregnancy. The combination of increasing placental surface area and placental thinning keeps up with the growth of the fetus and its increasing nutritional and energy demands (Garland, 1998). During pregnancy, the placenta also functions as an additional extra-hepatic site for biotransformation of drugs and, therefore, the metabolic activity of the placenta could

contribute to any changes observed in pharmacokinetic parameters of drugs administered during pregnancy.

There are no direct methods of measuring fetal drug exposure in the clinical setting (Garland, 1998). Animal experiments offer a limited alternative due to the complexity and diversity of the human placenta compared to that of any other species (Nanovskaya et al., 2002). Samples obtained at birth should also be used with caution, as this cannot truly be considered to be steady-state due to the unstable nature of the birthing process (Garland, 1998). Despite this, umbilical cord blood drug concentration is often taken as a measure of placental transfer of drugs and the *in vitro* model of dual perfusion of the human placenta has been shown to be a valuable experimental tool in providing data on the transfer and pharmacokinetics of several drugs, but does not take into consideration the role of fetal drug clearance (Garland, 1998; Nanovskaya et al., 2002).

As maternal plasma concentration usually correlates with the dose administered, determination of fetal exposure can be based on maternal drug intake. In order to determine the relationship it is also necessary to know the molecular weight and size, solubility, ionisation and degree of protein binding of the drug, which will help to determine how readily the drug will cross membranes and therefore the placenta (Garland, 1998; Szeto et al., 1982).

It has been suggested that the high incidence and severity of NAS observed due to MMT may be the result of the increasing transfer of methadone across the placenta as pregnancy progresses (Kandall et al., 1999). Similarly, the low incidence and severity of NAS observed in infants whose mothers are maintained on buprenorphine during pregnancy may be due to a decreased transfer of buprenorphine across the placenta.

1.5.6.1. Methadone

The transfer of methadone across the placenta occurs in both animals and humans as the presence of methadone in amniotic fluid, umbilical cord plasma and fetal urine has been observed in a number of studies.

Early animal work by Szeto and colleagues (1982) observed the disposition of morphine and methadone in the maternal-fetal circuit in pregnant ewes. It was observed that at steady-state, mean maternal: fetal concentrations of free methadone were 2.9 ± 0.6 compared with morphine that had a maternal: fetal ratio of 7.6 ± 0.6. This implies that the extent of fetal exposure to maternally administered morphine was less that that of methadone and may give some indication as to the transfer of buprenorphine across the placenta.

In 18 women with an average gestational age at delivery of 38.81 weeks and daily methadone doses ranging from 30-100 $mg.day^{-1}$ Blinick and colleagues (1974) observed amniotic fluid concentrations of methadone ranging from 0.1-0.45 $\mu g.ml^{-1}$. In 2 patients pregnancy was terminated at 14 and 18 weeks, which permitted the collection of amniotic fluid in the second trimester. Ten maternal plasma samples produced methadone concentrations between 0.14-0.48 $\mu g.ml^{-1}$ giving an average ratio of methadone in amniotic fluid to maternal plasma of 0.73.

Following on from this study Blinick and colleagues (1975) observed that in 12 women maintained on daily methadone doses between 40 and 100 $mg.day^{-1}$, maternal plasma concentrations varied between 5 and 38 $ng.ml^{-1}$ and the infants born to these women had umbilical cord plasma methadone concentrations of 3-14 $ng.ml^{-1}$. The average ratio of methadone in cord plasma to that in maternal plasma was 0.57. It was also observed that over

a wide range of urinary methadone concentrations, the concentration of methadone in the newborn urine was found to be much lower than the corresponding maternal urine value. The first day after birth methadone concentration in newborn urine was 37% of maternal urine methadone concentration and by the third day had decreased to 16% of maternal concentration.

At approximately 16 hrs after delivery Doberczak and colleagues (1993) observed maternal plasma methadone concentrations to be 183 ± 118 $ng.ml^{-1}$. At the same time, corresponding infant plasma concentrations were 26 ± 8 $ng.ml^{-1}$. This initial mean infant plasma concentration fell to 13 ± 5 $ng.ml^{-1}$ by approximately 73 hrs of life, therefore indicating that the rate of decrease in neonatal plasma methadone concentration falls following birth at a rate of 0.2 ± 0.3 $ng.ml.h^{-1}$. Maternal plasma methadone concentrations were also found to correlate with infant plasma methadone concentrations at day one of delivery, with neonatal level consistently lower than maternal levels. A positive correlation was also observed between the severity of CNS signs of neonatal withdrawal and the rate of decline in neonatal plasma methadone levels.

Mack and colleagues (1991) observed 9 methadone maintained women whose doses at delivery ranged between 25-60 $mg.day^{-1}$. Blood samples were taken from these mothers infants at 1, 6 and 24 hrs after delivery. In some infants, serum concentrations of methadone increased at 6 and 24 hrs after delivery compared with the sample taken at 1 hr after delivery. A possible explanation for this is the slow release of methadone from extravascular binding sites where it has gradually accumulated during gestation. The abrupt cessation of methadone at delivery is believed to prompt the release of methadone from fetal tissues to maintain plasma levels. The first urine passed by the infants had methadone concentrations ranging

from 4-20-fold higher than those in cord blood, and elimination half-lives were found to be 9 hrs in 1 infant, and greater than 24 hrs in 2 infants. In infants studied at 24, 48, 72 and 96 hrs after birth methadone urine concentrations were 6-87-fold higher than in cord blood. Estimations of half-lives revealed an average of 41 ± 22 hrs, indicating that the metabolism of methadone in neonates appears to be very slow. This may be because the fetal liver has less biotransformation capacity than the adult liver (Lacroix et al., 1997; Pelkonen et al., 1973; Shimada et al., 1994; Sonnier & Cresteil, 1998; Tateishi et al., 1997; Yang et al., 1994).

These above mentioned studies assessing placental transfer of methadone not only show that methadone is readily transferred across the placenta from the mother to the fetus towards delivery, but also demonstrate that methadone is transferred across the placenta at all stages of pregnancy. This may be one of the major reasons for the high incidence of NAS observed in infants whose mothers are maintained on methadone during pregnancy.

To further investigate this, in a series of studies using full term human placentas from uncomplicated pregnancies, Nanovskaya and colleagues (2005; 2004) and Nekhayeva and colleagues (2005) studied the effects of the placenta on methadone metabolism. The first study (Nanovskaya et al., 2004) was concerned with the metabolism of methadone by the placenta. In contrast to CYP3A4 being the major metabolic enzyme responsible for hepatic N-demethylation of methadone, it was observed that CYP19 (aromatase) is the major enzyme responsible for placental metabolism of methadone. The rate of methadone N-demethylation by the placenta was dependent on methadone concentration and exhibited typical Michaelis-Menten saturation kinetics. The intrinsic clearance of methadone by the placenta was 8.5×10^{-4} ± 2.6 ml.mg protein^{-1}.min^{-1} and this suggests that placental metabolism of methadone is significantly less than its hepatic metabolism. The involvement of CYP19 was recently confirmed in a study by the same group (Hieronymus et al., 2006) that also showed that the

affinity of methadone to CYP19 did not change with gestation but the activity of the enzyme increased and varied widely between individual placentas. It was suggested that this individual variability among placentas may be one of the factors affecting the incidence and intensity of NAS.

In the second *ex vivo* study, Nekhayeva and colleagues (2005) observed the bidirectional transfer of methadone across the human placenta in an experimental model using dual perfusion of the placental lobule obtained from full term uncomplicated pregnancies. The transfer of methadone in the maternal to fetal direction was biphasic and was initially fast with methadone appearing in the fetal circulation within 5 mins of introduction in the maternal reservoir, and then transfer was gradual. In contrast, when introduced to the fetal reservoir methadone transfer in the fetal to maternal direction was slow and gradual and not biphasic. When transferring from the maternal to fetal circuit the amount of methadone appearing in the fetal circulation was only a fraction of that lost from the maternal circulation, suggesting that methadone was retained by the placental tissue. This also occurred to some extent in the fetal to maternal direction, however higher amounts were retained by the tissue from the maternal to fetal direction. It was also observed that the transfer of methadone in the maternal to fetal direction is lower than that in the fetal to maternal direction, suggesting the involvement of the drug efflux transporter P-glycoprotein (P-gp).

As a result, the third study observed the expression and the activity of P-gp and its effects on the efflux of methadone from term placental trophoblast tissue with the suggestion that the placenta may act as a functional barrier protecting the fetus from the effects of potentially harmful xenobiotics (Nanovskaya et al., 2005). It was demonstrated in the study that P-gp does regulate the transfer of methadone across the placenta and returns it to the maternal circulation. This, in combination with the metabolism of methadone by the placenta is likely

to result in lower fetal than maternal concentrations of the drug observed in other studies. Therefore, the transfer of methadone across the placenta requires further investigation at both the *in vitro* and clinical level.

1.5.6.2. Buprenorphine

As previously mentioned, the physicochemical properties of a drug help to determine the extent of its placental transfer. Considering the octanol/water partition coefficient of morphine is significantly lower than that of methadone (6.23 compared to 116.33 (Kaufman et al., 1975)) this means that methadone is more lipid soluble and will therefore cross lipid membranes, including the placenta, more readily than morphine as observed in the early animal work by (Szeto et al., 1982). These findings provide the basis for speculations in regard to the disposition of buprenorphine in the maternal-fetal unit in that buprenorphine is more likely to cross the placenta than methadone considering its higher octanol/water partition coefficient (1943).

Nanovskaya and colleagues (2002) also studied the placental transfer of buprenorphine *in vitro,* in a series of experiments similar to those previously described for methadone, using dual perfusion of the isolated placental cotyledon. Buprenorphine was added to the maternal reservoir to achieve a concentration of 10 $ng.ml^{-1}$ (an average peak plasma buprenorphine concentration in patients maintained on buprenorphine) and the system was perfused for a period of 4 hrs. These results showed a rapid decline in buprenorphine concentration in the maternal circuit during the first 1 hr period followed by a slow decline over the next 3 hrs. There was a simultaneous uptake and retention of buprenorphine by the placental tissue (45% of the initial concentration in the maternal blood) in the first hour. Only 3% of the drug was transported to the fetal circulation during this period. After 4 hrs of perfusion the amount of buprenorphine retained by tissue was ~60% with ~30% remaining in the maternal circulation.

Less than 10% of buprenorphine appeared in the fetal circulation reaching a plateau concentration of 0.88 ± 0.14 $ng.ml^{-1}$. Specific binding experiments demonstrated that buprenorphine showed high binding affinity at placental κ-opioid receptors. "Wash-out" experiments showed that buprenorphine was slowly released from the placental tissue by passive diffusion into the maternal and fetal circulation with ~40% of buprenorphine retained by the tissue released over a 2 hr period. Buprenorphine concentration in the fetal circuit was below 1 $ng.ml^{-1}$ at all times. Buprenorphine had no adverse effects on the vascular integrity and morphology of the perfused lobule, its metabolic activity, oxygen transport or endocrine function.

Extrapolation of the results of this study to an *in vivo* situation suggests that buprenorphine administered to the mother is readily sequestered by the placental tissue with as little as 10% of the drug reaching the fetal circulation at peak maternal plasma concentrations. The accumulated drug is then slowly released into both maternal and fetal circulations over the interdosing interval with relatively low levels of the drug maintained in the fetal circulation at any time period. It is unknown, however, whether there is a gradual accumulation of the drug in the fetal circulation with repeated dosing, and whether there is indeed an overall decreased exposure of the fetus to buprenorphine during pregnancy. As yet there have been no studies investigating the involvement of P-gp in the transfer of buprenorphine across the placenta that may account for the decreased concentrations of buprenorphine observed in fetal circulation despite it high lipophilicity.

The only study to measure buprenorphine concentration in umbilical cord blood was that of Johnson and colleagues (2001). They reported a range of cord plasma concentrations from 3 infants of 101-137 $ng.l^{-1}$ compared with maternal post-delivery plasma samples ranging from 115-798 $ng.l^{-1}$. A blood sample from one infant taken 1 hr after delivery revealed a plasma

concentration of buprenorphine of 97 $ng.l^{-1}$. At approximately 3 hrs after birth it was observed in one infant that buprenorphine concentrations were 8-10-fold higher (1132 $ng.ml^{-1}$) in urine than in cord plasma.

Similar to methadone, buprenorphine is also subject to metabolism by the placenta and in a comparable fashion, buprenorphine displays saturation kinetics in the placenta. Intrinsic clearance of buprenorphine by the placenta (0.27 $\mu l.mgprotein^{-1}.min^{-1}$) is again lower than that showed by the liver (17 $\mu l.mgprotein^{-1}.min^{-1}$ (Kobayashi et al., 1998)). The major enzyme responsible for placental metabolism of buprenorphine is not CYP3A4, as is the case with its hepatic metabolism, but CYP19 (aromatase) similar to the placental metabolism of methadone (Deshmukh et al., 2003).

1.5.7. Breast milk transfer

Breast-feeding is an intimate interaction between the mother and her infant and has been shown to enhance bonding (Lawrence, 1989). Breast-feeding is therefore beneficial for both the mother and the infant for this and a number of other reasons. Breast-feeding may serve to boost a mother's self-esteem, as she is able to provide personal and optimal nourishment for her infant that it is also inexpensive (Howard & Lawrence, 1998). Breast milk provides benefits by means of reducing the infant's exposure to contaminated food sources, enhancing the nutritional status of at-risk infants and preventing many common infectious diseases due to a number of anti-inflammatory, immunologic-stimulating and anti-microbial factors, and preventing the development of food allergies (Howard & Lawrence, 1998).

However, concerns about the safety of breast-feeding arise when a woman who wishes to breast-feed her infant has a problem or history of illicit substance use (Howard & Lawrence,

1998) as many drugs are readily transferred in to the breast milk. Opportunities for substance using mothers to bond with their infants are of high importance, as these infants are known to be at increased risk for child abuse, maltreatment and neglect (Casado-Flores et al., 1993; Casado-Flores et al., 1990; Murphy et al., 1991). Therefore, the benefits of breast-feeding have to be weighed up against the possibility of transfer of the opioid maintenance drug into the breast milk and to the infant.

For most drugs the aim is to prevent the infant from receiving as much drug through breast milk as possible (Begg et al., 2001). To allow breast-feeding in substance using women a predicted cut off level of <10% infant exposure relative to maternal dosage has been recommended to prevent the risk of adverse effects (Bennett, 1988). Considering both methadone and buprenorphine are highly lipid soluble, the amount of both drugs appearing in breast milk will depend on the fat content of the milk (which varies depending on the individual and the time of day) (Ballard, 2002). Women maintained on opioids may also need additional support with breast-feeding if their infants are feeding poorly as a result of NAS (Philipp et al., 2003).

1.5.7.1. Methadone in breast milk

In an early study Blinick and colleagues (1973) observed that the milk of mothers maintained on methadone contained high concentrations of methadone in the range between 0.17 and 5.6 $\mu g.ml^{-1}$. As a result, questions were raised over the advisability of breast-feeding infants whose mothers were maintained on methadone. For this reason the transfer of methadone into breast milk has been further studied.

In 2000 McCarthy and colleagues (2000) observed that breast milk concentrations in 8 mothers who were maintained on methadone doses ranging from 25-180 $mg.day^{-1}$ were 27-

260 $ng.ml^{-1}$ with a mean of 95 $ng.ml^{-1}$, much lower than those observed by Blinick and colleagues (1973). Based on a newborn intake of 475 $ml.day^{-1}$, the mean daily methadone ingestion was estimated to be 0.05 $mg.day^{-1}$. Duration of breast-feeding ranged from 2.5 to 21 months with no adverse events associated with breast-feeding or the weaning process.

In a study examining the distribution of R(-)- and S(+)-methadone in human milk, Begg and colleagues (2001) observed 8 women maintained on daily methadone doses ranging from 40-105 mg of methadone. Maternal plasma samples and both immature (<15 days after delivery) and mature (>15 days after delivery) milk samples were collected over a 24 hr period and assayed to observe methadone concentrations. Results were presented as AUC of plasma/milk concentration versus time curve and presented as a ratio of milk to plasma AUC. For immature milk the mean milk to plasma AUC ratio for R(-)-methadone was 0.68 and for S(+)-methadone was 0.38. In 2 subjects milk to plasma AUC ratios for mature milk were 0.54 and 0.39 for R(-)-methadone and 0.30 and 0.24 for S(+)-methadone. The dose of R(-)-methadone that would be received by the infant in immature milk was estimated to be 3.5% of the maternal R(-)-methadone dose and 2.1% for S(+)-methadone. Percentages of R(-)- and S(+)-methadone received by the 2 infants in mature milk were 1.9% and 2.5% (1^{st} infant), and 1.6% and 2.2% (2^{nd} infant). In conclusion, it was found that milk to plasma ratios for high doses of methadone were similar to those of lower doses, and is therefore not dose-dependent, with ratios for R(-)-methadone higher compared to S(+)-methadone.

From the observations of Begg and colleagues (2001) it can be seen that <5% of maternal methadone dose is received by the infant, well below the recommended cut off level of <10% infant exposure. It has therefore been suggested that breast-feeding may protect against NAS by providing the infant with a potential dosing source of methadone (Begg et al., 2001). Importantly, abrupt cessation of breast-feeding in infants whose mothers are maintained on

methadone has been shown to cause NAS, particularly when mothers are maintained on higher doses of methadone (Malpas & Darlow, 1999).

For this reason, Ballard and colleagues (2002) assessed the treatment of NAS with breast milk containing methadone. Ten infants were treated with breast-feeding as the primary therapy for withdrawal from methadone. Two infants who were breast-fed with initial formula supplementation both had 6 day hospital stays and mild withdrawal symptoms with abstinence scores ranging from 4-6. No additional therapy was required. The remaining 8 infants who were exclusively breast-fed, had some difficulty with sucking, particularly once withdrawal symptoms began to present. As a result, pumping of the breast was required as the infants could not latch and suck effectively and the colostrum was fed to the infant by syringe, cup or bottle. The infant's withdrawal symptoms quickly abated once mature milk began to flow. Of the 8 infants, 1 had a 5 day hospital stay, 2 had 4 day stays, 3 had 3 day stays and 2 had 2 day stays. None of these infants required additional treatment. Gradually tapering the infant from methadone could be achieved in two ways: the mother tapers her own methadone dose or the mother may introduce formula and reduce breast-feeding. Mothers in this instance chose to taper their own methadone dose and withdrawal symptoms were not observed in the infant unless the mothers themselves were symptomatic. If this occurred the weaning process was stopped or slowed until both mother and infant were comfortable. It was therefore concluded by Ballard and colleagues (2002) that breast-feeding may be an appropriate treatment for managing symptoms of withdrawal in methadone exposed infants.

1.5.7.2. Buprenorphine in breast milk

Very little work has been performed observing the concentration of buprenorphine in breast milk or the effects of breast-feeding in exposed infants. Marquet and colleagues (1997) measured the amount of buprenorphine ingested by an infant at the age of 4 weeks at each

feeding time over a 24 hr period. The total amount ingested was 3280 ng of buprenorphine and 330 ng of norbuprenorphine. Breast-feeding was ceased abruptly due to maternal illness at the age of 8 weeks without the occurrence of withdrawal symptoms.

In a single case study Schindler and colleagues (2003) observed a mother maintained on 12 mg of buprenorphine who breast-fed and weaned her infant over 6 months with no observable complications.

Johnson and colleagues (2001) observed the concentration of buprenorphine in breast milk in one woman who decided to breast-feed. On postpartum days 3, 6 and 9 buprenorphine concentrations in breast milk were 520, 720 and 230 $ng.ml^{-1}$, respectively. On days 3 and 6 this was found to be at a one-to-one ratio with the mother's plasma buprenorphine concentrations of 520 and 642 $ng.l^{-1}$, respectively. A drop in day 9 buprenorphine levels was attributed to the cessation of breast-feeding activity after day 4. Despite the one-to-one breast milk plasma ratio observed by Johnson and colleagues (2001), due to the low oral bioavailability of buprenorphine (approximately 13%) (and immature hepatic functioning of infants previously mentioned) it was suggested that the infant would be exposed to low concentrations of the active drug. This is consistent with the absence of withdrawal symptoms on cessation of breast-feeding observed by Marquet and colleagues (1997).

Therefore due to the conflicting results observed for methadone use during breast-feeding and the small amount of research performed observing the effects of buprenorphine and breast-feeding, further research is required in this area to determine the transfer of both substances into breast milk and the effect while breast-feeding on these substances on NAS.

1.5.8. Conclusion

Data published to date concerning buprenorphine during pregnancy are limited by low subject numbers and do not directly compare the outcomes of buprenorphine maintenance with outcomes of non-drug exposed pregnancies. Furthermore, while the transfer of methadone across the placenta has been investigated, the transfer of buprenorphine across the placenta is less well understood.

1.6. Aims and hypotheses

The primary aim of the present study was to assess the efficacy and safety of buprenorphine use both during and after pregnancy compared to methadone and a non-opioid exposed population, specifically focussing on assessing the incidence and severity of NAS in infants born to both mothers maintained on buprenorphine and mothers maintained on methadone.

As a result of previous research the following main hypotheses were formulated:

1. Buprenorphine will be as efficacious as methadone in the management of illicit opioid dependence
2. The severity of NAS will present as control < buprenorphine < methadone.

Further aims and hypotheses relating to specific areas of research will be discussed in subsequent chapters.

2. RESEARCH METHODOLOGY AND STUDY PARTICIPANT CHARACTERISTICS

2.1. Introduction

The present clinical trial was conducted to compare methadone and buprenorphine maintenance therapies both during and after pregnancy with a non-opioid exposed control population. Women were recruited during the first two trimesters of pregnancy and assessed for the duration of the pregnancy and their infants studied for a 4 week postnatal follow up period. In Chapters 3 to 6 results relating to four specific areas of investigation (pregnancy outcomes, maintenance therapy outcomes, labour and delivery outcomes, and postnatal outcomes) included in the research design will be presented, as will methodological details that are specific to these respective areas of investigation. The purpose of the present chapter is to provide a brief overview of research methodology, and information regarding study participants that are common to all four subsequent chapters, with greater detail provided in the following chapters.

2.2. Study design

The current study was designed as a non-randomised, open-label, flexible dosing study with three experimental groups of subjects:

- Opioid dependent women maintained on buprenorphine during pregnancy
- Opioid dependent women maintained on methadone during pregnancy
- Non-opioid exposed control pregnant women.

All three groups were matched as an average to each other to enable approximate comparability for the following criteria that may effect pregnancy progression and outcome. Increasing maternal age has been shown to increase the chances of Downs Syndrome whereas increasing maternal parity and gravida increases the chances of other obstetric complications such as miscarriage (Crane & Morris, 2006; Llewellyn-Jones, 1999). Maternal alcohol consumption has been shown to cause fetal alcohol syndrome resulting in deleterious effects on the fetus including malformations (Merrick et al., 2006). Excessive alcohol consumption was an exclusion criterion and will be discussed in a later section. Maternal smoking of tobacco in the antenatal period not only results in infants of low birth weight, but can itself cause a mild withdrawal syndrome (Godding et al., 2004).

Therefore, groups were matched on average as follows:

- Maternal age:
    - Whether mothers were aged between 18-29 or 30-40
- Alcohol consumption:
    - Whether or not mothers drank at all during their pregnancy and if yes whether they consumed 1-3 standard drinks/week or 4-7 standard drinks/week
- Nicotine use:

  - Whether or not mothers smoked nicotine during their pregnancy and if yes whether they smoked 10 or less/day or 11 or more/day
- Parity:
  - Whether or not it was to be the mother's first born child or if she already had previous children
- Gravida:
  - Whether or not this was the mother's first pregnancy or if she had had previous pregnancies

Recruitment began and continued until approximately half of each of the required sample population was enrolled. At this time matching criteria were assessed. Recruitment then continued and matching criteria was adjusted accordingly so that each group was matched appropriately.

Mothers' newborn infants subsequently formed the following three groups:

- Neonates born to opioid dependent women maintained on buprenorphine during pregnancy
- Neonates born to opioid dependent women maintained on methadone during pregnancy
- Neonates born to non-opioid exposed control women.

2.3. Study participants

Ethical approval for the study was obtained from the Women's and Children's Hospital (WCH) Research Ethics Committee (REC 1330/6/2005). Statistical power analysis revealed that with α set at 0.01 and power at 90%, 25 subjects were needed to detect a 60% difference in the total amount of morphine (mg) required to control NAS (Fischer et al., 2000). To account for study non completions, approval was obtained to recruit a maximum of 120 participants (80 opioid maintained and 40 non-opioid exposed control women). This number was based on the average annual number of women who attended a specialist high risk pregnancy clinic at the WCH for women with substance use issues during pregnancy supervised by Drug and Alcohol Services South Australia (DASSA) staff. Subjects were recruited during the period between September 2002 and September 2004.

Subject participation in the study was on a voluntary basis. All subjects provided written informed consent prior to study commencement and were encouraged to discuss participation with family or friends prior to giving their consent. Participants were informed that all information collected as part of the trial would be confidential. Subjects were financially renumerated in AUD$50 instalments for their participation over the course of the study with a maximum amount of AUD$250, subject to completion of study requirements.

All subjects were to have a gestational age of up to 28 weeks upon enrolment into the current study. Opioid dependent subjects were recruited from outpatient clinics at DASSA metropolitan units, private medical practitioners registered as opioid maintenance therapy prescribers and women who were already attending the specialist high risk pregnancy clinic at the WCH as mentioned earlier in the current section (Section 2.3). It was apparent prior

to the commencement of the current trial that two subpopulations of subjects in each maintenance therapy group would be included. The first subpopulation would be women who reported that they became pregnant while already participating in a methadone or buprenorphine maintenance therapy program. The second subpopulation would be women who became pregnant while dependent on heroin, and as a result felt the need to begin an opioid maintenance therapy program to prepare for the birth of their child.

Control subjects (self-reported non-opioid using pregnant women) were recruited from standard midwifery care antenatal outpatient clinics at the WCH.

Women were excluded from study participation if they had concurrent medical illnesses requiring medication that could interact with their maintenance therapy or affect pregnancy outcome. This included medications used to treat HIV/AIDS, epilepsy, schizophrenia or other major psychiatric illnesses such as bipolar disorder. Women were also excluded if their current level of alcohol use was >1 standard drink/day (1std drink = 10g of alcohol) or >7 standard drinks/week (NHMRC, 2001). Women with twin pregnancies were also excluded along with any signs of congenital fetal malformations on admission. Women participating in another clinical research project that could interfere with the present study were also excluded.

Once enrolled, subjects were able to voluntarily withdraw from the study at any time for any reason without having to divulge the reason to the investigators or clinical staff without affecting their antenatal care. As buprenorphine is not yet approved for use during pregnancy in Australia, women who were maintained on buprenorphine were informed that if they chose to leave the study, for safety reasons it would be at the discretion of their maintenance therapy prescriber as to whether they would continue to be maintained on

buprenorphine, or be changed to methadone. If subjects were maintained on methadone and withdrew from the study this would not affect their maintenance therapy prescribing.

If subjects experienced unacceptable adverse effects to either buprenorphine or methadone they were withdrawn from the study. Women were also withdrawn if they developed a disease or illness that required therapy with medications that may have interacted with maintenance therapies or affect pregnancy outcome. Subjects were also informed that non-cooperation with study personnel and/or non-compliance with study protocol would also result in them being withdrawn from the study.

2.4. Research procedures and measures

The study featured four phases of data collection as follows: (1) eligibility and initial assessment including induction on to a maintenance therapy where applicable; (2) collection of maternal and fetal data throughout pregnancy (antenatal period); (3) collection of maternal, fetal and infant data during labour and delivery; and finally (4) collection of infant data (including breast-feeding) over a four week postnatal period. Measures taken during each of these stages are described below with further detail explained in the later relevant chapters.

2.4.1. Eligibility and initial assessment

In order to assess eligibility for enrolment into the study, prospective participants were screened for eligibility according to the criteria discussed above by either the researcher or medical staff from DASSA. They were informed of the requirements of the study and written consent was obtained. Once consent was obtained, women were assigned a subject identification code to maintain confidentiality. This code was indicative of which study group they belonged to with M indicating the methadone group, B indicating buprenorphine and C indicating they belonged to the control group. Following assignment of a subject code an initial interview was conducted by the researcher where a medical history, including obstetric and gynaecological history, was taken and any additional medications that did not interfere with the study were also recorded. Other standard demographic information, prior and current substance use, substance use treatment history and criminal and legal history were also collected at this time.

2.4.1.1. Opioid maintenance therapy dosing

Women enrolled in the study who were already participating in methadone or buprenorphine maintenance therapy programs continued on their current maintenance therapy throughout pregnancy and were not changed to a subsequent therapy. Pregnant heroin dependent women who requested opioid maintenance therapy, were offered a choice of methadone or buprenorphine maintenance therapy programs after being informed of the possible risks and benefits of being maintained on either therapy during pregnancy.

Pregnant heroin dependent women requesting opioid maintenance therapy programs underwent normal assessment procedures for induction onto maintenance treatment, including diagnosis of opioid dependence (using DSM-IV TR criteria for substance dependence) (American Psychiatric Association, 2000) and urinalysis. Subjects who were induced onto methadone were induced according to standard clinical guidelines (Henry-Edwards et al., 2003).

Due to current clinical practice, induction onto buprenorphine was not initiated until written consent to participate in the trial had been completed. Guidelines were introduced so that if subjects at the time of presentation were intoxicated or did not fully understand the implications of buprenorphine maintenance therapy during pregnancy, yet wished to be maintained on buprenorphine, they were to be administered an appropriate dose of methadone as per standard clinical guidelines and were asked to return in 24 hrs. These guidelines, however, did not have to be implemented and all women wishing to commence BMT were induced as discussed below. When subjects were inducted on to buprenorphine they were not to have used short acting opioids such as heroin or short acting preparations of morphine for at least 8 hours preceding their first buprenorphine dose, or 24 hrs for longer acting opioids such as methadone or sustained release preparations of morphine.

Following this abstinence period, a 2mg dose of buprenorphine was administered and subjects were monitored for signs of precipitated withdrawal. After a period of 2-3 hours with no signs of precipitated withdrawal and if deemed appropriate by medical staff, a further 2mg of buprenorphine was administered. On subsequent days buprenorphine dose adjustments were as per standard clinical guidelines (Lintzeris et al., 2001). In order to avoid any chance of withdrawal during pregnancy, women who were maintained on buprenorphine were maintained on a daily dosing regimen.

Induction (where applicable) onto either maintenance therapy along with maintenance therapy dose adjustments throughout pregnancy and thereafter was performed by medical practitioners registered to prescribe methadone and buprenorphine. There was no significant difference between the methadone and buprenorphine groups in the percentage of women who were already enrolled in a maintenance therapy program at the time of recruitment (methadone 88%, buprenorphine 80%) compared to the percentage of women who were seeking treatment at the time of recruitment (methadone 12%, buprenorphine 20%). Both maintenance therapies were administered under supervision and take-away doses were provided according to normal clinical practices. Subjects were provided with access to standard substance abuse counselling. Participants were also able to access social support through social workers at both DASSA metropolitan units and the WCH.

2.4.2. Monitoring of maternal and fetal outcomes

2.4.2.1. Pregnancy progression and obstetric measures

Following recruitment, pregnancy progression for both the mother and fetus in all three groups of women was assessed at routine antenatal appointments at the WCH antenatal outpatient clinic as determined by midwifery staff. Opioid dependent women attended the

specialist high risk pregnancy clinic and control women attended standard midwifery care antenatal clinics (Section 2.3).

Intrauterine life that reaches full term lasts for 40 weeks. The term pregnancy is separated into three trimesters. The first trimester lasts from weeks 0-12, the second from 13-28 and the third from 29-40. For normal uncomplicated pregnancies women should attend between 5-10 antenatal appointments with the first appointment to occur during the first trimester at approximately 10 weeks gestation. Appointments should then occur at approximately 15, 19-20, 24, 28, 32, 36, 38, 40 and 41 weeks if necessary. Women in successive pregnancies may attend less often (SAPPWG, 2005). Data collection included the number of standard antenatal appointments attended as well as the gestational age at which women first presented for antenatal care.

Of particular note should be the 28 week gestational age appointment. At this appointment an oral glucose challenge test (OGCT) is performed for each woman. This test is performed in order to identify those women who may develop gestational diabetes. Women are asked to have a light breakfast or lunch on the day of the test before their arrival at the antenatal clinic. Upon arrival a 50 mg glucose drink is consumed over a 10 minute period. After one hour and no additional food or drink, a venous blood sample is collected. A one hour blood glucose level of < 7.8 mmol.L^{-1} indicates normal blood glucose levels (SAPPWG, 2005).

For women receiving their antenatal care at the WCH other supplementary services or admissions in addition to standard antenatal care appointments that women may attend during pregnancy are discussed in brief below. These services may provide an indication as to any complications that may occur in the antenatal period. Data collection included the

number of women in each group who attended these supplementary services as well as the reason for attendance or admission.

Firstly, Women's Assessment Service (WAS) is an emergency outpatient facility provided at the WCH for women to attend should the need arise throughout their pregnancy. Women are informed that they are to attend this service during their pregnancy if they believe anything abnormal is occurring between their scheduled antenatal appointments. Reasons for women to attend WAS include but are not limited to suspected reduced fetal movements or abnormal or excessive abdominal pain or cramping.

Secondly, the antenatal Day Assessment Unit provides care for women experiencing high risk pregnancies who require assessment, monitoring or education. Women attend as day patients for reasons such as monitoring of gestational diabetes or mild pre-eclampsia.

Thirdly, women may also be admitted to the Antenatal and Gynecology Ward during pregnancy if required. The Antenatal and Gynecology Ward provides medical support for women with high risk pregnancies with complications that need to be monitored closely either overnight or for extended periods of time. Care includes assessment of maternal and fetal well-being, planning for birth and education.

2.4.2.2. Opioid maintenance therapy efficacy

Maintenance therapy efficacy was determined by means of maternal withdrawal severity and direct drug effects that were assessed at each antenatal appointment by means of questionnaire administration. Maternal withdrawal severity was assessed in all three groups as several signs and symptoms experienced by women are non-specific to withdrawal and may be related to pregnancy, therefore allowing control mothers to act as a baseline.

Illicit drug use was also used to determine opioid maintenance therapy efficacy. All women, including those in the control group, were assessed for drug use by self-reporting at each antenatal appointment and random urine analysis. Opioid maintenance therapy efficacy was also determined by retention in treatment.

2.4.3. Assessment of labour and delivery outcomes

Complications during labour and delivery as well as the requirement for analgesia and anaesthesia were recorded in maternal case notes and collected at a later date. Fetal condition during labour was assessed using cardiac tocography (CTG) to assess the presence of fetal stress. Similarly neonatal outcomes immediately proceeding delivery including infant size and Apgar scores as well as any complications were also recorded and collected.

In order to assess the transfer of both buprenorphine and methadone across the placenta, umbilical cord blood was taken upon delivery coinciding with a maternal blood sample to determine the concentration of buprenorphine or methadone reaching the fetus.

2.4.4. Postnatal outcomes

During hospital stay, infants were assessed by WCH midwives in accordance with study protocol. All data was recorded in the infant's case notes and collected by the researcher at a later date. Following hospital discharge, infants were followed up and assessed by the researcher once per week from the time of birth for a maximum of 4 weeks from birth. Postnatal weekly visits were carried out as a combination of mothers returning to the hospital with their infants if able to, or the researcher performing home visits if the mother was unable to return to the WCH. Whether or not infants were breast-fed was also recorded at each of the weekly postnatal visits.

2.4.4.1. Primary outcomes

Primary neonatal outcomes included NAS onset and severity, which were assessed using a modified Finnegan Withdrawal Scale (Finnegan & Kandall, 1997) and assessed over the 4 week postnatal follow up period. All three groups of infants, including the control group, were assessed using the modified Finnegan Withdrawal Scale as several signs and symptoms experienced by infants are non-specific to withdrawal, allowing control infants to act as a baseline. The requirement for pharmacological treatment to control NAS and the amount of medication used to control NAS over the 4 week postnatal follow up period were also used as primary outcome measures.

The length of infant hospital stay was another primary outcome measure. For non-complicated deliveries, WCH recommends mothers and their infants to be admitted to the postnatal ward for 2-3 days. For Caesarean deliveries a stay of up to 5 days for both the mother and infant is recommended. For women who attend the high risk pregnancy clinic for substance use, WCH offers an extended stay for mothers and infants of 7-10 days to monitor the infant for possible late presentation of NAS. Following non-complicated deliveries, if no medical complications arise for the mother or infant, the mother and infant are transferred to the postnatal ward where the infant is monitored for signs of withdrawal. If infant withdrawal presents, the infant is transferred to a Special Care Baby Unit (SCBU). Here the infant can be closely monitored and a decision can be made by the treating neonatologist as to whether pharmacological treatment is required and if so, when initiation is to begin.

2.5. Research participants

The following section provides a description of the research participants recruited in the present study based on data collected in the initial interview conducted by the researcher following subject consent. Information on subject recruitment, matching, study retention and demographic characteristics will be presented as mean ± standard error of the mean (SEM) unless otherwise indicated.

2.5.1. Subject recruitment and retention

As stated previously in Section 2.3, 25 women were required for each group based on power analysis for the major outcomes chosen. During the course of the study, 4 women in the methadone, 6 in the buprenorphine and 1 woman in the control group did not complete the study or their data were not utilised. Therefore, subject recruitment was continued until sufficient numbers were obtained for each group. Three women in the buprenorphine group were recruited into the study twice for 2 separate pregnancies. This resulted in 29, 31 and 26 women being recruited for the methadone, buprenorphine and control groups, respectively. A summary of study non-completions is presented in Table 2-1.

Table 2-1 Summary of study non-completions.

	Methadone (n)	**Buprenorphine (n)**	**Control (n)**
Sample population recruited	29	31	26
Withdrawn due to possible drug interactions (pregnancy or maintenance therapy interactions)	1	-	1
Voluntary withdrawal	1	-	-
Lost to follow up	1	-	-
Change of maintenance therapy	-	1	N/A
Autosomal defect	-	1	-
Termination/Phantom pregnancy	1	1	-
Miscarriage (involuntary loss of pregnancy in the first 20 weeks, (SAPPWG, 2005))	-	3	-
Total sample completed	**25**	**25**	**25**

Data collected from one woman in the methadone group (M27) (55 $mg.day^{-1}$) was unable to be utilised for the current study actually completed the study protocol. Due to underlying mental health issues, all self-reporting of medications consumed that could possibly interact with methadone was not deemed to be reliable. Other self-reporting measures obtained were also inconsistent throughout the study and therefore the data collected was not included in statistical analysis.

One woman in the control group (C06) who did not complete the study was withdrawn at 16 weeks gestation due to possible drug interactions with the pregnancy. The woman was taking isoniazid for possible tuberculosis exposure, which has been shown to cause CNS related abnormalities in slightly more than 1% of infants exposed (Royal Pharmaceutical Society of Great Britain, 2005).

One woman in the methadone group (M09) (10 mg twice daily) removed herself voluntarily from the study at a gestational age of 28 weeks. The woman stated that she did not feel emotionally stable to continue in the trial and that outside factors had influenced her decision to discontinue. She continued her antenatal care with the specialist high risk pregnancy clinic as normal.

One woman from the methadone group who was lost to follow up (M21) (22.5 $mg.day^{-1}$) was incarcerated at the time of recruitment into the study. At approximately 24 weeks gestation she was released from prison. Following her release the woman failed to attend her next scheduled antenatal appointment at the WCH. She was unable to be contacted through the contact details she provided the prison at the time of her release and therefore was lost to follow up.

After commencing buprenorphine maintenance following conception at 25 weeks gestation, one woman (B03) considered herself stable enough to withdraw from 2.4 $mg.day^{-1}$ buprenorphine at 28 weeks gestation. In accordance with ethics protocols the woman remained in the study and continued to be followed up. At 36 weeks gestation the woman claimed she was not coping and wished to be placed on a maintenance pharmacotherapy. As the cut off of 28 weeks gestation to begin buprenorphine had passed,

the woman was offered methadone and was maintained on 15 mg.day^{-1} methadone for the remainder of her pregnancy.

A fetal autosomal defect diagnosed later in pregnancy resulted in another woman (B21) (10 mg.day^{-1}) in the buprenorphine group being unable to complete the trial. A repeat ultrasound at 32 weeks as a result of abnormal palpation and small fundal height of 27cm at 29 weeks gestation, revealed the fetus to have autosomal recessive polycystic kidney disease with oligohydramnios (reduced volume of amniotic fluid) and enlarged fetal kidneys. An elective Caesarean delivery was performed at 34 weeks gestation at the request of the mother due to constant emotional stress. Following delivery oxygen and intravenous therapy were provided to the infant however fetal death occurred 4 hours after delivery. Infant autopsy revealed the cause of death to be due to infantile polycystic kidney disease and secondary severe pulmonary hypoplasia. Maternal data was therefore not analysed.

One woman in the methadone group (M10) (45 mg.day^{-1}) admitted herself for a voluntary termination of pregnancy at a gestational age of approximately 14 weeks. Exact details of the termination were unable to be obtained due to subject distress and unwillingness to provide information as to where the procedure was performed. A phantom pregnancy at approximately 9 weeks gestation also prevented a woman from the buprenorphine (B23) (14 mg.day^{-1}) from completing the study.

Details of miscarriages will be discussed in Chapter 3. All statistical analyses in the current and subsequent chapters utilise data from 25 women and their infants in each group who completed the study.

2.5.1.1. Location of recruitment

Location of subject recruitment details are presented below in Table 2-2. The majority of women in both the methadone (84%) and buprenorphine (48%) groups were recruited from the WCH high risk pregnancy outpatient clinic. As previously mentioned, all control women were recruited from standard midwifery care antenatal outpatient clinics at the WCH.

Table 2-2 Summary of subject recruitment location

	Methadone (n, (%))	**Buprenorphine (n, (%))**
WCH high risk pregnancy outpatient clinic	21 (84)	12 (48)
DASSA metropolitan unit	1 (4)	6 (24)
Private practitioners	1 (4)	7 (28)
Correctional services	2 (8)	2 (8)

2.5.2. Subject matching

As mentioned previously, subjects were recruited so that the groups were approximately matched for age, alcohol consumption, nicotine use, parity and gravida. There were no statistically significant differences in these variables between the three groups as presented below in Table 2-3.

Table 2-3 Subject matching criteria.

	Methadone (n/n)	Buprenorphine (n/n)	Control (n/n)
Age 18-29/30-40 years	16/9	18/7	16/9
Alcohol consumption past 30 days Yes/No 1-3/4-7 standard drinks per week	8/17 5/3	13/12 13/0	12/13 10/2
Nicotine use past 30 days Yes/No <10/>11 cigarettes	24/1 11/13	22/3 12/10	21/4 13/8
Parity 1st/More	8/17	9/16	14/11
Gravida 1st/More	2/23	4/21	8/17

2.5.3. Subject characteristics

2.5.3.1. Subject demographics

Demographic variables are presented for the 25 women in each group in Table 2-4. The majority of women in all three groups were Caucasian (88% methadone, 88% buprenorphine, 92% controls). No women in the control group were positive for Hepatitis C and significantly more women in the methadone group (84%) were positive than women in the buprenorphine group (52%, $p<0.05$). There were no significant differences in the level of education between the three groups, as measured by the percentage of women who had completed 10 or less years of education (52% methadone, 32% buprenorphine, 20%

controls). A similar percentage of women in each group were also unemployed (20% methadone, 16% buprenorphine, 4% controls).

Table 2-4 Subject demographics

	Methadone (n, (%))	**Buprenorphine (n, (%))**	**Control (n, (%))**
Age years (mean ± SEM)	29.16 ± 1.24 (19-40)	27.36 ± 1.20 (16^{NB}-39)	27.40 ± 1.24 (16^{NB}-39)
Ethnicity:			
Caucasian	22 (88)	22 (88)	23 (92)
Aboriginal/Torres Strait Islander	2 (8)	2 (8)	0 (0)
Asian	0 (0)	0 (0)	1 (4)
Other	1 (4)	1 (4)	1 (4)
Hepatitis C positive	21 (84)*	13 (52)	0 (0)
Highest level of education:			
Year 10 or less	13 (52)	8 (32)	5 (20)
Year 11	5 (20)	6 (24)	7 (28)
Year 12	3 (12)	2 (8)	3 (12)
Technical college/apprenticeship	4 (16)	9 (36)	7 (28)
University degree	0 (0)	0 (0)	3 (12)
Employment (occupation over last 3 years):			
Unemployed	5 (20)	4 (16)	2 (8)
Unskilled	6 (24)	6 (24)	5 (20)
Skilled/Trade	4 (16)	4 (16)	11 (44)
Professional	0 (0)	1 (4)	2 (8)
Student	1 (4)	4 (16)	1 (4)
Home duties	9 (36)	6 (24)	2 (8)
Marital/parental status:			
Has partner	19 (76)	22 (88)	13 (52)
Living with partner	14 (56)	15 (60)	12 (48)
Married	0 (0)	2 (8)	11 (44)
Ever divorced/separated	2 (8)	6 (24)	4 (16)

*$p<0.05$ compared to buprenorphine

^{NB}Where it was necessary to recruit subjects (for reasons such as continuation with buprenorphine maintenance and subject matching) who were younger than the required age of 18 years of age, as stated in the application to ethics, where appropriate the parent/guardian consent for the subject to participate was obtained and the ethics committee notified of the inclusion of the subject.

2.5.3.2. Concurrent medical conditions

Table 2-5 highlights the three most common medical conditions experienced by research subjects within the last 6 months. There was no significant difference between the three groups for those tabled medical conditions. In addition, methadone maintained subjects also reported hypothyroidism (as a result of thyroid removal, n=1, 4%), insomnia (n=1, 4%), schleroderma (n=1, 4%) and panic attacks (n=1, 4%). Buprenorphine maintained subjects reported Guillain Barré Syndrome (n=1, 4%), anaemia (n=1, 4%) and reflux (n=1, 4%). Control subjects also reported polynephritis (n=1, 4%), thrush (n=1, 4%) and hay fever (n=1, 4%).

Table 2-5 Concurrent medical conditions.

	Methadone (n, (%))	**Buprenorphine (n, (%))**	**Control (n, (%))**
Depression	6 (24%)	3 (12%)	3 (12%)
Anxiety	4 (16%)	1 (4%)	-
Asthma	-	2 (8%)	3 (12%)

2.5.3.3. Drug use history

Ninety two percent of women in the methadone group reported being dependent on heroin and 8% reported being dependent on various morphine preparations. Similarly, 96% of women in the buprenorphine group reported being dependent on heroin and 4% reported being dependent on various morphine preparations. There was no significant difference in the age reported for first opioid use between the methadone and buprenorphine groups (methadone: 18.96 ± 0.75, 14-28 years, buprenorphine: 19.48 ± 0.74, 13-28 years), nor was there any significant difference in the age at which they started daily use (methadone 20.08 ± 0.77, 14-28 years; buprenorphine 20.59 ± 0.81, 13-28 years). Ninety six percent of

women in the methadone group reported daily use of opioids prior to treatment entry and 88% of women in the buprenorphine group. The mean number of days on which opioids were used in the 30 days prior to commencing treatment was not significantly different between the methadone and buprenorphine groups (methadone: 29.08 ± 0.92, 7-30 days, buprenorphine: 28.16 ± 1.15, 4-30 days). The mean length of consistent opioid use (no interruptions of greater than one week) prior to commencing treatment was not significantly different between the two groups (methadone 1.91 ± 0.53, 0.04-10 years; buprenorphine 2.10 ± 0.59, 0.06-12 years). Despite the number of uses per day not being significantly different between the two groups (methadone 4.04 ± 1.20, 1-30 uses per day; buprenorphine 1.96 ± 0.23, 1-6 uses per day), women in the methadone group spent significantly more per day on heroin prior to treatment entry than those in the buprenorphine group (methadone: AUD$306.00 ± 83.87, 50-2000, buprenorphine: AUD$134.70 ± 21.64, 40-500; $p<0.05$). With regard to morphine use, data was not available for one woman and the remaining woman in the methadone group used 100 mg of morphine on days used and the woman in the buprenorphine group used 250 mg morphine on days used. The frequency with which subjects reported ever using and reported using in the 30 days prior to study enrolment for drugs other than heroin and morphine is summarised in Table 2-6.

Table 2-6 Maternal drug use history prior to enrolment with the exclusion of heroin and morphine use.

		30 days prior to enrolment		
Drug Class/Study Group	**Ever used (n, (%))**	**Used at all (n, (%))**	**Daily use (n, (%))**	**Days of use (mean ± SEM)**
Tobacco:				
Methadone	25 (100)	24 (96)	24 (96)	30.00 ± 0.00
Buprenorphine	24 (96)	22 (88)	19 (76)	28.64 ± 0.81
Control	25 (100)	21 (84)	17 (68)	26.05 ± 1.91
Marijuana:				
Methadone	25 (100)	19 (76)	10 (40)	16.79 ± 3.01
Buprenorphine	25 (100)	17 (68)	11 (44)	22.76 ± 2.81
Control	22 (88)	5 (20)	2 (8)	18.40 ± 5.30
Benzodiazepines:				
Methadone	22 (88)	2 (8)	0 (0)	0 ± 0
Buprenorphine	21 (84)	2 (8)	0 (0)	0 ± 0
Control	6 (24)	0 (0)	0 (0)	0 ± 0
Alcohol:				
Methadone	25 (100)	8 (32)	0 (0)	6.63 ± 1.56
Buprenorphine	25 (100)	13 (52)	0 (0)	2.46 ± 0.68
Control	25 (100)	12 (48)	0 (0)	2.33 ± 0.61
Diverted methadone:				
Methadone (n=23)	8 (35)	0 (0)	0 (0)	0 ± 0
Buprenorphine	11 (44)	0 (0)	0 (0)	0 ± 0
Control	1 (4)	0 (0)	0 (0)	0 ± 0
Other opioids:				
Methadone	20 (80)	5 (20)	0 (0)	7.40 ± 4.00
Buprenorphine	16 (64)	6 (24)	1 (4)	8.83 ± 4.43
Control (includes heroin)	3 (12)	1 (4)	0 (0)	1.00 ± 0.00
Cocaine:				
Methadone	20 (80)	0 (0)	0 (0)	0 ± 0
Buprenorphine	20 (80)	0 (0)	0 (0)	0 ± 0
Control	5 (20)	0 (0)	0 (0)	0 ± 0
Ecstasy:				
Methadone	14 (56)	1 (4)	0 (0)	1.00 ± 0.00
Buprenorphine (n=24)	16 (67)	2 (8)	0 (0)	2.00 ± 1.00
Control	12 (48)	0 (0)	0 (0)	0 ± 0
Amphetamines:				
Methadone	24 (96)	5 (20)	0 (0)	1.80 ± 0.58
Buprenorphine	25 (100)	5 (20)	1 (4)	11.00 ± 5.93
Control	14 (56)	0 (0)	0 (0)	0 ± 0
Hallucinogens:				
Methadone	19 (76)	0 (0)	0 (0)	0 ± 0
Buprenorphine	16 (64)	1 (4)	0 (0)	2.00 ± 0.00
Control	11 (44)	0 (0)	0 (0)	0 ± 0
Inhalants:				
Methadone	14 (56)	0 (0)	0 (0)	0 ± 0
Buprenorphine	5 (20)	0 (0)	0 (0)	0 ± 0
Control	4 (16)	0 (0)	0 (0)	0 ± 0

2.5.3.4. Drug treatment history

For those women in the methadone and buprenorphine groups who were already maintained on a program at the time of recruitment, there was no significant difference in the number of years they had been maintained prior to recruitment (methadone 2.36 ± 0.69, buprenorphine 1.84 ± 0.84).

Table 2-7 summarises maternal drug treatment history. No women in the control group had been previously treated for opioid dependence, however one woman had been treated previously once for amphetamine dependence (not shown). The percentage of women who had received any previous treatment for opioid dependence was similar in both the methadone (88%) and buprenorphine groups (100%). The number of times they had received any treatment was also not significantly different between the two groups (methadone 10.27 ± 4.83, buprenorphine 5.84 ± 1.52). When opioid treatments were separated into their individual categories, the percentage of women who received each treatment was also not significantly different. The number of times the women had received each treatment was also not significantly different with the exception of drug-free counselling, of which the methadone group had attended significantly more sessions than the buprenorphine group (methadone: 11.68 ± 8.85, buprenorphine 1.30 ± 0.21; $p<0.05$). Other forms of treatment for opiate dependence included acupuncture, hypnotherapy, referral through drug court and treatment with benzodiazepines.

Table 2-7 Drug treatment history.

Treatment Type/Study Group	**Ever tried (n, (%))**	**Number of times Mean ± SEM**	**Number of times Range**
Opioid dependence			
Any previous treatment:			
Methadone	22 (88)	10.27 ± 4.83	1-110
Buprenorphine	25 (100)	5.84 ± 1.52	1-37
Methadone maintenance:			
Methadone	14 (56)	2.57 ± 0.63	1-10
Buprenorphine	17 (68)	1.65 ± 0.27	1-5
Buprenorphine maintenance:			
Methadone	5 (20)	1.40 ± 0.40	1-3
Buprenorphine	7 (28)	1.43 ± 0.20	1-2
Detoxification-buprenorphine:			
Methadone	2 (8)	1.00 ± 0.00	1
Buprenorphine	2 (8)	3.00 ± 1.00	2-4
Detoxification-clinic:			
Methadone	12 (48)	2.33 ± 0.48	1-6
Buprenorphine	12 (48)	1.75 ± 0.28	1-3
Detoxification-home (medically supervised):			
Methadone	6 (24)	2.17 ± 0.31	1-3
Buprenorphine	7 (28)	5.86 ± 4.04	1-30
Drug-free counselling:			
Methadone	11 (44)	11.68 ± 8.85*	1-100
Buprenorphine	10 (40)	1.30 ± 0.21	1-3
Therapeutic community:			
Methadone	3 (12)	1.67 ± 0.33	1-2
Buprenorphine	1 (4)	1.00 ± 0.00	1
Narcotics anonymous:			

Methadone	3 (12)	1.75 ± 0.25	1-2
Buprenorphine	5 (20)	4.20 ± 1.59	1-10
Naltrexone:			
Methadone	3 (12)	1.00 ± 0.00	1
Buprenorphine	3 (12)	1.33 ± 0.33	1-2
Slow release oral morphine:			
Methadone	0 (0)	0.00 ± 0.00	0
Buprenorphine	1 (4)	1.00 ± 0.00	1
LAAM:			
Methadone	0 (0)	0.00 ± 0.00	0
Buprenorphine	0 (0)	0.00 ± 0.00	0
Other:			
Methadone	3 (12)	1.00 ± 0.00	
Buprenorphine	1 (4)	1.00 ± 0.00	
Other drug classes			
Any:			
Methadone	3 (12)	1.33 ± 0.33	1-2
Buprenorphine	4 (16)	2.00 ± 0.57	1-3
Benzodiazepines:			
Methadone	1 (4)	1.00 ± 0.00	1
Buprenorphine	1 (4)	1.00 ± 0.00	1
Amphetamines and Ecstasy:			
Methadone	0 (0)	0.00 ± 0.00	0
Buprenorphine	4 (16)	1.75 ± 0.48	1-3
Alcohol:			
Methadone	2 (8)	1.50 ± 0.50	1-2
Buprenorphine	1 (4)	1.00 ± 0.00	1

*$p<0.05$ compared to buprenorphine

2.5.3.5. Criminal and legal history

Criminal and legal histories are summarised for all subjects in Table 2-8. Control subjects reported that they had never been involved with dealing heroin, break and enters (whether they be domestic or commercial), snatch and grabs, fraud, armed robbery or stolen a car. Methadone maintained subjects did not report any previous involvement ever in snatch and grabs. Buprenorphine maintained women did not report any previous involvement in snatch and grabs or armed robberies ever. Significantly more ($p<0.05$) methadone (40%) and buprenorphine (36%) maintained subjects reported ever having any involvement in dealing other drugs compared to control (8%) subjects. Significantly more ($p<0.05$) methadone maintained women (32%) reported ever being involved in injurious assaults compared to control women (4%). Significantly more methadone ($p<0.01$, 80%) and buprenorphine ($p<0.05$, 72%) maintained women reported ever previously shoplifting compared to control women (36%) with significantly more ($p<0.05$) methadone maintained subjects (36%) reporting shoplifting within the previous 12 months compared to control subjects (8%). Significantly more ($p<0.01$) methadone (44%) and buprenorphine (40%) maintained subjects reported involvement with prostitution ever compared to control subjects (4%).

When observing contact with police and the courts, control subjects did not report any previous imprisonments. Significantly more methadone and buprenorphine maintained women had ever been previously cautioned by the police ($p<0.01$ methadone 96%, $p<0.01$ buprenorphine 92%, control 56%) and ever placed in lock-up ($p<0.0001$ methadone 72%, $p<0.001$ buprenorphine 60%, control 8%) than control subjects. Significantly more ($p<0.0001$) methadone (72%) and buprenorphine (68%) maintained subjects had ever previously been arrested compared to control subjects (4%). Significantly more methadone

(48%) maintained women had ever been imprisoned compared to buprenorphine (16%) maintained women. Significantly more women reported attending a court appearance ever ($p<0.05$ methadone 76%, $p<0.01$ buprenorphine 80%, control 36%) and in the last 12 months ($p<0.01$ methadone 48%, $p<0.01$ buprenorphine 48%, control 8%) in the methadone and buprenorphine maintained groups compared to controls.

In addition, there was no significant difference in the percentage of women in the methadone (8%) and buprenorphine (12%) groups who had commenced their current maintenance therapy program as a result of legal pressures.

There was no significant differences in the mean ages at which criminal activity or contact with the police and courts began between the three groups, with the exception of methadone maintained subjects (17.78 ± 1.37 years) who attended court appearances significantly earlier ($p<0.05$) in life compared to both buprenorphine maintained subjects (21.79 ± 1.30 years) and control subjects (22.43 ± 1.94 years).

Table 2-8 Criminal and legal history.

	Frequency (n, (%))			Age 1st occurrence (years)	
	Ever	**Last 6 months**	**Last 12 months**	**Mean ± SEM**	**Range**
Crime/behaviour					
Dealing heroin:					
Methadone	9 (36)	0 (0)	0 (0)	19.25 ± 1.57	14-26
Buprenorphine	3 (12)	0 (0)	1 (4)	21.67 ± 1.76	19-25
Control	0 (0)	0 (0)	0 (0)	0.00 ± 0.00	0
Dealing other drugs:					
Methadone	10 (40)*	2 (8)	2 (8)	17.50 ± 1.08	13-25
Buprenorphine	9 (36)*	4 (16)	5 (20)	20.11 ± 1.27	15-27
Control	2 (8)	1 (4)	1 (4)	15.00 ± 0.00	15
Break/enter-domestic:					
Methadone	8 (32)	0 (0)	1 (4)	20.00 ± 1.86	13-25
Buprenorphine	5 (20)	1 (4)	1 (4)	17.20 ± 1.56	13-21
Control	0 (0)	0 (0)	0 (0)	0.00 ± 0.00	0
Break/enter-commercial:					
Methadone	5 (20)	0 (0)	0 (0)	17.20 ± 2.11	13-25
Buprenorphine	3 (12)	1 (4)	1 (4)	13.67 ± 0.33	13-14
Control	0 (0)	0 (0)	0 (0)	0.00 ± 0.00	0
Snatch and grab:					
Methadone	0 (0)	0 (0)	0 (0)	0.00 ± 0.00	0
Buprenorphine	0 (0)	0 (0)	0 (0)	0.00 ± 0.00	0
Control	0 (0)	0 (0)	0 (0)	0.00 ± 0.00	0
Injurious assault:					
Methadone	8 (32)*	3 (12)	3 (12)	14.50 ± 1.27	10-21
Buprenorphine	2 (8)	0 (0)	0 (0)	16.00 ± 0.00	16
Control	1 (4)	0 (0)	0 (0)	13.00 ± 0.00	13
Fraud:					
Methadone	13 (52)	0 (0)	3 (12)	20.83 ± 0.94	16-27
Buprenorphine	7 (28)	1 (4)	2 (8)	20.29 ± 1.02	17-24
Control	0 (0)	0 (0)	0 (0)	0.00 ± 0.00	0
Shoplifting:					
Methadone	20 (80)**	7 (28)	9 (36)*	13.79 ± 1.52	7-31
Buprenorphine	18 (72)*	3 (12)	4 (16)	18.00 ± 1.85	10-37
Control	9 (36)	0 (0)	2 (8)	16.00 ± 1.56	13-26
Prostitution:					
Methadone	11 (44)**	4 (16)	5 (20)	20.82 ± 1.26	16-27
Buprenorphine	10 (40)**	3 (12)	4 (16)	22.30 ± 1.30	18-31
Control	1 (4)	0 (0)	1 (4)	21.00 ± 0.00	21
Armed robbery:					
Methadone	4 (16)	0 (0)	0 (0)	24.25 ± 3.09	16-31
Buprenorphine	0 (0)	0 (0)	0 (0)	0.00 ± 0.00	0
Control	0 (0)	0 (0)	0 (0)	0.00 ± 0.00	0
Stolen car:					
Methadone	7 (28)	2 (8)	4 (16)	24.29 ± 3.08	14-34

Buprenorphine	2 (8)	0 (0)	0 (0)	22.50 ± 7.50	15-30
Control	0 (0)	0 (0)	0 (0)	0.00 ± 0.00	0
Contact with police/courts					
Police caution:					
Methadone	24 (96)**	9 (36)	15 (60)	16.75 ± 1.04	8-31
Buprenorphine	23 (92)**	7 (28)	10 (40)	20.87 ± 1.63	11-39
Control	14 (56)	2 (8)	4 (16)	19.86 ± 1.62	13-33
Police lock-up:					
Methadone	18 (72)****	3 (12)	7 (28)	20.89 ± 1.41	14-33
Buprenorphine	15 (60)***	3 (12)	6 (24)	22.00 ± 1.81	13-39
Control	2 (8)	0 (0)	0 (0)	15.50 ± 0.50	15-16
Arrested:					
Methadone	18 (72)****	3 (12)	7 (28)	19.33 ± 1.50	12-33
Buprenorphine	17 (68)****	3 (12)	7 (28)	20.69 ± 1.28	13-36
Control	1 (4)	0 (0)	0 (0)	22.00 ± 0.00	22
Imprisoned:					
Methadone	12 (48)*	2 (8)	3 (12)	22.33 ± 1.71	11-33
Buprenorphine	4 (16)	2 (8)	2 (8)	24.75 ± 3.88	15-31
Control	0 (0)	0 (0)	0 (0)	0.00 ± 0.00	0
Community service:					
Methadone	14 (56)	2 (8)	2 (8)	23.21 ± 1.83	15-33
Buprenorphine	9 (36)	4 (16)	4 (16)	21.63 ± 2.12	13-30
Control	6 (24)	0 (0)	0 (0)	22.00 ± 1.82	16-27
Court appearance:					
Methadone	19 (76)*	7 (28)	12 (48)**	17.78 ± 1.37*$^{\blacktriangle}$	12-29
Buprenorphine	20 (80)**	9 (36)	12 (48)**	21.79 ± 1.30	13-39
Control	9 (36)	0 (0)	2 (8)	22.43 ± 1.94	13-29

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 compared to controls

$^{\blacktriangle}$p<0.05 compared to buprenorphine

2.6. Statistical analysis

All data was statistically analysed using GraphPad Prism v4.03® (GraphPad Software, CA, USA) with an α level set at 0.05. Where appropriate all data was first assessed for normality.

If data were normally distributed the appropriate parametric analysis was performed. Where comparisons were made between 2 groups, a two-tailed unpaired t-test was performed. Where comparisons were made between 3 groups, a one-way analysis of variance was performed with a Tukey's post-hoc test. Where correlations were performed for normally distributed data a two-tailed Pearson correlation test was performed.

If data were not normally distributed the appropriate non-parametric tests were performed. Where comparisons were made between 2 groups, a two-tailed Mann-Whitney test was performed. Where comparisons were made between 3 groups, a Kruskal-Wallis test was performed with a Dunns post-hoc test. Where correlations were performed for non-parametric data a Spearman correlation test was performed.

A Chi-square test was used to assess differences in frequencies of the occurrence of an event between the three groups of women.

2.6.1. Presentation of results

All results are presented as mean ± SEM and where measurements are taken over time, results are presented as mean ± SEM of the area under the curve (AUC) of the measurement versus time curve.

2.7. Discussion

The primary aim of the present study was to assess the efficacy and safety of buprenorphine use both during and after pregnancy compared to methadone and a non-opioid exposed population. The methodology used to assess this was a non-randomised open-label flexible dosing study where women were recruited during their pregnancy and followed along with their infants for a 4 week postnatal period. Results relating to the four specific areas studied are presented in Chapters 3 to 6. To assist in comprehension of later sections, the present chapter provided an overview of study methodology and research subject characteristics with emphasis on those aspects that are common to subsequent chapters. The following discussion will consider issues pertaining to the ethical and scientific integrity of the present research in reference to trial design and methodology.

2.7.1. Study design considerations

In Australia both methadone and buprenorphine are classed as Category C Drugs by the Therapeutic Goods Administration (TGA). These are "Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details" (Therapeutic Goods Administration, 1999). Consequently, it was ethically desirable to ensure that the current study be designed in such a way as to minimise impact to the mother, fetus and neonate by means of adequately informing the mother of potential risks and also stabilising the intrauterine milieu for both the fetus and subsequent newborn.

The primary consideration in the design of the current study related to the small amount of published evidence for the use of buprenorphine during pregnancy and, on the contrary, the

large amount of published data reporting the benefits of methadone use during pregnancy and the implications that this may have.

Randomised controlled trials are a widely acknowledged choice for evaluating differences in medical treatments (Featherstone & Donovan, 1998). The main purpose of randomisation is to avoid bias on the basis of patient characteristics that may influence outcome between treatment groups. Randomisation allows for any differences in outcome to be explained only by the differing treatments and not the differing characteristics of the subjects (Roberts & Torgerson, 1998). The two large scale trials in the USA (Jones et al., 2005) and Austria (Fischer et al., 2006) discussed in Section 1.5.5 that are currently underway are randomised controlled trials, utilising women who are not currently on a maintenance pharmacotherapy. Women in these trials are illicit opioid users who conceive and are wishing to commence opioid maintenance therapy during pregnancy. This raises several topics for discussion in relation to the design of the current study.

The current study was a non-randomised trial. It was desirable to conduct the study in this manner for several reasons. Firstly the current study is the first to report results from a comparative study of methadone and buprenorphine that also utilised a control population. The study was conducted in this manner as to not only observe any differences or similarities in outcomes between methadone and buprenorphine maintained women during pregnancy, but to also observe if outcomes differed significantly from non-opioid exposed women. It was therefore not possible to randomise all women as it would be unethical to place non-opioid exposed pregnant women on a maintenance pharmacotherapy. Similarly it would not be possible to randomise a pregnant opioid dependent woman to the control group.

Secondly, as predicted, the current study enrolled two subpopulations of women in the treatment groups. The two prior mentioned ongoing comparison studies (Fischer et al., 2006; Jones et al., 2005) are only utilising women who were not currently participating in opioid maintenance therapies. Women in these studies are commenced on slow release oral morphine preparations and then randomised to either methadone or buprenorphine under blinded conditions.

The first subpopulation in the current study included women already participating in a maintenance therapy program at the time of recruitment. As it is important to limit fetal exposure to as few exogenous substances as possible throughout the course of pregnancy, it was therefore unethical to randomise those women who were already participating in a maintenance therapy program. If this were done it may have involved transferring them to the alternative maintenance therapy medication, thereby introducing the fetus to a greater number of unnecessary exogenous substances while concurrently placing the mother in a situation where she may experience withdrawal in the medication transfer process.

The second subpopulation included women seeking maintenance treatment at the time of recruitment. Based on the current limited data relating to buprenorphine use during pregnancy, lack of comparison to a control population and the lack of long term follow up studies on infants exposed to buprenorphine during pregnancy, it would have been difficult to recruit and randomise those women who were seeking treatment. Instead, for those women seeking treatment upon enrolment into the trial and who did not already have an opinion as to which maintenance therapy they would prefer (this was largely based on previous experiences with maintenance therapies, whether they be positive or negative), an informed maternal choice approach was taken. Mothers were informed of the limited data concerning buprenorphine use during pregnancy and possible risks associated with it use in

pregnancy along with the possible benefits it may have. They were also informed of the extensive research performed in the area of methadone use during pregnancy and its use over an extended period of time. Women had the opportunity to discuss their choice with the researcher, prescribing medical practitioner and other people as they considered appropriate. With this information mothers were able to make an informed choice of the maintenance therapy they were to be maintained on that was best for themselves and their expected child.

The inclusion of the 2 subpopulations in the current study highlights another issue. As women in the trials being conducted by Fischer and colleagues (2006) and Jones and colleagues (2005) are not participating in a maintenance pharmacotherapy at the time of recruitment, these trials are focused on comparing the outcomes of these treatments as to which is more efficacious and minimises NAS in the exposed neonates, and therefore which should be recommended during pregnancy. This becomes less relevant for the current study, as some women were already on buprenorphine at the time of recruitment, and more relevant to ensure that buprenorphine does not pose any greater risk, or at least produces similar outcomes to methadone, in terms of efficacy to allow women who are already maintained on buprenorphine at the time of conception to remain on their current treatment and not be transferred to the alternative medication.

Interim data reported in both of the randomised controlled trials conducted by Fischer and colleagues (2006) and Jones and colleagues (2005) exclude women with polysubstance use issues at recruitment and have so far screened 146 opioid dependent women over a 3 year period and 1490 opioid dependent pregnant women over almost a 4 year period, respectively. Once again this highlights several issues in regard to the design of the current study. The stringent inclusion and exclusion criteria in the above mentioned trials, along

with the randomisation process, despite the screening of large numbers of women, has so far resulted in outcomes reported for very small subject numbers in these two trials. With the exclusion of a large amount of women from those screened, outcomes that have been reported in the two studies to date may actually present results from a non-representative opioid dependent sample. In relation to the current study, is the much smaller sample population of which women could be recruited from. As mentioned in Section 2.3, approximately 80 opioid dependent women attend the specialist high risk pregnancy clinic at the WCH for women with substance use issues each year. While a very small percentage of opioid dependent women may attend other hospitals in early pregnancy for their antenatal care, most women are referred to this service at the WCH due to the high level of antenatal care that can be provided to them. It was therefore vital to recruit as many women from this population while still maintaining a representative sample. This may not have been possible had the study been designed as a randomised controlled trial.

In order to increase the likelihood of retention in maintenance therapy in the current study, a flexible dosing strategy was employed where maintenance therapy doses for each woman were discussed and decided upon by the prescribing medical practitioner in conjunction with the subject herself. This allowed for reporting of any lack of withdrawal suppression and any appearance of undesirable side effects and ensure that both were managed with an adequate dose and therefore maximise the chances of continuation in treatment.

Therefore, the current study was designed as a non-randomised, open-label, flexible dosing study. This enabled the recruitment of the maximum number of representative women from the sample population available while also maximising maternal and fetal comfort and allowing comparison to be made to a control population.

2.7.2. Validity of current study design

In addition to the above mentioned study design, it is important that possible threats to internal and external validity of the study methodology be identified and reported. Following are factors that may be important when assessing the validity of the current study.

Despite the above mentioned justification of conducting a non-randomised trial, the first possible threat to the validity of the current study was that is was non-randomised. This therefore means that any differences in treatment outcome may be the result of patient characteristics as distinct from actual differences in treatment. However, subject demographics, drug use history, drug treatment history, criminal and legal history as well as current medical conditions were not as a whole significantly different between experimental groups, and this would therefore indicate minimal variation as a result of subject characteristics.

A second possible threat to the validity of the current study concerns the use of an open-label design. In general, a double-blind method of approach is preferable, as treatment conditions are concealed from both patients and research staff, therefore limiting the likelihood that results are not due to expectations and other biases and are related to the treatment condition itself. The use of a double-blind approach was not considered practical for the present study for the following reasons. Firstly, considering the limited evidence base for the use of buprenorphine during pregnancy, for safety reasons it was preferable that research staff and subjects both be aware of the maintenance therapy and dosage being administered to each woman. This also allowed for immediate reporting of adverse events that may have been due to maintenance therapy medications. Secondly, women in both experimental groups had reported previous experience with the alternative maintenance

therapy medication and were aware of the differing subjective and physiological effects of both maintenance medications and this would therefore have limited the likelihood that blinding would have been effective.

The current study also used a flexible dosing protocol. However, it was desirable and appropriate to maintain the mothers' comfort and minimise withdrawal severity at all times and this was best achieved by providing a flexible dosing strategy.

Finally, when assessing the effectiveness of a medication, a placebo medication as a comparison is often used. However, it was unethical for the use of placebo methodologies to be employed with the current maintenance therapy medications during pregnancy due to the inevitable risk of severe withdrawal and subsequent risk of miscarriage and premature labour.

2.8. Summary

The current study assessed the efficacy and safety of buprenorphine use during and after pregnancy in comparison with methadone and a non-opioid exposed control population. The study was a non-randomised, open-label, flexible dosing study where three groups (buprenorphine, methadone and control) of 25 mother/infant dyads were assessed throughout their pregnancy and for a 4 week postnatal follow up period. The approach taken to the current study was ethically advantageous while still maintaining high statistical power at the same time as minimising discomfort for the mother and risk of subsequent pregnancy complications. Although limitations of subject numbers and possible non-representativeness of a very small sample were the main reason not to use a randomised, double-blind approach, the limitations associated with an open-label approach are unlikely to apply to a number of the objective safety measures assessed in the current study. Furthermore, subject demographics, drug use history, drug treatment history, criminal and legal history as well as current medical conditions were not as a whole significantly different between experimental groups, and this would therefore indicate minimal variation as a result of subject characteristics. A flexible maintenance therapy dosing scheme was also justified for ethical and safety reasons. The methodological approach to the current study represents a scientifically and ethically suitable means of assessing the safety and efficacy of buprenorphine use during pregnancy.

3. MATERNAL AND FETAL OUTCOMES: ANTENATAL OBSTETRIC MEASURES

3.1. Introduction

Previously published data presented in Chapter 1 relating to buprenorphine use during pregnancy have focussed primarily on the effects of buprenorphine on neonatal outcomes, with little mention of obstetric outcomes for the mother or fetus. While Fischer and colleagues (1998) reported normal fetal ultrasound test results following buprenorphine administration and Lacroix and colleagues (2004) made reference to obstetric complications, very little data has been published focussing on the effects of buprenorphine used during the antenatal period in regard to obstetric measures. Therefore, the following chapter will present and discuss the hypotheses, methods used and results obtained during the antenatal period that relate to both maternal and fetal obstetric outcomes.

In the first instance hypotheses relating specifically to the current chapter will be presented. Results relating to obstetric outcomes during the antenatal period for both the mother and fetus will then be presented. Finally, a closing discussion will review all results obtained during the antenatal period that related to maternal and fetal obstetric outcome.

3.1.1. Aims and hypotheses

As a result of the lack of data published concerning women maintained on buprenorphine and obstetric outcomes in the antenatal period, the following hypotheses were developed:

3.1.1.1. Antenatal obstetric outcomes

3.1.1.1.1. Hypotheses

- The incidence of obstetric complications in women maintained on buprenorphine or methadone will be no greater than that observed in control women. This will be determined by:
    a. Number of visits to WAS, Day Assessment Unit and Antenatal and Gynecology Ward (Section 2.4.2.1).
    b. Frequency of individual complications.

(Note: Visits to WAS, Day Assessment Unit and Antenatal and Gynecology Ward will be analysed statistically however individual frequencies of complications were low and will not be analysed in the same way.)

- Fetal growth will be slower in the methadone group than in the buprenorphine or control group as determined by the assessment of fundal height.

3.2. Methods of data collection

3.2.1. Maternal data

Pregnancy progression in all three groups of women was assessed and the data recorded at routine antenatal appointments at the specialist high risk antenatal clinic (maintenance therapy mother) and standard midwifery clinic (control mothers) as previously described in Section 2.3. Blood pressure and patients progress including gestational age and any additional symptoms or questions asked were recorded by a midwife in maternal case notes. The number of antenatal appointments mothers attended throughout their pregnancy was also documented with some of this information collected retrospectively.

3.2.1.1. Obstetric complications

The type and frequency of obstetric complications during the antenatal period were assessed on the basis of maternal visits to WAS, Day Assessment Unit and admissions to the Antenatal and Gynecology Ward as described in Section 2.4.2.1. Visits to these 3 services give an indication of the severity of obstetric complications experienced during the antenatal period. Figure 3-1 presents a flow chart of the order in which women attending the WCH present to these services, in conjunction with regular antenatal appointments.

WAS contends with common obstetric presentations and routine management of these presentations is described below. Management may involve direction to the Day Assessment Unit for further non-emergency or routine monitoring of an existing complication, or admission to the Antenatal and Gynecology Ward where more complex complications may

be suspected, for more extensive monitoring and treatment. Therefore the most severe of complications will result in admission to the Antenatal and Gynecology Ward.

On presentation to WAS abdominal pain/cramping is monitored and if no other symptoms present and pain decreases women are sent home and advised to return if any changes are observed. If pain/cramping is diagnosed as being due to constipation, women are advised to increase their water intake, along with plenty of fresh fruit and vegetables and use Metamucil® (psyllium husk) if required. If women present with reduced fetal movements, the fetus is monitored using CTG. If women present reporting spotting or bleeding they are closely monitored. If symptoms or pain do not persist and/or reduce in severity and if otherwise appropriate, women are sent home and advised to return if any changes are observed. If necessary, women are admitted to hospital for further monitoring. For severe morning sickness Maxolon® (metoclopramide) is administered and where necessary women are admitted for intravenous fluid replacement. Urinary tract infections (UTI) are treated with antibiotics. Women who present with false or threatened premature labour are monitored and if symptoms do not persist or reduce they are sent home and advised to return if any changes occur. Where necessary women are admitted to the Antenatal and Gynaecology Ward for further monitoring. Antenatal care is arranged through the appropriate clinics for those women who have had no previous antenatal care.

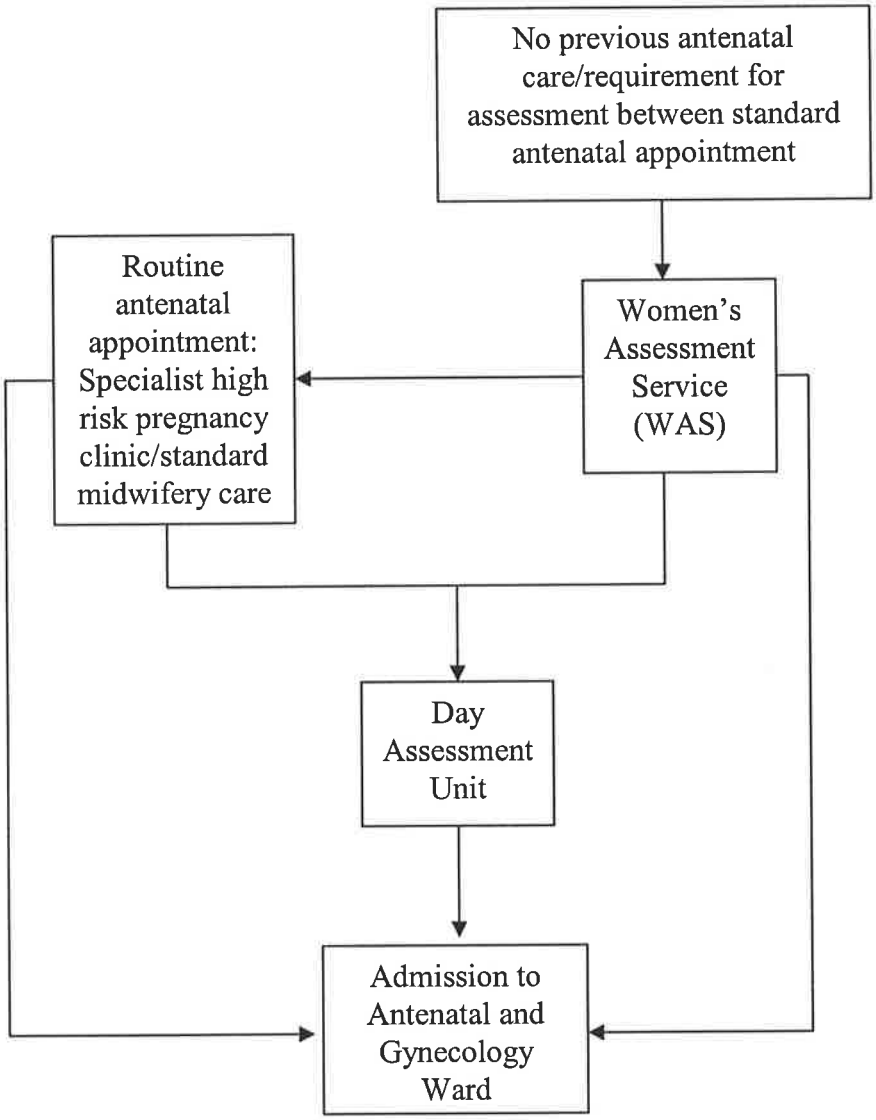

Figure 3-1 Flow chart of order of visits to antenatal services.

3.2.2. Fetal data

Fetal development was assessed by a midwife on the basis of the following data collected during routine antenatal progress appointments:

- Gestational age at recruitment was determined from menstrual history and confirmed at routine ultrasound scans between weeks 18 and 20.
- Any fetal malformations or defects were also detected at the routine ultrasound scan between weeks 18 and 20.
- Fetal size and fetal presentation were determined by palpation and tape measurement of fundal height at routine antenatal progress appointments.

Fundal height is the height of the fundus or the distance between the symphysis pubis to the top of the palpated uterus (Llewellyn-Jones, 1994).

3.3. Results

3.3.1. Gestational age at recruitment and trimester of recruitment

The gestational age at which buprenorphine maintained mothers were recruited into the study was significantly earlier than control mothers (buprenorphine 14.68 ± 1.46 weeks, control 20.77 ± 0.72 weeks; $p<0.01$) (Figure 3-2). There was no significant difference in the gestational age at recruitment between methadone maintained mothers and the other two groups.

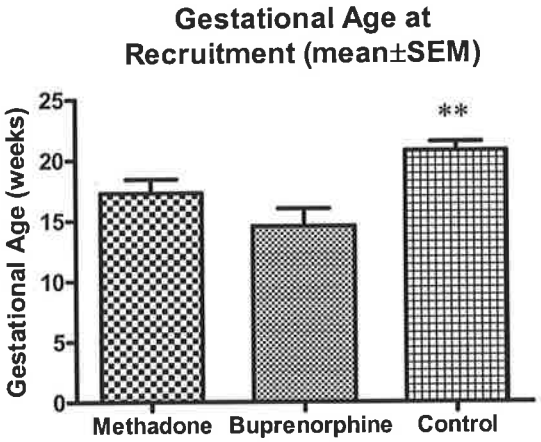

Figure 3-2 Gestational age in weeks at time of study recruitment for methadone maintained, buprenorphine maintained and control mothers. **p<0.01 compared to buprenorphine.

No women from the control group were recruited in the first trimester. However, significantly more buprenorphine maintained mothers were recruited into the study in the first trimester of pregnancy compared to methadone maintained mothers (methadone 21%; buprenorphine 48%; $p<0.05$). No control mothers were recruited during the first trimester (Figure 3-3).

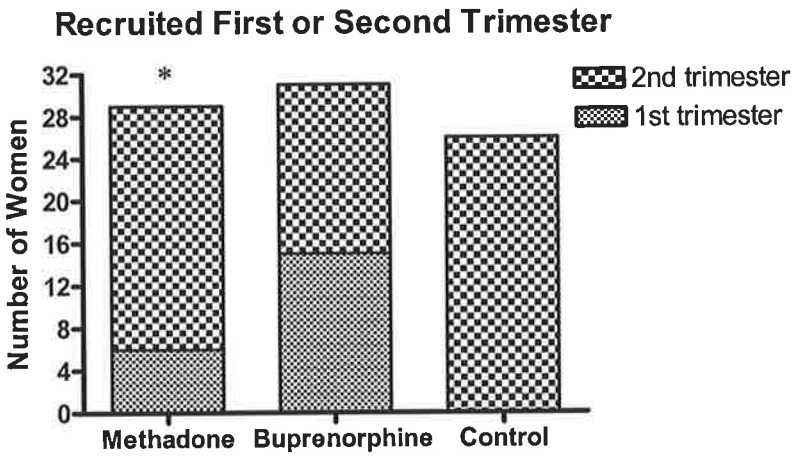

Figure 3-3 Trimester of recruitment for methadone maintained, buprenorphine maintained and control mothers. *p<0.05 compared to buprenorphine 1st trimester.

3.3.2. Gestational age at first antenatal appointment and number of routine antenatal appointments

The gestational age at which mothers presented for their first antenatal appointment at the WCH was significantly later for mothers in the methadone group compared to the control group (methadone 16.24 ± 0.94 weeks, control 11.56 ± 0.55 weeks; p<0.01) (Figure 3-4).

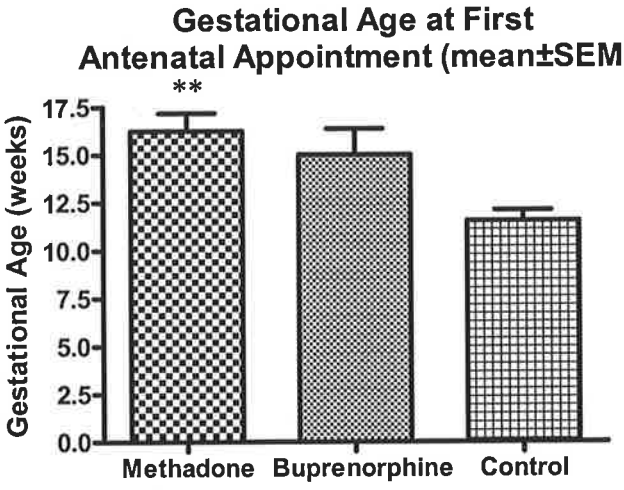

Figure 3-4 Gestational age in weeks at first antenatal appointment for methadone maintained, buprenorphine maintained and control mothers. **p<0.01 compared to control.

There was no significant difference in the gestational age at first antenatal appointment between methadone and buprenorphine mothers, or buprenorphine and control mothers. Despite the later presentation at the first antenatal appointment in the methadone group compared to the control group, there was no significant difference between each of the three groups for the number of routine antenatal appointments that mothers attended (Figure 3-5).

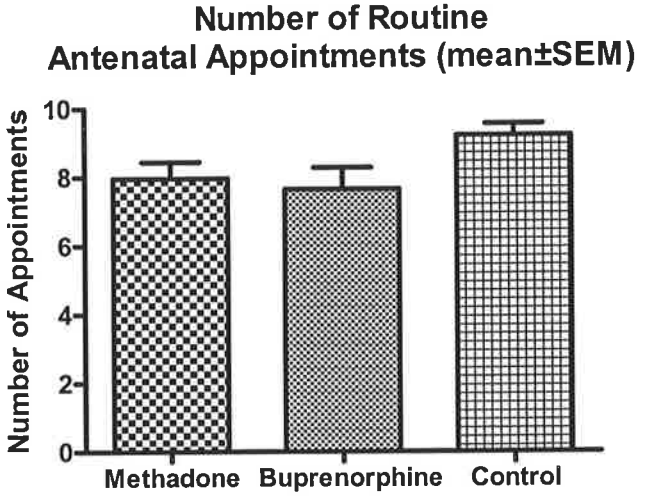

Figure 3-5 Number of routine antenatal appointments throughout pregnancy for methadone maintained, buprenorphine maintained and control mothers.

3.3.3. Obstetric outcomes: clinical presentations and diagnoses

3.3.3.1. Miscarriage

As previously discussed, three women in the buprenorphine group (B02, B10 and B25) experienced incomplete miscarriages. This equates to 9.7% of women recruited in the buprenorphine group. The first woman (B02, 20 years of age) was dependent on heroin and was recruited in to the trial at 8 weeks gestation and commenced BMT following the conception of her first pregnancy. She suffered an incomplete miscarriage at 13 weeks at which time she was maintained on 10 $mg.day^{-1}$ buprenorphine. Suction dilation and curettage was performed with an uncomplicated recovery. The remaining 2 women (B10,

25 years of age and B25, 29 years of age) were already maintained on buprenorphine at the time of conception. The first of these women (B10) was recruited into the trial at 7 weeks gestation. She had a past medical history of 3 voluntary terminations of pregnancy and 2 children aged 10 and 3 years. She suffered an incomplete miscarriage at 12 weeks gestation at which time she was maintained on 10 $mg.day^{-1}$ buprenorphine. Suction dilation and curettage was performed with an uncomplicated recovery. The second of the women (B25) already maintained on buprenorphine was recruited into the trial at 11 weeks gestation. She had a past medical history of 1 previous miscarriage and 2 children aged 11 years and 18 months. The subject suffered an incomplete miscarriage at 12 weeks gestation at which time she was maintained on 9.6 $mg.day^{-1}$ buprenorphine. Suction dilation and curettage was performed with an uncomplicated recovery. In all three cases, specimens collected contained no obvious fetal parts, however, products of conception were confirmed.

3.3.3.2. Attendance at WAS

There was no significant difference in the percentage of women in each group who attended WAS throughout their pregnancy with 40% of methadone maintained, 68% of buprenorphine maintained and 52% of control women attending for at least one reason (Figure 3-6).

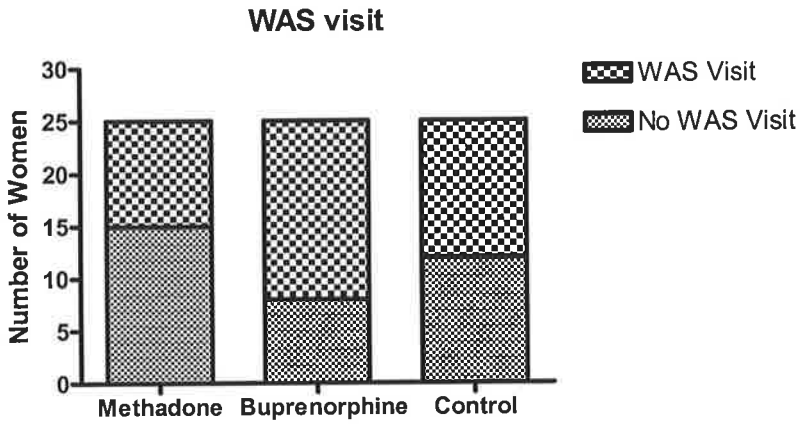

Figure 3-6 Number of women from the methadone maintained, buprenorphine maintained and control groups who attended WAS throughout pregnancy.

Reasons for attendance at WAS are presented below in Table 3-1. It should be noted that some women attended WAS on more than one occasion for different reasons. Admissions to the Antenatal and Gynecology Ward as a result of presentation to WAS will be discussed below in Section 3.3.3.4.

Table 3-1 Reasons for attendance at WAS for methadone maintained, buprenorphine maintained and control mothers.

	Methadone (n)	Buprenorphine (n)	Control (n)
Abdominal pain/cramping	6	4	5
Constipation	2	1	1
Reduced fetal movements	2	2	2
Spotting/bleed/abruption	1	3	-
Severe morning sickness	-	2	-
UTI	-	1	2
False/threatened labour	-	1	4
No previous antenatal care	1	4	-
Deep vein thrombosis (DVT)	-	2	-

For women who required CTG monitoring for reduced fetal movements, test results for all cases were within normal limits.

In addition to the above-tabled visits, one woman (M13) in the methadone group attended WAS for a repeat of routine blood tests due to insufficient sample quantity. Another woman in the methadone group (M29) presented at WAS for a methadone overdose as a

result of the incorrect dose being administered by the dosing pharmacist and was admitted to the Antenatal and Gynecology Ward.

One woman (B07) in the buprenorphine group presented for domestic violence reasons and was later housed in a women's domestic violence shelter. Another woman (B11) in the buprenorphine group presented with the sudden appearance of a lump in her breast that was discovered to be benign. Another women (B08) presented to WAS with an irritating skin rash that responded to cortisone ointment and hydroderma cream. Another woman (B28) in the buprenorphine group presented to WAS with an allergic reaction to Maxolon® administered for morning sickness. The final woman (B16) in the buprenorphine group presented to WAS for administration of Anti-D prophylaxis that is routinely administered to rhesus negative women during pregnancy.

Additional reasons for visits in the control group of women included one woman (C02) presenting with suspected premature rupture of membranes. This was discovered to be normal vaginal discharge and no further action was taken. One woman (C04) presented with severe thrush that was treated with an antifungal ointment. She also attended for suspected chicken pox exposure during pregnancy. Tests confirmed she had already been exposed to chicken pox and therefore was unlikely to contract it during pregnancy. During a routine ultrasound one woman (C11) in the control group was found to have a shortened cervix (indication for premature delivery) and was referred to WAS for further assessment, which revealed no causes for concern with the cervix responding to tests appropriately. The same woman also attended another public hospital for increased vaginal discharge. All observations were found to be within normal limits and she was therefore discharged. The final woman (C16) in the control group presented to WAS and was diagnosed to have bacterial vaginosis which was treated with antibiotics.

3.3.3.3. Admission to Day Assessment Unit and outcomes

There was also no significant difference in the percentage of women in each group who were admitted to the Day Assessment Unit for complications throughout pregnancy, with 24% methadone maintained, 14% buprenorphine maintained and 16% of control women being admitted on at least one occasion (Figure 3-7).

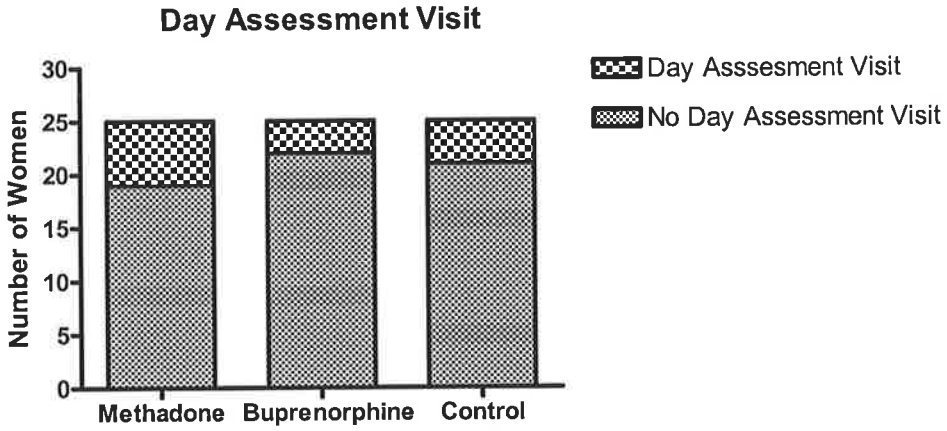

Figure 3-7 Number of women from the methadone maintained, buprenorphine maintained and control groups who were admitted to the Day Assessment Unit throughout pregnancy.

Reasons for admission to the Day Assessment Unit are presented in Table 3-2.

Table 3-2 Reasons for admission to the Day Assessment Unit for methadone maintained, buprenorphine maintained and control mothers.

	Methadone (n)	Buprenorphine (n)	Control (n)
Repeat of OGCT	1	-	2
Monitoring of gestational diabetes	-	-	1
BP monitoring	2	-	1
Fall	1	-	-
Placental praevia	-	1	-
Reduced fetal growth	1	-	-
Reduced fetal movement	1	-	-
Abnormal fetal heart rate	-	2	-

3.3.3.3.1. Methadone

A repeat OGCT to exclude gestational diabetes was performed in the woman (M06) as she ate in the fasting period when the original test was performed in the antenatal clinic. One woman (M13) was diagnosed with gestational hypertension without significant proteinuria at approximately 32 weeks gestation. She was monitored on 3 occasions in the Day Assessment Unit and was finally induced as a result of preeclampsia at 37 weeks gestation. Increased blood pressure was detected in one other woman (M24) at 39 weeks gestation during a routine antenatal appointment. However, further monitoring in the Day Assessment Unit did not identify this to be a threat and no further action was necessary. One woman (M12) in the methadone group experienced a fall at approximately 30 weeks

gestation. Fetal monitoring via CTG revealed all parameters to be within normal limits and no further action was necessary. Reduced fetal growth was observed in one woman (M20) requiring fetal monitoring via CTG in the Day Assessment Unit. All parameters were within normal limits; however, due to the intrauterine growth retardation induction of labour was performed at 38 weeks gestation. Reduced fetal movement was observed in one woman (M23) at approximately 33 weeks gestation at a routine antenatal appointment, however further fetal monitoring via CTG indicated all parameters to be within normal limits.

3.3.3.3.2. Buprenorphine

One woman (B17) was diagnosed with placenta praevia type 2 (placenta displaced in to the lower segment of the uterus) and was therefore admitted to the Day Assessment Unit for further monitoring which revealed all parameters to be within normal limits. An elective Caesarean section was booked to avoid any further complications, but the woman presented to hospital in the advanced stages of labour and progressed to a vaginal delivery. Two women (B06, B28) were found at routine antenatal appointments to have abnormal fetal heart rates that were either variable or reduced. Additional fetal monitoring in the Day Assessment Unit via CTG showed all parameters to be within normal limits for both women.

3.3.3.3.3. Control

OGCT testing revealed one woman (C20) to have gestational diabetes. This was managed by a controlled diet and additional blood glucose monitoring at the Day Assessment Unit throughout the pregnancy. A repeat OGCT was performed for 2 women (C10, C16) as original testing revealed the possible presence of gestational diabetes. Repeat testing did not lead to the diagnosis of gestational diabetes in these 2 women. Increased blood pressure

was also observed in one woman (C23), but additional monitoring in the Day Assessment Unit did not indicate this to be of risk, and blood pressure had returned to normal by the next routine antenatal appointment.

3.3.3.4. Antenatal and Gynecology Ward admissions

There was no significant difference in the percentage of women who were admitted for medical support into the Antenatal and Gynecology Ward for complications throughout their pregnancy, with 20% of methadone maintained, 28% of buprenorphine maintained and 12% of control women being admitted (Figure 3-8).

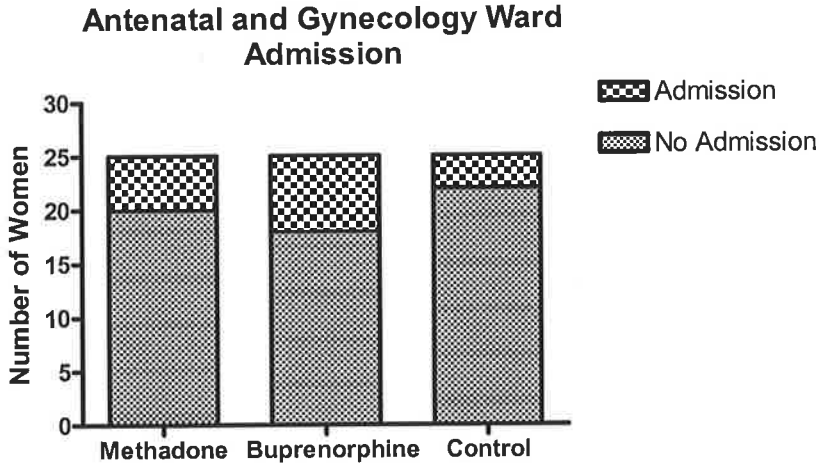

Figure 3-8 Number of women from the methadone maintained, buprenorphine maintained and control groups who were admitted to the Antenatal and Gynecology Ward throughout pregnancy.

Reasons for antenatal admission are presented in Table 3-3.

Table 3-3 Reasons for admission to the Antenatal and Gynecology Ward for methadone maintained, buprenorphine maintained and control mothers.

	Methadone (n)	Buprenorphine (n)	Control (n)
False/threatened labour	1	1	1
Abruption/trauma	2	1	-
DVT	1	1	-
Abdominal pain/cramping	1	2	2

3.3.3.4.1. Methadone

One woman (M05) was admitted for false/threatened premature labour at 36 weeks gestation. After an overnight stay and consultation with the physiotherapist for back pain, signs and symptoms abated and the patient was discharged home. At 30 weeks gestation one woman (M13) was admitted to another public hospital for a Valium® (diazepam) overdose. Another woman (M14) was admitted to the Antenatal and Gynecology Ward three times throughout the course of her pregnancy. The first admission was the result of a placental abruption (detachment of the placenta) at 28 weeks gestation. The woman was admitted and monitored for three nights, and fetal CTG results were within normal limits. She was administered a single course of steroids and discharged home the next day. She was admitted once again at 35 weeks overnight after suffering trauma and bruising to the abdomen. All observations were within normal limits and the subject was discharged home. The third admission was for suspected DVT and abdominal pain at 38 weeks gestation. The patient was given thrombo embolism deterrent stockings and a further ultrasound did not reveal DVT. After further observation, the patient was discharged after 2

nights. The same woman was admitted for a fourth time at another public hospital for pneumonia at 33 weeks. Another woman (M22) was admitted at approximately 20 weeks gestation complaining of abdominal cramping with no antenatal care history. She was admitted overnight and observed, and with no further complications she was discharged home. The final woman (M29) was admitted for the methadone overdose previously mentioned in Section 3.3.3.2. She presented as drowsy and lethargic and was admitted to the high dependency unit for observation and administered oxygen as a precaution, however all observations were within normal limits and she was discharged the following morning. The overdose was unintentional and was the result of incorrect dosing by the subject's pharmacist.

3.3.3.4.2. Buprenorphine

An ultrasound revealed a clot in the right leg of a woman (B05) admitted for DVT. The woman was started on a course of Clexane® (enoxaparin), 60 mg twice daily, intramuscularly; she was monitored for 2 nights and discharged home. She was admitted for the second time at 38 weeks gestation to commence heparin infusion prior to induction of labour. Another woman (B12) was admitted for threatened preterm labour at 26 weeks gestation. She was admitted and administered 20 mg oral nifedipine and observed for 2 nights. However, with no further indication of labour, she was discharged home. The next woman (B15) was admitted for a vaginal bleed that occurred during a routine antenatal appointment at 34 weeks gestation. She was observed for 2 nights. On the second morning 2 further significant bleeds occurred and an emergency Caesarean section was performed. Another woman (B19) was admitted for abdominal pain and a bleed and was monitored overnight. No other signs or symptoms presented and observations were all within normal limits, therefore she was discharged home the following day. Another woman (B31) was admitted at 39 weeks for abdominal pain and it was observed that the fetus was small for

gestational age and a decision was then made to induce labour. In addition to those data presented, one woman (B18) was admitted for severe morning sickness at 34 weeks gestation with the inability to hold solids or liquids down. Intravenous fluids were administered overnight for re-hydration and she was then discharged home. Another woman (B28) was admitted with an allergic reaction to Maxolon®. She was administered 1mg of benztropine and transferred to the Royal Adelaide Hospital for further monitoring.

3.3.3.4.3. Control

The first woman from the control group (C15) was admitted for abdominal cramping at 38 weeks gestation. All observations were within normal limits and hospital discharge had been planned. However, she then went into labour and was transferred to the delivery suite. The second woman (C16) was admitted for observation for abdominal pain at 35 weeks gestation but discharged herself within an hour stating that she wanted to go home and the abdominal tightenings had ceased. She was informed to return if any changes were noticed. The final woman (C26) was admitted for threatened preterm labour at 25 weeks gestation. After nifedipine administration and 2 nights observation, contractions and pain had ceased and the woman was discharged home.

3.3.4. Fetal growth

As mentioned in Section 3.3.2, women in the methadone group presented for antenatal care significantly later than the control group. The average gestational age at which the groups presented for antenatal care were 16.24 ± 0.94 weeks for methadone, 15.00 ± 1.35 weeks for buprenorphine and 11.56 ± 0.55 weeks for control. Therefore analysis of the differences in fundal height (as a representation of fetal growth) between the three groups include data starting from gestational week 17 through to delivery. Results are presented as AUC of

fundal height versus time. The AUC for fundal height versus time from week 17 to delivery was significantly less for the methadone and buprenorphine groups compared to the control group (methadone $p<0.01$, buprenorphine $p<0.001$). However, AUC was not significantly different between the three groups for the third trimester alone (Figure 3-9).

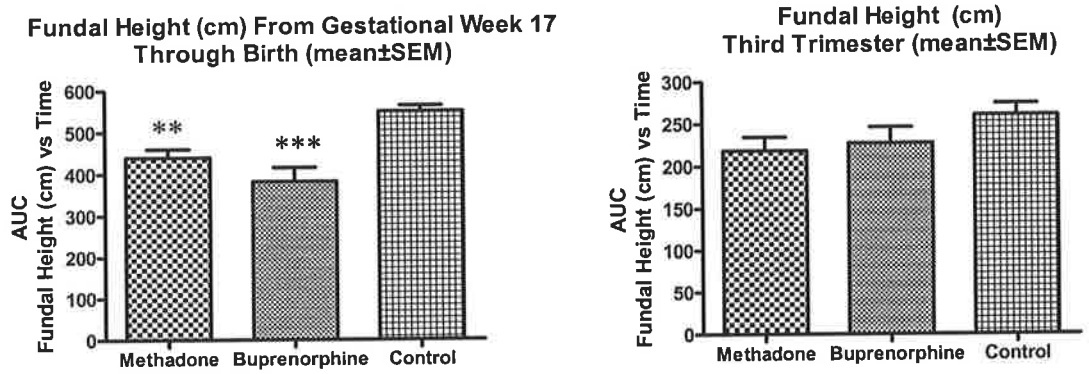

Figure 3-9 AUC of fundal heights for methadone maintained, buprenorphine maintained and control mothers for the whole of pregnancy from gestational week 17 through until birth and the third trimester alone. **p<0.01, ***p<0.001 compared to control.

3.4. Discussion

The current chapter presented results obtained in the antenatal period that compared methadone maintained, buprenorphine maintained and control pregnancies for obstetric outcomes during this period. With the exception of the higher miscarriage rate, results presented in this chapter suggest that buprenorphine is at least as safe as methadone and not significantly different to controls in terms of obstetric outcomes in the antenatal period, as hypothesised. Fetal growth was significantly slower throughout pregnancy for both treatment groups compared to controls, although appeared to improve as pregnancy progressed into the third trimester.

3.4.1. Gestational age at first antenatal appointment

The gestational age at which methadone maintained mothers presented for antenatal care was significantly later than that of control mothers. The tendency of opioid using or opioid maintained pregnant women to present later for antenatal care has been shown previously and discussed by Finnegan (1997). Substance dependent women who discover they are pregnant not only present later for antenatal care but often do not present for antenatal care at all. This occurs for a number of reasons but, mainly because of fear of judgment by medical staff and services. Substance using women may have had previously unpleasant experiences with pregnancies that involved child protection authorities that resulted in the loss of a child to alternative care. The belief that the discovery of their substance use or maintenance therapy may result in the removal of a second child from their care often results in late presentation or prevents them from presenting for antenatal care at all.

A second reason discussed by Finnegan (1997) for late presentations at antenatal care is that of denial or guilt. The woman realises that due to her substance use she is unable to

cope with the prospect of having children. She may also feel guilty at the harm she may have already caused to the unborn child as a result of her substance use. She may therefore deny she is pregnant not only to others but to herself and therefore will not present until later for antenatal care.

Finally the woman may not even know she is pregnant. It has been previously been shown that women maintained on methadone have higher rates of amenorrhoea than the general population and will often go for months or even years without menstruating (Schmittner et al., 2005). Therefore the woman may not suspect that she is pregnant until other bodily changes occur and will therefore not present until later in the pregnancy for antenatal care.

In the present study despite methadone maintained women presenting later for antenatal care, there was no significant difference in the number of antenatal appointments attended by each group. This may be a reflection of the follow up practices of the high risk pregnancy clinic at the WCH. If women present later for antenatal care, the clinic will book the woman in for additional antenatal appointments. This is in order to account for those appointments the woman did not attend at the beginning of her pregnancy and ensure she has had sufficient antenatal care throughout her pregnancy. The number of antenatal appointments attended by mothers in both the methadone and buprenorphine groups in the present study is in accordance with the number of antenatal appointments attended by methadone maintained women reported in previous studies in Section 1.5.4. Connaughton and colleagues (1977) observed methadone maintained women to attend on average 8.2 antenatal appointments during pregnancy and Doberczak and colleagues (1993) observed methadone maintained women to attend on average 7 antenatal appointments. Women in the current study attended on average 8.0, 7.6 and 9.2 antenatal appointments for methadone, buprenorphine and control groups, respectively. Therefore all women in the

present study received equal standards of antenatal care. In addition this is in accordance with the recommended guidelines discussed in Section 2.4.2.1 of between 5-10 antenatal appointments throughout pregnancy.

3.4.2. Obstetric complications

The only matter that may be of concern regarding obstetric outcomes were the miscarriages observed in the buprenorphine group. According to buprenorphine product information, early unpublished animal data presented in rats and rabbits observed difficulties with parturition and feto-toxicity, including post-implantation loss and decreased postnatal survival (MIMS Australia, 2005). However, miscarriages in buprenorphine maintained women during pregnancy have not been reported in previous clinical studies and was therefore an unexpected outcome for the current study. In the general population miscarriages have been shown to occur in 10-20% of clinically diagnosed pregnancies with this figure increasing to 50% if all pregnancies including those that are undiagnosed are included (Llewellyn-Jones, 1999; SAPPWG, 2005). In results presented so far by Fischer and colleagues (Fischer et al., 2006), one still birth was observed in the methadone group and with the low number of subjects in this study equates to 11% of the sample population recruited for the methadone group. If for the purposes of predicting the event of miscarriages in the current study populations we assume that the rate of miscarriages is 15% (average of the above presented figure), we would therefore have expected to observe the following: 4.35 miscarriages in the methadone group (29 women recruited), 4.65 miscarriages in the buprenorphine group (31 women recruited) and 3.9 miscarriages in the control group (26 women recruited). There were no miscarriages observed in the methadone and control groups, and the three previously mentioned miscarriages in the buprenorphine group. Therefore, despite the three miscarriages observed in the buprenorphine group they were still below the predicted number based on the general

population as was obviously the case in the methadone and control groups. Furthermore the rate at which they did occur in the buprenorphine group was 9.7% which is below the 10-20% observed in the general population.

Furthermore over 80% of miscarriages occur in the first 12 weeks (first trimester) of gestation with the risk of miscarriage decreasing significantly following the first trimester (Llewellyn-Jones, 1999; SAPPWG, 2005). All miscarriages that occurred in the buprenorphine group occurred in the first trimester. Therefore if we observe the gestational age at which all three groups were recruited, this supports the fact that more miscarriages would have been observed in the buprenorphine group compared to the methadone or control groups. Firstly, no mothers from the control group were recruited into the study in the first trimester and it is therefore less likely that miscarriages would be observed in this group. Secondly, significantly more women from the buprenorphine group were recruited into the study in the first trimester compared to methadone maintained mothers and we are therefore more likely to see miscarriages in buprenorphine maintained mothers compared to methadone maintained mothers.

Other obstetric complications for the antenatal period were not significantly different between the three groups. Previous research has reported obstetric complications during pregnancy in 29% of buprenorphine maintained women (Lacroix et al., 2004). If we are to assume that the most serious obstetric complications result in admissions to the Antenatal and Gynecology Ward, the current study reports such complications in 28% of buprenorphine maintained women, which is in accordance with Lacroix and colleagues (2004). In addition the percentage of women who attended WAS, Day Assessment Unit as well as those admitted to the Antenatal and Gynecology Ward were similar for all three groups, as were the reasons for presentation at these services. Therefore, the current study

demonstrates that neither methadone nor buprenorphine maintenance increases the rate of obstetric complications in the antenatal period compared to the general population.

3.4.3. Fetal growth

Fundal height was significantly lower throughout the whole of pregnancy, with the exception of the third trimester alone, for both the methadone and buprenorphine groups compared to the control group. Despite previous research performed reporting disruptions to fetal movement as a result of methadone use (Jansson et al., 2005; Wittmann & Segal, 1991; Wouldes et al., 2004) discussed in Section 1.5.4.1.1, no data has been published to date reporting fetal growth in methadone exposed pregnancies as measured by fundal height. An obvious link that could be made, however, is that disruptions to fetal movement and fetal stress as a result of opioid exposure could possibly lead to decreases in fetal growth and therefore fundal height. Importantly, the present study did not observe significant differences in fundal height between methadone and buprenorphine groups and thus it is possible to conclude that buprenorphine poses no greater risk than methadone in slowing fetal growth.

In addition, for the third trimester alone there was no significant difference in fundal height between the three groups and this may be due to several different reasons. Firstly, as discussed in Section 3.4.1, despite methadone maintained women presenting significantly later for antenatal care than the control group, there was no significant difference in the number of antenatal appointments attended between the three groups throughout pregnancy. Therefore increased antenatal care towards the end of pregnancy to account for late presentation for antenatal care may have resulted in improvements to fetal growth in the third trimester. Secondly, the lack of significant difference in fundal heights in the third trimester may be a reflection of those women induced in the methadone and buprenorphine

groups as a result of small for gestational age (intrauterine growth retardation (IUGR)) having already delivered. This would result in mothers with smaller fundal heights from the treatment groups being excluded from analysis in the latter portion of the third trimester if they have already delivered, and therefore fundal heights would not significantly differ to controls. This aspect along with other indicators of fetal growth including birth weight and infant size will be discussed further in Chapter 5.

3.5. Conclusion

In conclusion, buprenorphine produces similar obstetric outcomes to methadone and control pregnancies when used in the antenatal period. While miscarriages were observed in the buprenorphine group and not in the remaining groups, these were fewer than were predicted based on the general population. In addition, the miscarriages observed may have been due to significantly more women in the buprenorphine group compared to the methadone and control groups being recruited in the first trimester where there is an increased risk of miscarriage. The prevalence of other obstetric complications throughout the antenatal period were similar for both methadone and buprenorphine maintained mothers, and were not dissimilar to the control group as hypothesised. Fetal growth was slower throughout pregnancy in both methadone and buprenorphine maintained women compared to controls, although appeared to have drawn nearer to control outcomes in the third trimester.

4. MATERNAL OUTCOMES: MAINTENANCE THERAPY MEASURES

4.1. Introduction

As mentioned previously in Section 3.1, literature presented in Chapter 1 relating to buprenorphine use during pregnancy has focussed primarily on the effects of buprenorphine on neonatal outcomes, including NAS. Early reports from Johnson and colleagues (2001) indicate maternal liking or acceptance of buprenorphine during pregnancy. According to Fischer and colleagues (1998; 2000; 2006), maternal withdrawal appears to be either absent or no different to methadone. There are, however, conflicting reports as to the effects of additional opioids consumed during pregnancy by mothers maintained on buprenorphine compared to methadone (Fischer et al., 2006; Jones et al., 2005). Therefore buprenorphine's efficacy as a maintenance therapy during pregnancy requires further investigation. The following chapter will present and discuss hypotheses, methods used and results obtained during the antenatal period that relate to BMT outcomes, including maintenance dose, maternal opioid withdrawal, direct maintenance therapy drug effects, additional substance use and symptoms experienced. These outcomes will be compared to methadone maintained mothers, and where applicable, control mothers.

In the first instance hypotheses relating specifically to the current chapter will be presented. Secondly, aspects of the methods described in Chapter 2 that pertain to the current chapter will be presented in more detail where required. Following this, results relating to the aims and hypotheses presented below will be discussed in relation to maintenance therapy outcomes including maternal opioid withdrawal, direct drug effects and other symptoms experienced. Finally, a closing discussion will review all results obtained during the

antenatal period in relation to buprenorphine's efficacy as a maintenance therapy during pregnancy.

4.1.1. Aims and hypotheses

As a result of the lack of data published directly assessing the efficacy and safety of buprenorphine as a maintenance therapy during the antenatal period, the following hypotheses were developed.

4.1.1.1. Maintenance therapy outcomes

4.1.1.1.1. Hypotheses

- Women who are maintained on buprenorphine will experience similar withdrawal symptoms to women maintained on methadone
- Women who are maintained on buprenorphine will have similar direct drug effects to women maintained on methadone
- Women maintained on buprenorphine will suffer similar adverse drug effects to women maintained on methadone
- Buprenorphine will be as efficacious as methadone in terms of treatment outcomes, including maintenance therapy treatment compliance and additional opioid and other substance use

4.2. Methods of data collection

As previously mentioned in Chapter 1 changes in methadone pharmacokinetics during pregnancy, particularly in the third trimester, may lead to maternal withdrawal and its associated signs and symptoms. This may result in a requirement to increase maternal maintenance therapy doses as pregnancy progresses. Therefore, parameters presented in this chapter will be presented and analysed on the basis of data collected throughout the entire pregnancy and, in addition, separated into individual trimesters and compared as appropriate. As women were recruited in the first trimester in the methadone and buprenorphine groups and there was no significant difference between the gestational age at which data collection began in these groups (Section 3.3.1), data can be presented for pregnancy as an entirety and each of the three individual trimesters. However, comparisons to the control group could not be presented in the same manner. As no women in the control group were recruited in the first trimester, maternal outcomes assessed between the three groups were compared starting from gestational week 21, the average gestational age at which the control group (the latest group recruited) was recruited and the third trimester alone assessed.

4.2.1. Maternal withdrawal

Maternal withdrawal severity at each antenatal appointment was determined using a self-report Short Opioid Withdrawal Scale (SOWS) (Gossop, 1990) and objectively using a Clinical Opioid Withdrawal Scale (COWS) (Handelsman et al., 1987). The SOWS is a 19-item scale where subjects tick a box to indicate whether they have experienced a range of symptoms in the previous 24 hours, separated into 4 categories of not at all, a little, moderately or extremely. A minimum score of 0 indicates no withdrawal and a maximum score of 76 indicates severe withdrawal. The COWS is an 11-item scale where the

researcher rates the subject's appearance on 11 signs ranging in severity according to the individual signs observed. A minimum observed score of 0 indicates withdrawal is absent, and a maximum observed score of 36 indicates severe withdrawal.

These two measures of withdrawal were also assessed in the control group as several symptoms that may have been interpreted as signs of opioid withdrawal are non-specific and occur commonly during pregnancy.

4.2.2. Direct maintenance therapy drug effects

Direct maintenance therapy drug effects were measured at each antenatal appointment in the methadone and buprenorphine groups using a 7-item self-reported visual analogue scale (VAS) ranging from 0-10 where each item was a separate question and scored alone (Appendix 1). The questions and their ratings were as follows:

1. "How well has this drug been holding you?": too low-0 to too high-10.
2. "How much of a buzz does this drug give you?": none-0 to a lot-10.
3. "How many side effects do you feel from this drug?": none-0 to a lot-10.
4. "How much do side effects from this drug bother you?": not at all-0 to a lot-10.
5. "How much do you like this drug?": not at all-0 to a lot-10.
6. "Does this drug make you feel more normal?": definitely no-0 to definitely yes-10.
7. "How much do you crave heroin while on this drug?": not at all-0 to a lot-10.

In addition there were 2 open ended questions at the end of this survey that asked the subject to record "What are the best things about this drug?" and "What are the worst things about this drug?".

4.2.3. Additional substance use

Additional substance use in all three groups was monitored at each antenatal appointment using a self-report questionnaire and results of urine analysis from random collection as described below. The self-report questionnaire asked subjects to report their use of the three main categories of drugs that may affect infant withdrawal: additional opioids; cannabis and benzodiazepines (Appendix 2). Subjects were questioned as to whether they had used the substance since their previous appointment and, if so, the number of days in this time period they had used it on.

Where possible, up to 3 random urine samples were collected during the first and second trimester of pregnancy (this was dependent on gestational age at enrolment). In all women 3 random urine samples were collected during the third trimester of pregnancy. Urine analysis detected additional opioids the subject had taken which included all opioid preparations that were both licit and illicit, including codeine (as morphine), oxycodone, morphine and heroin (as morphine). Urine analysis also detected cannabis and all benzodiazepines.

4.2.4. Symptoms check list

Symptoms experienced were monitored in all three groups using a symptom checklist based on a list of adverse events for both methadone and buprenorphine (MIMS Australia, 2001). The symptom checklist was separated into 8 different categories and asked women to state "yes" or "no" as to whether they had experienced symptoms since their previous antenatal appointment in the categories of: body as a whole; digestive system; musculoskeletal system; nervous system; respiratory system; skin and appendages; special senses and other (Appendix 3).

4.3. Results

4.3.1. Maintenance therapy dosing

For all women in the methadone group, including those who were not receiving maintenance therapy at the time of recruitment, the average daily dose at the time of delivery was 48.40 ± 5.95 mg.day^{-1} methadone. For all women in the buprenorphine group, including those who were not maintained at the time of recruitment, the average daily dose at the time of delivery was 7.46 ± 0.84 mg.day^{-1} buprenorphine.

For those women who were already receiving maintenance therapy at the time of recruitment into the study, there was no significant change in their dose from the time of recruitment to the time of delivery in either the methadone or buprenorphine maintained groups (Figure 4-1).

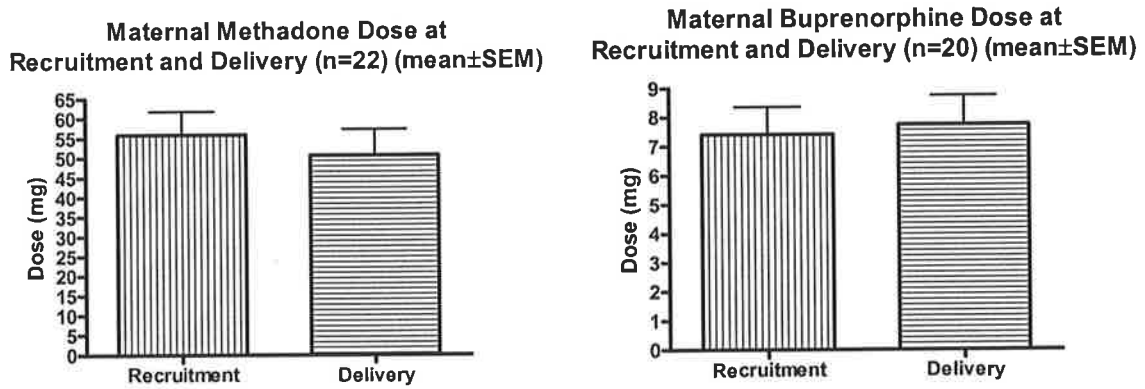

Figure 4-1 Maternal maintenance therapy dose at time of recruitment and delivery for those women in the methadone and buprenorphine groups already participating in maintenance therapy programs at the time of recruitment.

4.3.2. Maternal opioid withdrawal

Maternal opioid withdrawal observations are presented as AUC of maternal withdrawal score versus time (weeks) as discussed in Section 4.2. In addition, data was compared between all three trimesters for the methadone and buprenorphine groups to assess any changes in maternal withdrawal (which may indicate changes in pharmacokinetic parameters of the 2 maintenance therapies) as pregnancy progressed.

4.3.2.1. SOWS

The AUC from week 21 through to delivery for SOWS scores was significantly greater in the methadone compared to both the buprenorphine ($p<0.01$) and control ($p<0.01$) groups. When the third trimester alone was considered, the AUC for the methadone group was significantly higher than the control group ($p<0.001$), however the AUC for the buprenorphine group was not significantly different compared to either the methadone or control group in the third trimester (Figure 4-2).

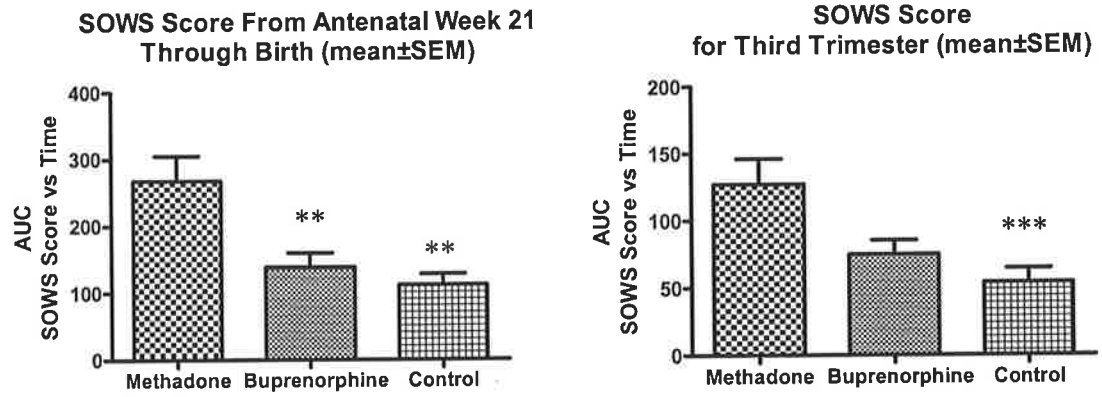

Figure 4-2 AUC SOWS score versus time for pregnancy from gestational week 21 and for the third trimester alone for methadone maintained, buprenorphine maintained and control mothers. **p<0.01, ***p<0.001 compared to methadone.

There was no significant difference in AUC for SOWS score versus time between trimesters for either methadone maintained or buprenorphine maintained women (Figure 4-3).

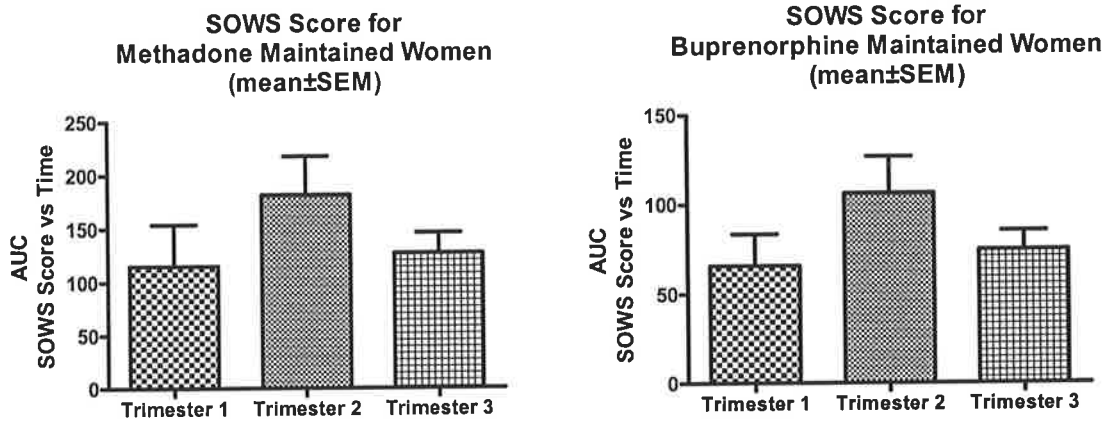

Figure 4-3 Comparison of AUC SOWS score versus time between trimesters for methadone and buprenorphine maintained women.

4.3.2.2. COWS

The AUC from week 21 through to delivery for COWS scores was significantly greater for methadone compared to buprenorphine maintained women ($p<0.05$), however the AUC for control women was not significantly different to either the methadone or buprenorphine groups. When the third trimester alone was considered the AUC was significantly greater for methadone maintained compared to control women ($p<0.05$), however the AUC for buprenorphine maintained women was not significantly different to either the methadone or the control group (Figure 4-4).

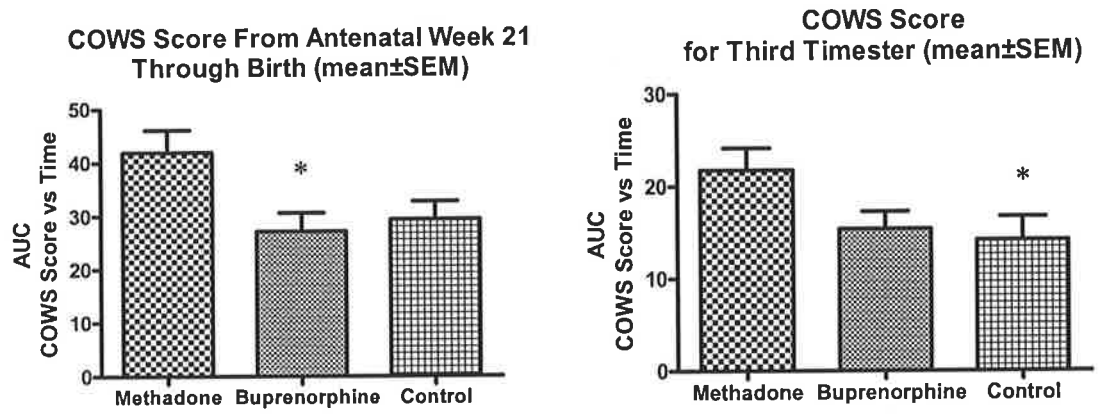

Figure 4-4 AUC COWS score versus time for pregnancy from gestational week 21 and for the third trimester alone for methadone maintained, buprenorphine maintained and control mothers. *p<0.05 compared to methadone.

There was no significant difference in AUC for COWS score versus time between trimesters for either methadone maintained or buprenorphine maintained women (Figure 4-5).

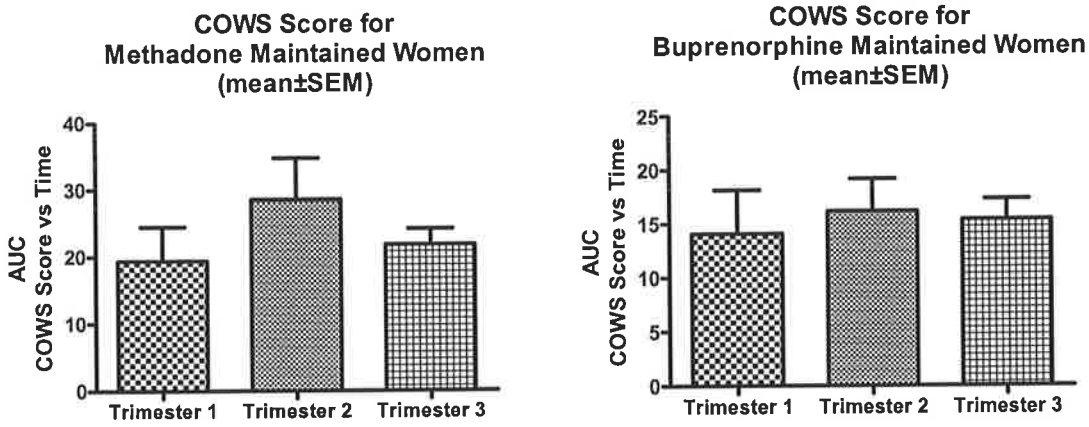

Figure 4-5 Comparison of AUC COWS score versus time between trimesters for methadone and buprenorphine maintained women.

4.3.3. Direct maintenance therapy drug effects

Results for direct drug effects are again presented as AUC of VAS score versus time (weeks). As there was no significant difference in the gestational age at which methadone and buprenorphine maintained mothers were recruited, all results from recruitment through to delivery were compared between the two groups.

4.3.3.1. Holding ability

There was no significant difference in the AUC for VAS holding scores between methadone and buprenorphine maintained groups, which is indicative of the ability of the maintenance therapy to suppress withdrawal symptoms over a 24-hour dosing period. In addition, when the trimesters were assessed individually there was no significant difference between the two groups in either the first, second or third trimester (Figure 4-6).

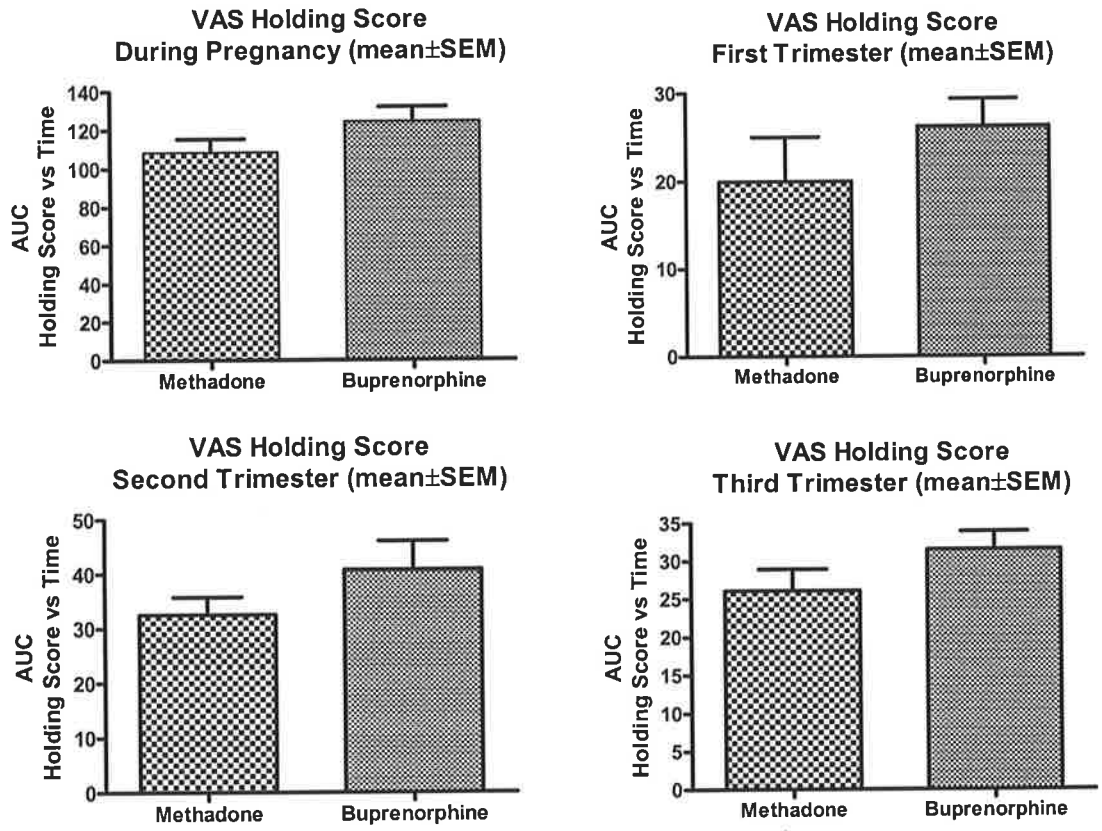

Figure 4-6 AUC VAS holding score versus time throughout pregnancy and the individual trimesters alone for methadone and buprenorphine maintained women.

There was no significant difference in AUC for VAS holding score versus time between trimesters for either methadone or buprenorphine maintained women (Figure 4-7).

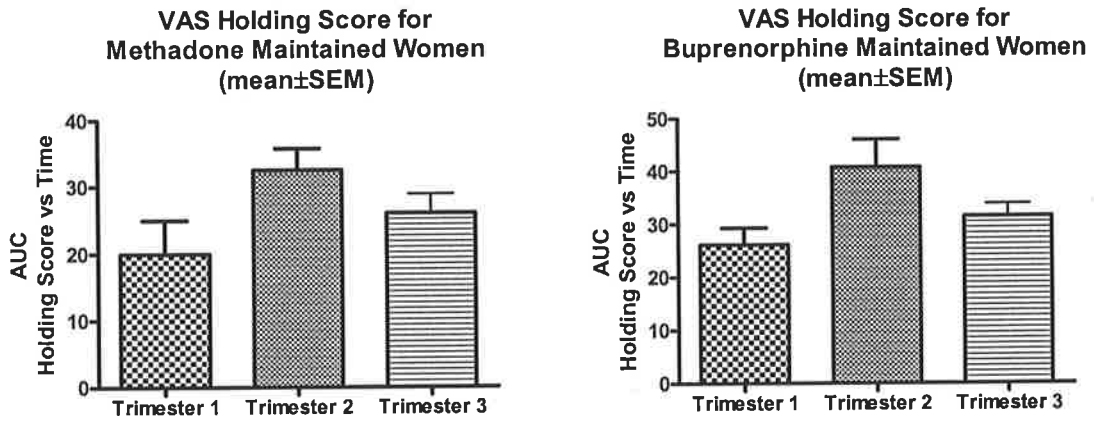

Figure 4-7 Comparison of AUC VAS holding score versus time between trimesters for methadone and buprenorphine maintained women.

4.3.3.2. Buzz experience

There was no significant difference in the AUC for VAS buzz experience scores between the methadone and buprenorphine maintained groups when throughout pregnancy or the individual trimesters alone (Figure 4-8).

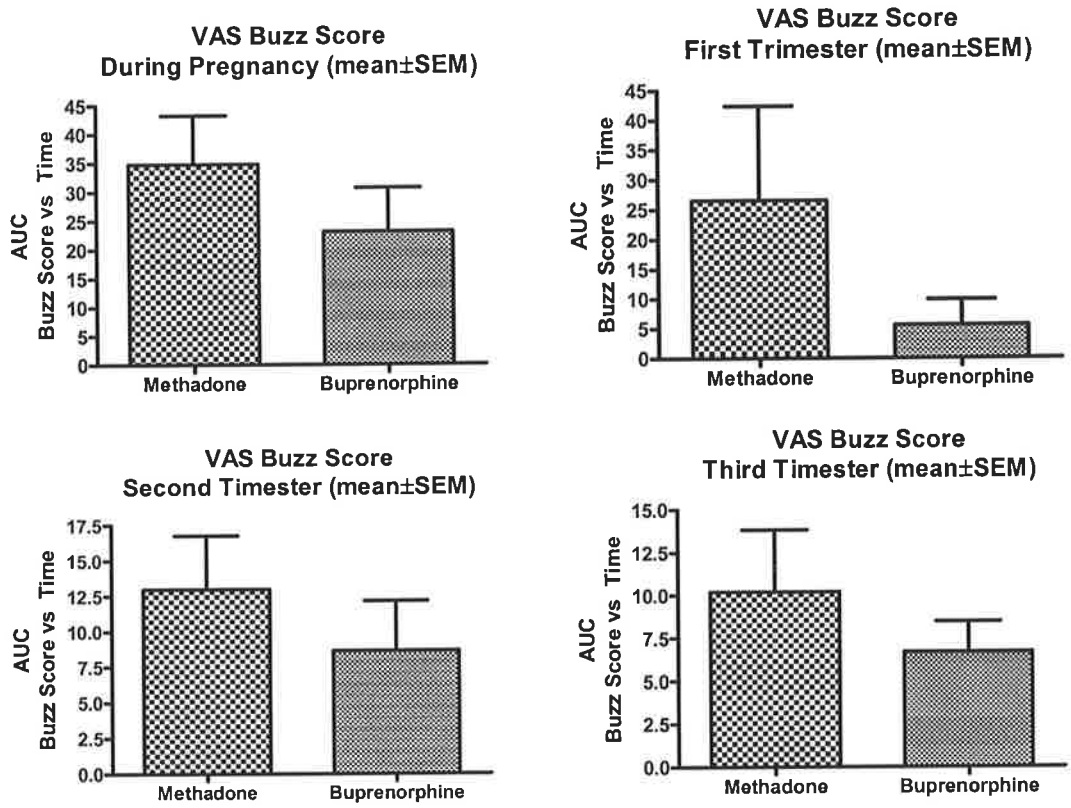

Figure 4-8 AUC VAS buzz score versus time throughout pregnancy and the individual trimesters alone for methadone and buprenorphine maintained women.

There was no significant difference in AUC for VAS buzz score versus time between trimesters for either methadone or buprenorphine maintained women (Figure 4-9).

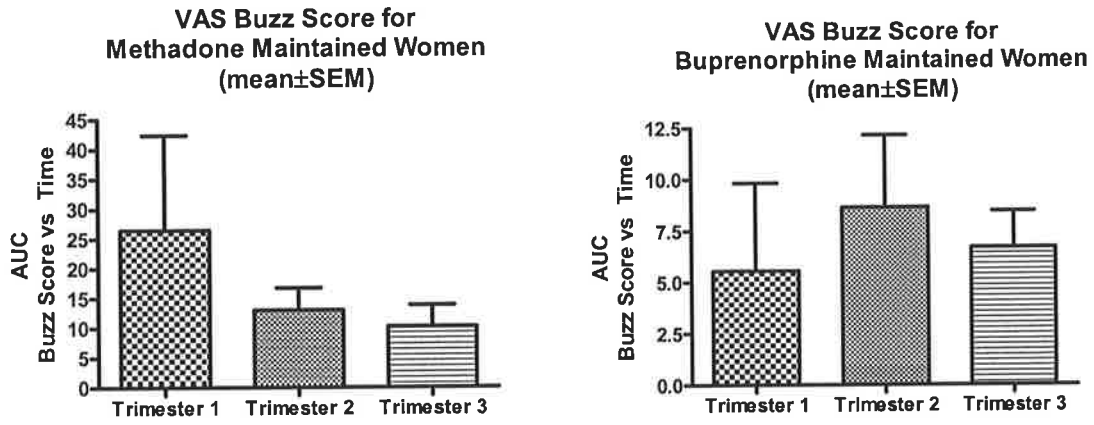

Figure 4-9 Comparison of AUC VAS buzz score versus time between trimesters for methadone and buprenorphine maintained women.

4.3.3.3. Prevalence of side effects

There was no significant difference in AUC for VAS prevalence of side effects scores between the methadone and buprenorphine maintained groups when assessed throughout pregnancy or the individual trimesters alone (Figure 4-10).

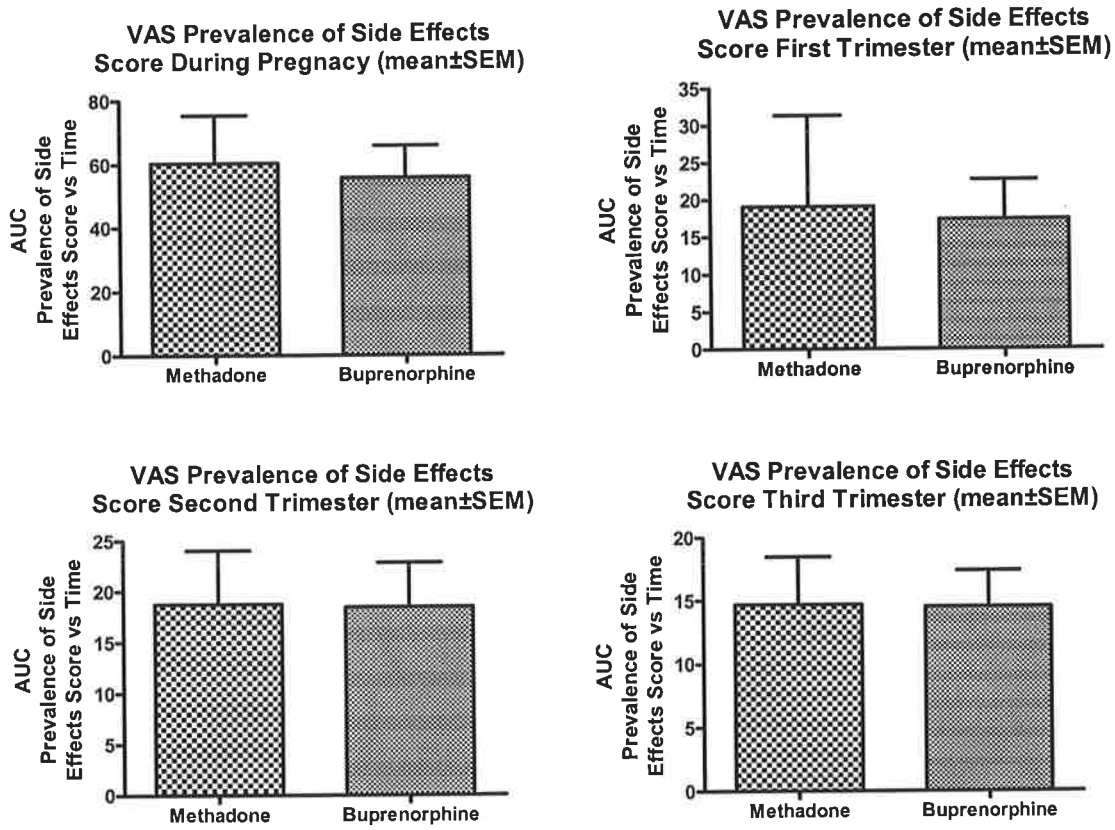

Figure 4-10 AUC VAS prevalence of side effects score versus time throughout pregnancy and the individual trimesters alone for methadone and buprenorphine maintained women.

There was no significant difference in AUC for VAS prevalence of side effects score versus time between trimesters for either methadone or buprenorphine maintained women (Figure 4-11).

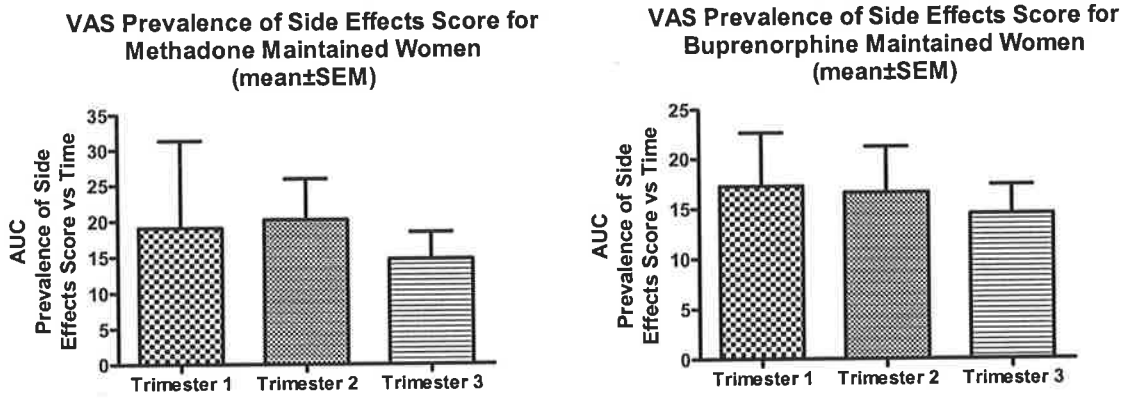

Figure 4-11 Comparison of AUC VAS prevalence of side effects score versus time between trimesters for methadone and buprenorphine maintained women.

4.3.3.4. Inconvenience of side effects

There was no significant difference in AUC for VAS inconvenience of side effects scores between the methadone and buprenorphine maintained groups when assessed throughout pregnancy or the individual trimesters alone (Figure 4-12).

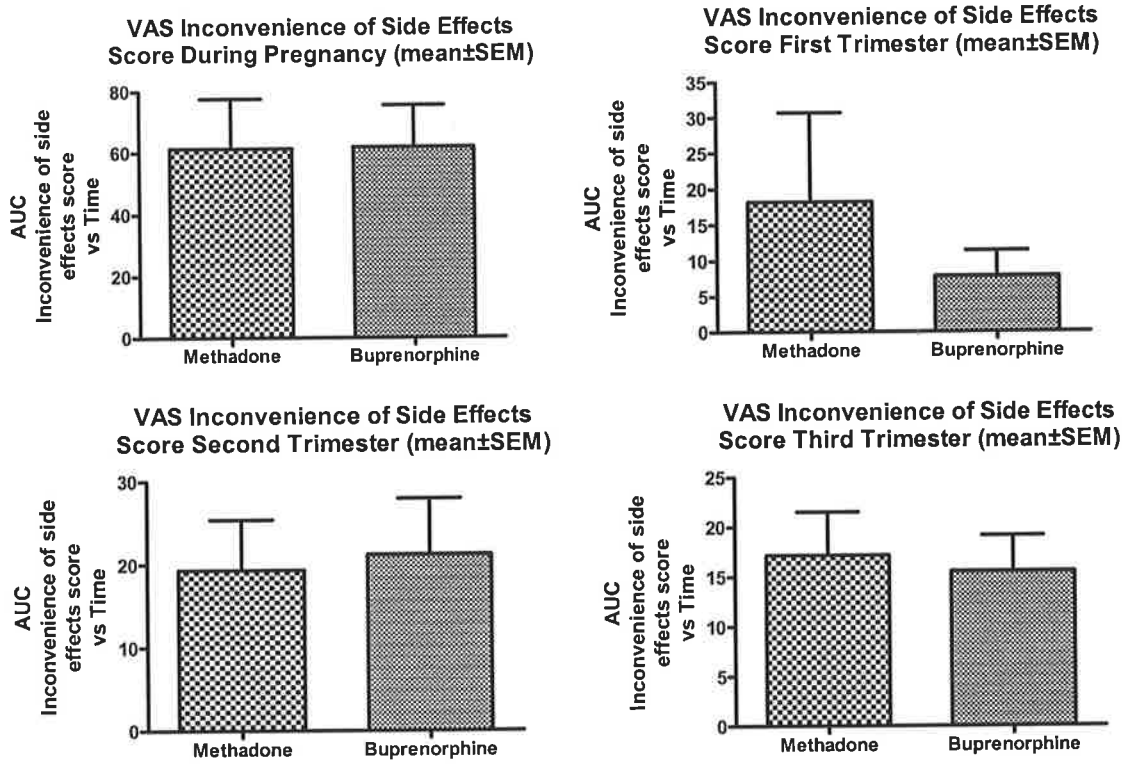

Figure 4-12 AUC VAS inconvenience of side effects score versus time throughout pregnancy and the individual trimesters alone for methadone and buprenorphine maintained women.

There was no significant difference in AUC for VAS inconvenience of side effects score versus time between trimesters for either methadone or buprenorphine maintained women (Figure 4-13).

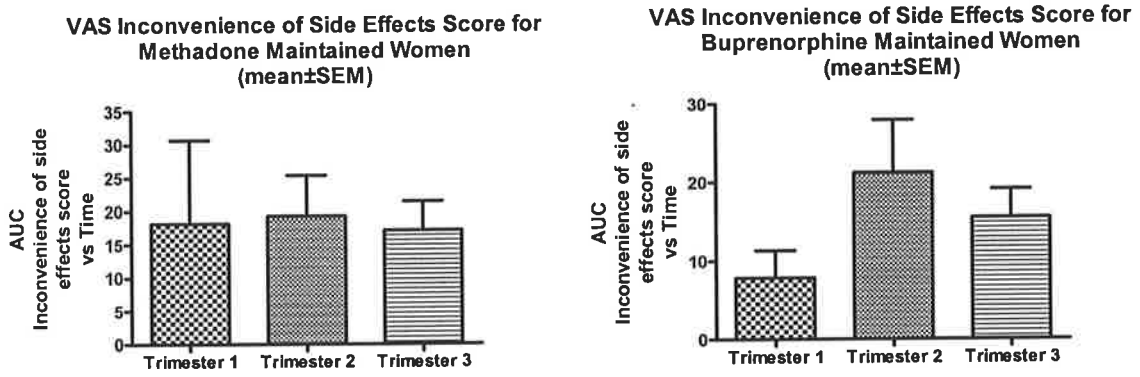

Figure 4-13 Comparison of AUC VAS inconvenience of side effects score versus time between trimesters for methadone and buprenorphine maintained women.

4.3.3.5. Drug liking/acceptability

The AUC for VAS drug liking score was significantly greater for the buprenorphine group compared to the methadone group throughout pregnancy ($p<0.01$) as well as the second trimester alone ($p<0.01$). In contrast, there was no significant difference between the 2 groups for the first and third trimester (Figure 4-14).

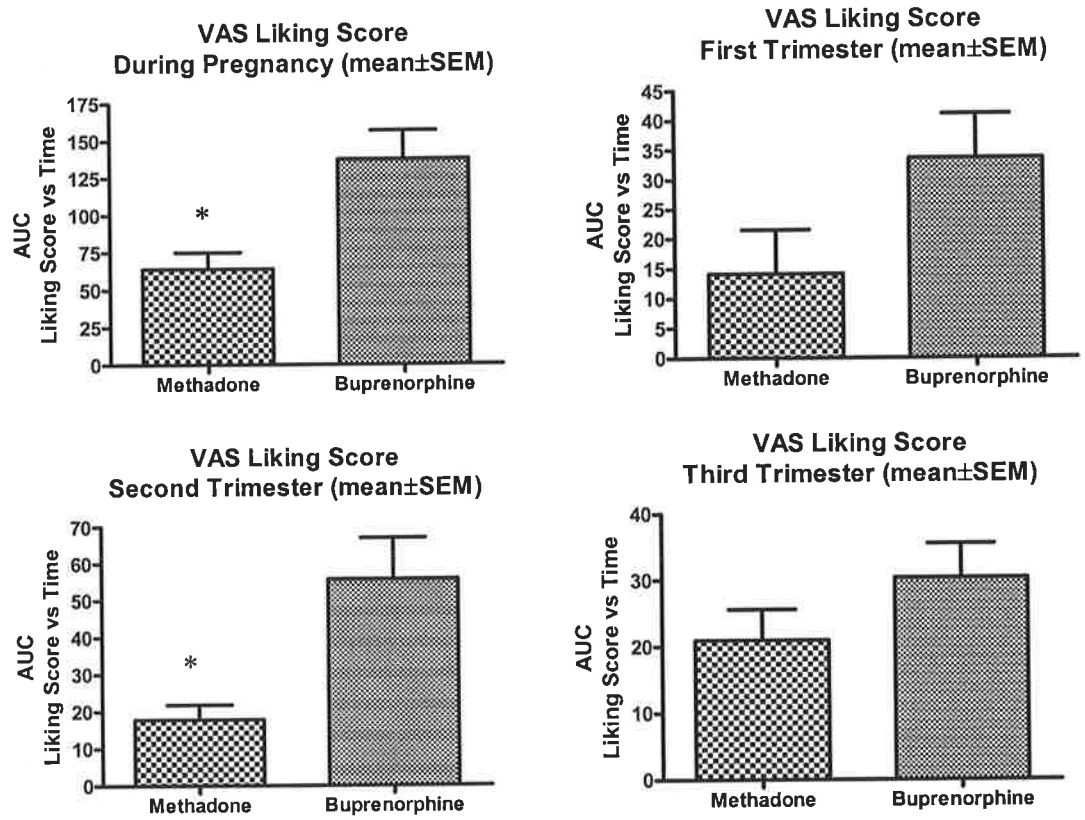

Figure 4-14 AUC VAS liking score versus time throughout pregnancy and the individual trimesters alone for methadone and buprenorphine maintained women. *p<0.05 compared to buprenorphine.

There was no significant difference in AUC for VAS liking score versus time between trimesters for either methadone or buprenorphine maintained women (Figure 4-15).

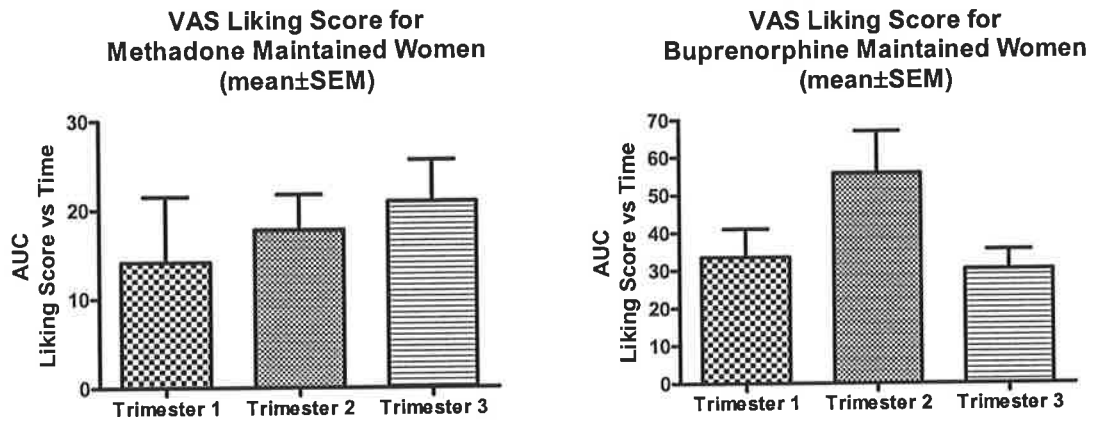

Figure 4-15 Comparison of AUC VAS liking score versus time between trimesters for methadone and buprenorphine maintained women.

4.3.3.6. Feeling of normal

There was no significant difference in the AUC for VAS normal scores between the methadone and buprenorphine maintained groups when assessed throughout pregnancy or the individual trimesters alone (Figure 4-16).

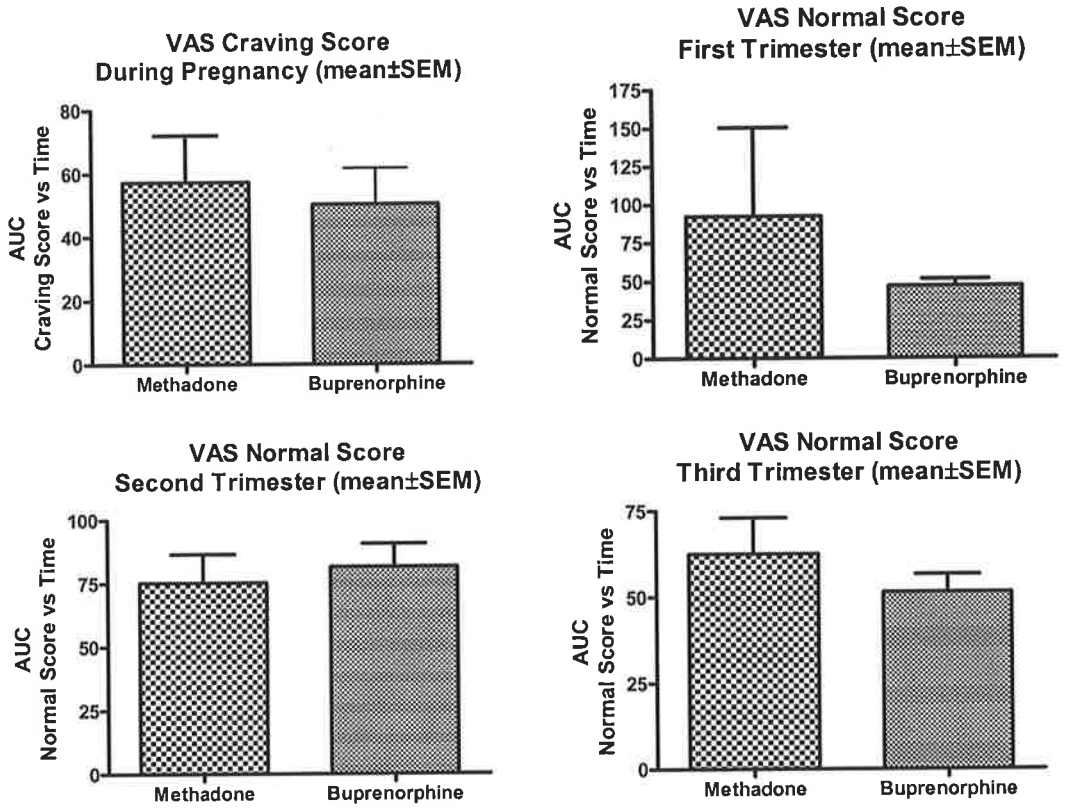

Figure 4-16 AUC VAS normal score versus time throughout pregnancy and the individual trimesters alone for methadone and buprenorphine maintained women.

There was no significant difference in AUC for VAS normal score versus time between trimesters for methadone maintained women. Normality scores were significantly higher for buprenorphine maintained women in the second trimester compared to both the first and third trimester ($p<0.05$) Figure 4-17.

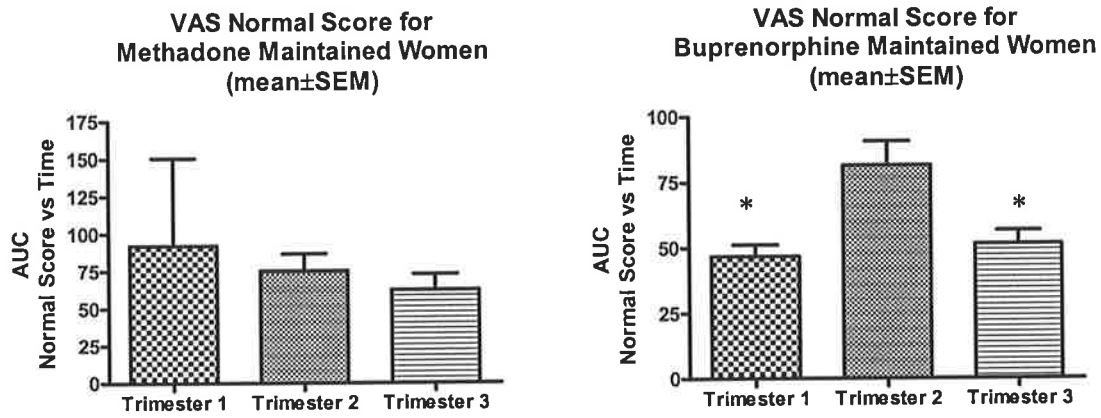

Figure 4-17 Comparison of AUC VAS normal score versus time between trimesters for methadone and buprenorphine maintained women. *p<0.05 compared to trimester 2.

4.3.3.7. Opioid craving

There was no significant difference in the AUC for VAS additional opioid craving scores between the methadone and buprenorphine maintained groups when assessed throughout pregnancy or the individual trimesters alone (Figure 4-18).

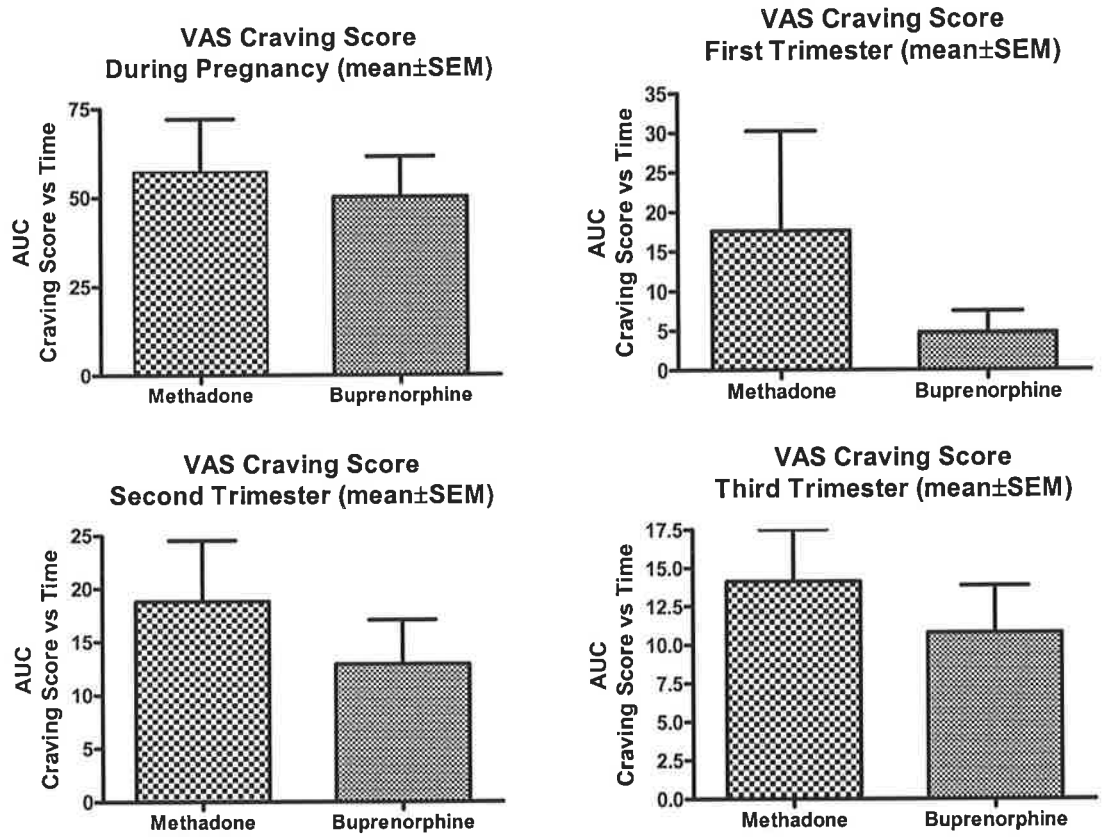

Figure 4-18 AUC VAS craving score versus time throughout pregnancy and the individual trimesters alone for methadone and buprenorphine maintained women.

There was no significant difference in AUC for VAS craving score versus time between trimesters for either methadone or buprenorphine maintained women (Figure 4-19).

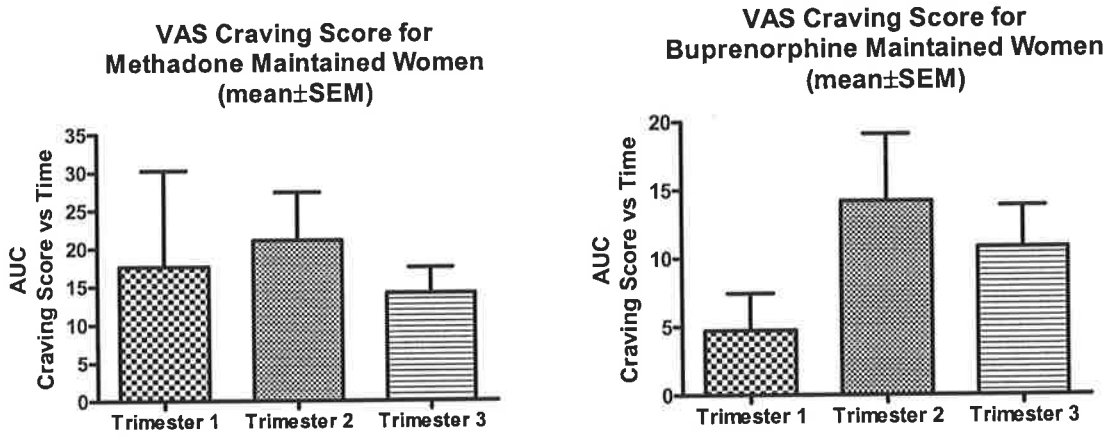

Figure 4-19 Comparison of AUC VAS craving score versus time between trimesters for methadone and buprenorphine maintained women.

4.3.3.8. Best aspects of maintenance therapy

Table 4-1 categorises the most common best aspects of each maintenance therapy for methadone and buprenorphine maintained women. It should be noted that women may have reported more than one best aspect of maintenance therapy on different scoring occasions. None of the aspects reported were significantly different between the methadone and buprenorphine groups.

Table 4-1 Best aspects of maintenance therapy during pregnancy for methadone and buprenorphine maintained women.

Best aspects	**Methadone (n, (%))**	**Buprenorphine (n, (%))**
Feeling normal	16 (64)	12 (48)
Not wanting/using or stopped heroin use	14 (56)	7 (28)
No withdrawal/hanging	12 (48)	10 (40)
No craving	6 (24)	7 (28)
Helps with pain	3 (12)	3 (12)
Helps with sleeping	3 (12)	1 (4)
Good for baby	2 (8)	2 (8)
Stability	2 (8)	4 (16)
Feeling well/healthy/not feeling sick	4 (16)	3 (12)
Holding	2 (8)	1 (4)
Cost	3 (12)	1 (4)
Ability to relax/not stress	1 (4)	3 (12)
Stopped iv drug use	1 (4)	1 (4)
No/minimal side effects	-	4 (16)
Ability to cope/function/get on with life	2 (8)	4 (16)
No need to score	1 (4)	1 (4)
Better than methadone/more clear headed	-	9 (36)

Women in the methadone group also mentioned other best aspects of the drug such as: "not having to commit crime or prostitution"; children do not have to see the subject stoned; "a chance to repair broken relationships"; feeling more human; and also seeing methadone as the road to being off opiates. Women in the buprenorphine group also mentioned the best aspects of buprenorphine such as: that "when buprenorphine works it works well"; that "if you use heroin on top then nothing happens"; buprenorphine makes them a nicer, better person; and that buprenorphine is a very effective drug after the induction period. One woman also mentioned it to be "no more monkey on her back feeling", another that it helps her with her drugs, and finally one woman mentioned the best aspects to be that it was easily accessible through chemists and that the absorption is not affected when vomiting occurs.

4.3.3.9. Worst aspects of maintenance therapy

Table 4-2 categorises the most common worst aspects of each maintenance therapy for women in the methadone and buprenorphine groups. Once again it should be noted that women may have reported more than one worst aspect of maintenance therapy on different scoring occasions. Significantly more women in the methadone group reported that they just did not like the drug or being on the drug compared to the buprenorphine group (methadone 28%, buprenorphine 4%; $p<0.05$). Significantly more women in the buprenorphine group reported that they did not like the side effects of the drug compared to the methadone group (methadone 4%; buprenorphine 28%, $p<0.05$). No other worst aspects reported were significantly different between the two groups.

Table 4-2 Worst aspects of maintenance therapy during pregnancy for methadone and buprenorphine maintained women.

Worst aspects	Methadone (n, (%))	Buprenorphine (n, (%))
Addictive drug/being dependent on it	11 (44)	6 (24)
Picking up all the time	9 (36)	9 (36)
Withdrawal from the drug	8 (32)	5 (20)
The drug/just being on it	7 (28)*	1 (4)
Being chained down/held back by it	8 (32)	-
Feeling sick	5 (20)	2 (8)
Having to rely on it to function	4 (16)	-
Stigma	3 (12)	-
Does not mask pain	3 (12)	-
Constipation	3 (12)	5 (20)
Dose not holding	1 (4)	1 (4)
Taste	2 (8)	6 (24)
Expense	2 (8)	-
Induction period	1 (4)	2 (8)
Side effects (including nausea, headaches, dizziness, loss of appetite, vomiting, feeling faint or weird, depression, itchiness)	1 (4)*	7 (28)

*$p<0.05$ compared to buprenorphine

Other comments made by women in the methadone group regarding the worst aspects of the drug were that "it seems to be just another substitute which you become immune to" and that it was "fear of the unknown". Another woman commented on "not feeling normal until 'done kicks in". Another woman raised concerns about preparing herself to come down and wondering what will happen when she comes off. Another woman felt that being on methadone was a "false normality", and finally one woman commented on the worst aspect of methadone being "nodding off".

Additional comments made by women in the buprenorphine group were "feeling like a test dummy or guinea pig". The same woman also commented on not knowing what the long-term effects of buprenorphine were on her body and also how much it would affect her baby. Along similar lines one woman commented on the worst thing while being on buprenorphine was being pregnant. Another woman commented on feeling normal when she didn't want to, and finally one woman commented on still being able to get "stoned" while taking buprenorphine.

4.3.4. Additional substance use

4.3.4.1. Prevalence of additional substance use

Table 4-3 highlights additional substance use in the three groups from gestational week 21 and also in the 4 weeks prior to delivery where if substance use occurs the infant is most likely to suffer withdrawal as a result of exposure to the drug. Results presented are combined urine analysis test results and self-report. A positive result was recorded if women either self-reported to substance use, or urine analysis was positive for the particular substance.

Results were not able to be included for one woman in the buprenorphine group (B31) for 4 weeks prior to delivery as the last antenatal appointment she attended was at 31 weeks and she delivered at 38 weeks. For the same reason, results could also not be included for 3 women in the methadone group for 4 weeks prior to delivery. The first woman (M12) attended her last antenatal appointment at 35 weeks and delivered at 39 weeks, the second (M16) attended her last antenatal appointment at 27 weeks and delivered at 36 weeks and the third woman (M28) attended her last antenatal appointment at 29 weeks and also delivered at 36 weeks.

Table 4-3 Prevalence of additional substance use from gestational week 21 for women in the methadone maintained, buprenorphine maintained and control groups.

		Methadone (n, (%))	**Buprenorphine (n, (%))**	**Control (n, (%))**
Additional opioids	All pregnancy	18 (72)*	18 (72)*	8 (32)
	4 weeks prior to delivery	12 (55)	12 (50)	6 (25)
Benzodiazepines	All pregnancy	15 (60)**	13 (52)**	3 (12)
	4 weeks prior to delivery	9 (41)**	4 (17)	1 (4)
Cannabis	All pregnancy	21 (84)****	21 (84)****	5 (20)
	4 weeks prior to delivery	17 (77)***	18 (75)***	5 (21)

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 compared to control

Significantly more women in both the methadone and buprenorphine groups used additional opioids during their pregnancy compared to control women (methadone 72%, buprenorphine 72%, control 32%; $p<0.05$), however there was no significant difference between methadone and buprenorphine groups. There was also no significant difference between the three groups for additional opioid use in the 4 weeks prior to delivery.

Significantly more women in the methadone and buprenorphine groups used benzodiazepines during their pregnancy (methadone 60%, buprenorphine 52%, control 12%; $p<0.01$) than control women, however there was no significant difference between use in the methadone and buprenorphine groups. In the 4 weeks prior to delivery, significantly more women in the methadone group used benzodiazepines than women in the control group (methadone 41%, control 4%; $p<0.01$). In contrast, there was no significant difference between the methadone and buprenorphine or buprenorphine and control groups for benzodiazepine use.

Significantly more women in the methadone and buprenorphine groups used cannabis during their pregnancy (methadone 84%, buprenorphine 84%, control 20%; $p<0.0001$) and in the 4 weeks prior to delivery (methadone 77%, buprenorphine 75%, control 21%; $p<0.001$) than control women. There was no significant difference between the methadone and buprenorphine groups for cannabis use throughout pregnancy or in the 4 weeks prior to delivery.

4.3.4.2. Frequency of additional substance use

For those women who were able to report the number of days they had used a substance, results in Table 4-4 reveal the percentage of days (mean ± SEM) the women had used the substance compared to the number of days she was involved in the study. For example, if a

woman was involved in the study for 50 days and reported the number of days she had used a substance to be 25 days, the percentage of days she used would be 50%. For the 4 weeks prior to delivery, if women used daily this was reported as 100% of the 28 days. Results are again separated into the percentage of days used from gestational week 21 and the percentage of days used in the 4 weeks prior to delivery.

Table 4-4 Frequency of additional substance use presented as percentage of days involved in the study amongst those women who used and were able to report the frequency of use (for prevalence of additional substance use among women refer Table 4-3).

		Methadone % days	**Buprenorphine % days**	**Control % days**
Additional opioids	All pregnancy	14.64 ± 3.97*	13.85 ± 2.89**	1.70 ± 0.46
	4 weeks prior to delivery	20.67 ± 5.91	8.57 ± 0.97	5.95 ± 1.06
Benzodiazepines	All pregnancy	44.00 ± 11.37	14.61 ± 7.62	1.12 ± 0.19
	4 weeks prior to delivery	76.32 ± 13.34	55.95 ± 25.45	3.57 ± 0.00
Cannabis	All pregnancy	52.31 ± 8.79	44.58 ± 7.99	57.71 ± 13.25
	4 weeks prior to delivery	57.14 ± 11.30	50.15 ± 10.15	76.66 ± 14.30

*p<0.05, **p<0.01 compared to control

As a percentage of days involved in the study both methadone and buprenorphine maintained mothers used additional opioids for longer during pregnancy compared with control mothers (methadone 14.64 ± 3.97%; p<0.05, buprenorphine 13.85 ± 2.89%; p<0.01, control 1.70 ± 0.46%). There was no significant difference between the three

groups for additional opioid use in the 4 weeks prior to delivery. There was also no significant difference between the three groups for benzodiazepine or cannabis use from gestational week 21 or in the 4 weeks prior to delivery.

4.3.5. Symptoms checklist

Results obtained for the symptom checklist were separated into two main categories: symptoms experienced during pregnancy from the gestational age of week 21 (for reasons explained in Section 4.2); and those symptoms experienced only in the third trimester. As one woman in the methadone groups did not attend any antenatal appointments in the third trimester, percentages of women who experienced an individual symptom are calculated out of a total of 24. Each category is further separated into sections of symptoms experienced: Body as a Whole, Digestive System, Musculo-skeletal System, Nervous System, Respiratory System, Skin and Appendages and Special Senses. Symptoms reported at least once were included in the analysis.

4.3.5.1. Symptoms experienced during pregnancy from gestational week 21

Table 4-5 presents the percentage of women in each group reporting symptoms experienced at least once during pregnancy from gestational week 21 for Body as a Whole section of the symptom checklist.

Table 4-5 Symptoms experienced from gestational week 21 for the body as a whole for methadone maintained, buprenorphine maintained and control women.

Body as a Whole	Methadone (n(%))	Buprenorphine (n(%))	Control (n(%))
Fatigue	25(100)	25(100)	23(92)
Chills	21(84)**	14(56)	9(36)
Fever	22(88)	20(80)	15(60)
Headache	22(88)	19(76)	20(80)
Pain	17(68)	16(64)	15(60)
Pain abdominal	23(92)	22(88)	22(88)
Pain back	22(88)	24(96)	25(100)

**p<0.01 compared to control

Significantly more women in the methadone group experienced chills compared to women in the control group (methadone 84%, control 36%; p<0.01) however, there was no significant difference between women in the buprenorphine group and the remaining 2 groups.

Table 4-6 presents the percentage of women in each group reporting symptoms experienced at least once during pregnancy from gestational week 21 for the Digestive System section of the symptom checklist.

Table 4-6 Symptoms experienced from gestational week 21 for the digestive system for methadone maintained, buprenorphine maintained and control women.

Digestive System	Methadone (n(%))	Buprenorphine (n(%))	Control (n(%))
Loss of appetite	22(88)**	20(80)	11(44)
Constipation	20(80)	18(72)	17(68)
Diarrhoea	8(32)	9(36)	11(44)
Dry mouth	22(88)****	13(52)	12(48)
Indigestion	20(80)	22(88)	22(88)
Nausea	23(92)	22(88)	20(80)
Nausea + vomiting	23(92)**	22(88)	15(60)
Vomiting	23(92)***	23(92)***	13(52)

**p<0.01, ***p<0.001 compared to control

****p<0.01 compared to buprenorphine

Significantly more women in the methadone group experienced loss of appetite compared to women in the control group (methadone 88%, control 44%; p<0.01). However there was no significant difference between women in the buprenorphine group and the remaining 2 groups. Significantly more women in the methadone group experienced dry mouth compared to women in both the buprenorphine and control groups (methadone 88%, buprenorphine 52%, control 48%; p<0.01). Nausea and vomiting were experienced by significantly more women in the methadone than the control group (methadone 92%,

control 60%; p<0.01), however there was no significant difference between the buprenorphine and the 2 remaining groups. Significantly more women in both the methadone and buprenorphine group experienced vomiting alone compared to the control group (methadone 92%, buprenorphine 92%, control 52%; p<0.01).

Table 4-7 presents the percentage of women in each group reporting symptoms experienced at least once during pregnancy from gestational week 21 for the Musculo-skeletal System section of the symptom checklist.

Table 4-7 Symptoms experienced from gestational week 21 for the musculo-skeletal system for methadone maintained, buprenorphine maintained and control women.

Musculo-skeletal System	**Methadone (n(%))**	**Buprenorphine (n(%))**	**Control (n(%))**
Joint pain	19(76)	19(76)	16(64)
Muscle pain	23(92)	17(68)	17(68)
Bone pain	16(64)	16(64)	15(60)

There was no significant difference between the three groups for symptoms experienced in this category.

Table 4-8 presents the percentage of women in each group reporting symptoms experienced at least once during pregnancy from gestational week 21 for the Nervous System section of the symptom checklist.

Table 4-8 Symptoms experienced from gestational week 21 for the nervous system for methadone maintained, buprenorphine maintained and control women.

Nervous System	Methadone (n(%))	Buprenorphine (n(%))	Control (n(%))
Agitation	22(88)	18(72)	17(68)
Anxiety	22(88)	19(76)	18(72)
Depression	21(84)*	18(72)	12(48)
Abnormal or vivid dreams	20(80)	21(84)	18(72)
Muscle tension	22(88)	19(76)	20(80)
Insomnia	23(92)	18(72)	20(80)
Nervousness	20(80)*	15(60)	10(40)
Somnolence	15(60)	12(48)	8(32)
Tremor	7(28)	6(24)	1(4)
Twitch	10(40)**	5(20)	1(4)
Dizzy spells	19(76)	17(68)	18(72)

*p<0.05, **p<0.01 compared to control

Significantly more women in the methadone group experienced depression, nervousness and twitches compared to women in the control groups, however there was no significant difference between the buprenorphine group and the remaining two groups (depression: methadone 84%, control 48%; p<0.05, nervousness: methadone 80%, control 40%; p<0.05, twitches: methadone 40%, control 4%; p<0.01).

Table 4-9 presents the percentage of women in each group reporting symptoms experienced at least once during pregnancy from gestational week 21 for the Respiratory System section of the symptom checklist.

Table 4-9 Symptoms experienced from gestational week 21 for the respiratory system for methadone maintained, buprenorphine maintained and control women.

Respiratory System	Methadone (n(%))	Buprenorphine (n(%))	Control (n(%))
Shortness of breath	22(88)	24(96)	20(80)
Hiccup	6(24)	8(32)	11(44)
Sniffily nose	21(84)	23(92)	24(96)

There was no significant difference between the three groups for symptoms experienced in this category.

Table 4-10 presents the percentage of women in each group reporting symptoms experienced at least once during pregnancy from gestational week 21 for the Skin and Appendages section of the symptom checklist.

Table 4-10 Symptoms experienced from gestational week 21 for the skin and appendages for methadone maintained, buprenorphine maintained and control women.

Skin and Appendages	**Methadone (n(%))**	**Buprenorphine (n(%))**	**Control (n(%))**
Acne	9(36)	5(20)	9(36)
Dermatitis	8(32)	3(12)	8(32)
Rash	9(36)	4(16)	10(40)
Sweat	25(100)*** ♣♣♣	16(64)	14(56)

***p<0.001 compared to control

♣♣♣p<0.001 compared to buprenorphine

Significantly more women in the methadone group experienced sweats compared to women in both the buprenorphine and control groups (methadone 100%, buprenorphine 64%, control 56%; p<0.001).

Table 4-11 presents the percentage of women in each group reporting symptoms experienced at least once during pregnancy from gestational week 21 for the Special Senses section of the symptom checklist.

Table 4-11 Symptoms experienced from gestational week 21 for the special senses for methadone maintained, buprenorphine maintained and control women.

Special Senses	Methadone (n(%))	Buprenorphine (n(%))	Control (n(%))
Dry eyes	9(36)	3(12)	8(32)
Watery eyes	19(76)*	10(40)	12(48)
Photophobia	15(60)****	6(24)	6(24)
Strange tastes	16(64)	15(60)	10(40)
Reduced libido	19(76)	17(68)	16(64)

**p<0.01 compared to control

*p<0.05, **p<0.001 compared to buprenorphine

Significantly more women in the methadone group experienced watery eyes than women in the buprenorphine group however there was no significant difference between women in the control group and the remaining 2 groups (methadone 76%, buprenorphine 40%; p<0.05). In addition, significantly more women in the methadone group experienced photophobia compared to women in both the buprenorphine and control groups (methadone 60%, buprenorphine 44%, control 24%; p<0.01).

Other symptoms or conditions reported during pregnancy from gestational week 21 were oedema (methadone 12%, buprenorphine 16%, control 32%), cold or flu (methadone 28%, buprenorphine 24%, control 52%), chest infection/cough/bronchitis (methadone 12%,

buprenorphine 8%, control 24%), food poisoning (methadone 4%), varicose veins (methadone 4%, buprenorphine 8%, control 4%), tooth ache (methadone 20%, buprenorphine 24%, control 20%), haemorrhoids (methadone 4%, control 4%), blocked sinuses (control 4%), gastroenteritis (buprenorphine 4%, control 8%), throat/ear infection (buprenorphine 4%, control 4%), UTI (buprenorphine 4%, control 4%), gestational diabetes (control 4%), nose bleeds (control 4%), thrush (buprenorphine 4%, control 4%), strange smells (buprenorphine 4%), yawning (buprenorphine 4%), itchy (buprenorphine 4%), sprained ankle (buprenorphine 4%), heart palpitations (methadone 4%, buprenorphine 4%), tingling fingers (buprenorphine 4%), abscess/infection (methadone 4%) and viral infection (buprenorphine 4%). None of the above mentioned symptoms were significantly different between the three groups.

4.3.5.2. Third trimester

Table 4-12 presents the percentage of women in each group reporting symptoms experienced at least once in the third trimester for the Body as a Whole section of the symptom checklist.

Table 4-12 Symptoms experienced in the third trimester of pregnancy for the body as a whole for methadone maintained, buprenorphine maintained and control women.

Body as a Whole	Methadone (n(%))	Buprenorphine (n(%))	Control (n(%))
Fatigue	24(100)	24(96)	23(92)
Chills	15(63)	12(48)	9(36)
Fever	18(75)	19(76)	13(52)
Headache	20(83)	17(68)	17(68)
Pain	14(58)	12(48)	15(60)
Pain abdominal	21(88)	21(84)	21(84)
Pain back	20(83)	23(92)	25(100)

There was no significant difference between the three groups for symptoms experienced in this category.

Table 4-13 presents the percentage of women in each group reporting symptoms experienced at least once in the third trimester for the Digestive System section of the symptom checklist.

Table 4-13 Symptoms experienced in the third trimester of pregnancy for the digestive system for methadone maintained, buprenorphine maintained and control women.

Digestive System	Methadone (n(%))	Buprenorphine (n(%))	Control (n(%))
Loss of appetite	22(92)***	19(76)***	10(40)
Constipation	18(75)*	18(72)	11(44)
Diarrhoea	5(21)	6(24)	9(36)
Dry mouth	17(71)	16(64)	11(44)
Indigestion	19(79)	18(72)	22(88)
Nausea	20(83)	21(84)	20(80)
Nausea +vomit	19(79)	22(88)*	13(52)
Vomit	18(75)**	21(84)**	11(44)

*p<0.05, **p<0.01, ***p<0.001 compared to control

Loss of appetite was experienced by significantly more women in both the methadone and buprenorphine groups compared to the control group (methadone 92%, buprenorphine 76%, control 40%; p<0.001). Significantly more women in the methadone group experienced constipation compared to women in the control group (methadone 75%, control 44%; p<0.05). Significantly more women in the buprenorphine group experienced nausea and vomiting compared to the control group, however the methadone group was not significantly different to the two remaining groups (buprenorphine 88%, control 52%; p<0.05). Significantly more women in both the methadone and buprenorphine groups experienced vomiting alone compared to the control group (methadone 75%, buprenorphine 84%, control 44%; p<0.01).

Table 4-14 presents the percentage of women in each group reporting symptoms experienced at least once in the third trimester for the Musculo-skeletal System section of the symptom checklist.

Table 4-14 Symptoms experienced in the third trimester of pregnancy for the musculo-skeletal system for methadone maintained, buprenorphine maintained and control women.

Musculo-skeletal System	**Methadone (n(%))**	**Buprenorphine (n(%))**	**Control (n(%))**
Joint pain	13(54)	15(60)	16(64)
Muscle pain	19(79)	16(64)	16(64)
Bone pain	12(50)	14(56)	15(60)

There was no significant difference between the three groups for symptoms experienced in this category.

Table 4-15 presents the percentage of women in each group reporting symptoms experienced at least once in the third trimester for the Nervous System section of the symptom checklist.

Table 4-15 Symptoms experienced in the third trimester of pregnancy for the nervous system for methadone maintained, buprenorphine maintained and control women.

Nervous System	Methadone (n(%))	Buprenorphine (n(%))	Control (n(%))
Agitation	17(71)	17(68)	16(64)
Anxiety	19(79)	18(72)	17(68)
Depression	17(71)***	21(84)***	8(32)
Abnormal or vivid dreams	19(79)	20(80)	16(64)
Muscle tension	21(88)	18(72)	20(80)
Insomnia	21(88)	21(84)	20(80)
Nervousness	13(54)	15(60)	10(40)
Somnolence	12(50)	9(36)	7(28)
Tremor	5(21)	6(24)	1(4)
Twitch	8(33)*	5(20)	1(4)
Dizzy spells	15(63)	17(68)	14(56)

*p<0.05, ***p<0.001 compared to control

Depression was experienced by significantly more women in both the methadone and buprenorphine groups compared to the control group (methadone 71%, buprenorphine 84%, control 32%; p<0.001). Significantly more women in the methadone group experienced twitches compared to women in the control group, however there was no

significant difference between the buprenorphine group and the remaining 2 groups (methadone 33%, control 4%; $p<0.05$).

Table 4-16 presents the percentage of women in each group reporting symptoms experienced at least once in the third trimester for the Respiratory System section of the symptom checklist.

Table 4-16 Symptoms experienced in the third trimester of pregnancy for the respiratory system for methadone maintained, buprenorphine maintained and control women.

Respiratory System	Methadone (n(%))	Buprenorphine (n(%))	Control (n(%))
Shortness of breath	21(88)	22(88)	20(80)
Hiccup	4(17)	7(28)	8(32)
Sniffily nose	17(71)	17(68)	22(88)

There was no significant difference between the three groups for symptoms experienced in this category.

Table 4-17 presents the percentage of women in each group reporting symptoms experienced at least once in the third trimester for the Skin and Appendages section of the symptom checklist. Once again significantly more women in the methadone group experienced sweats compared to women in both the buprenorphine and control groups (methadone 92%, buprenorphine 64%, control 48%; $p<0.01$).

Table 4-17 Symptoms experienced in the third trimester of pregnancy for the skin and appendages for methadone maintained, buprenorphine maintained and control women.

Skin and Appendages	**Methadone (n(%))**	**Buprenorphine (n(%))**	**Control (n(%))**
Acne	8(33)	4(16)	5(20)
Dermatitis	5(21)	6(24)	6(24)
Rash	6(25)	5(20)	10(40)
Sweat	22(92)** **	16(64)	12(48)

**p<0.01 compared to control

** p<0.001 compared to buprenorphine

Table 4-18 presents the percentage of women in each group reporting symptoms experienced at least once in the third trimester for the Special Senses section of the symptom checklist.

Table 4-18 Symptoms experienced in the third trimester of pregnancy for the special senses for methadone maintained, buprenorphine maintained and control women.

Special Senses	Methadone (n(%))	Buprenorphine (n(%))	Control (n(%))
Dry eyes	5(21)	5(20)	4(16)
Watery eyes	18(75)*	12(48)	10(40)
Photophobia	13(54)	13(52)	6(24)
Strange tastes	13(54)	12(48)	8(32)
Reduced libido	17(71)	14(56)	15(60)

*p<0.05 compared to control

Significantly more women in the methadone group reported watery eyes compared to women in the control group, however there was no significant difference between buprenorphine and the remaining two groups (methadone 75%, control 40%; p<0.05).

Other symptoms reported during the third trimester were oedema (methadone 13%, buprenorphine 16%, control 32%), cold or flu (methadone 25%, buprenorphine 20%, control 40%), chest infection/cough/bronchitis (methadone 13%, buprenorphine 8%, control 12%), varicose veins (buprenorphine 8%, control 4%), tooth ache (methadone 21%, buprenorphine 20%, control 12%), haemorrhoids (methadone 4%, control 4%), gastroenteritis (buprenorphine 4%), throat/ear infection (buprenorphine 8%), UTI (buprenorphine 4%, control 4%), gestational diabetes (control 4%), nose bleeds (control 4%), thrush (buprenorphine 4%), strange smells (buprenorphine 4%), sprained ankle

(buprenorphine 4%), heart palpitations (methadone 4%, buprenorphine 4%) and tingling fingers (buprenorphine 4%). None of the above mentioned symptoms were significantly different between the three groups.

4.4. Discussion

The current chapter presented results obtained in the antenatal period that compared methadone and buprenorphine as maintenance pharmacotherapies to be used during pregnancy. Direct drug effects were compared between the two experimental groups and where appropriate, several measures were compared with control pregnancies. From the results presented in this chapter it is apparent that buprenorphine is at least as efficacious as a maintenance pharmacotherapy compared to methadone when used during pregnancy. Maternal withdrawal was significantly improved for buprenorphine maintained women whereas there was no significant difference in direct drug effects, symptoms experienced, treatment compliance or additional substance use between the two groups as was hypothesised.

4.4.1. Treatment compliance

One means of measuring the effectiveness of a maintenance pharmacotherapy is to assess retention rates in treatment. Subject attrition and reasons for study non-completion or data exclusion were mentioned in Section 2.5.1. With the exception of the woman lost to follow up (M21) (as it was not possible to determine if she had remained in maintenance therapy despite leaving the trial), none of the women in the methadone group discontinued maintenance therapy. One woman in the buprenorphine group did discontinue maintenance therapy, but not for dislike of the drug. On the contrary, she believed that buprenorphine had stabilised her life sufficiently to move on and continue her life opioid free. It was unfortunate that this was not the case, however, and she requested that she return to maintenance therapy. She had passed the 28-week cut off to begin buprenorphine treatment and was therefore commenced onto methadone. Therefore, in terms of retention in

treatment and study retention, buprenorphine is at least as effective as methadone as a maintenance pharmacotherapy during pregnancy.

4.4.2. Maintenance therapy dose

For women already receiving maintenance therapy at the time of recruitment, there was no significant change in their maintenance dose from the time of recruitment to the time of delivery for both methadone and buprenorphine maintained groups. When all women were included, at the time of delivery maintenance doses for both groups of women were relatively low. The average maternal methadone dose at delivery, 48.40 ± 5.95 $mg.day^{-1}$, was slightly below doses recommended to retain clients in treatment (i.e. 50 $mg.day^{-1}$ or higher) as discussed in Section 1.4.3.2. Similarly, the average maternal dose of buprenorphine at delivery of 7.46 ± 0.84 $mg.day^{-1}$ was well below the recommended level exceeding 12 $mg.day^{-1}$ or greater to effectively retain clients in buprenorphine treatment. Although maternal maintenance therapy doses in the current study were below average doses recommended to prevent illicit opioid use in the general maintenance therapy population, this did not appear to affect retention in treatment.

Despite information provided to women in the current study to ensure they remain comfortable on their doses and avoid withdrawal at all times during pregnancy, the maternal belief that lowering or at least not increasing their dose would minimise the chances of NAS, may have contributed to the below recommended maintenance therapy doses observed in the current study. This is in accordance with Lacroix and colleagues (2004), who also reported a similar wish of mothers to decrease their dose towards the end of pregnancy in order to prevent NAS. In contrast to Lacroix and colleagues (2004), Fischer and colleagues (2006) observed a slight increase (although not reported as

significant) in maintenance therapy doses in the third trimester of 5 mg.day^{-1} and 0.5 mg.day^{-1} in both methadone and buprenorphine maintained women, respectively. The current study did not show significant changes in maternal maintenance therapy doses from the time of recruitment to the time of delivery in either methadone or buprenorphine maintained mothers (Figure 4-1) nor was there a significant increase in maternal withdrawal as pregnancy progressed (Figure 4-3, Figure 4-5, discussed below). However maternal maintenance therapy doses should be closely monitored during pregnancy at all times to ensure that maternal withdrawal is minimised in order to prevent associated obstetric complications.

4.4.3. Maternal withdrawal

Withdrawal scores in the current study did not increase across pregnancy for either methadone or buprenorphine maintained mothers. However, both subjective and objective measures of withdrawal were poorer for women in the methadone group compared to both the buprenorphine and control groups. When pregnancy was assessed from gestational week 21, AUC scores for both subjective and objective measures of withdrawal were lower for the buprenorphine compared to the methadone group. When the third trimester alone was considered, scores were higher for the methadone compared to the control group with no differences between buprenorphine and the other 2 groups. In the study assessing only buprenorphine maintained women, Fischer and colleagues (1998; 2000) reported absent or minimal maternal withdrawal in these maintained mothers on buprenorphine doses ranging from 1-10 mg.day^{-1}. In the later comparison study, when buprenorphine maintained women on average doses of 13.5 mg.day^{-1} were compared to methadone maintained mothers on average doses of 47.5 mg.day^{-1} there was no significant difference in maternal withdrawal (Fischer et al., 2006). Therefore, while previous studies report no differences between maternal withdrawal scores, the present results indicate that that buprenorphine may in fact

be more effective in preventing maternal withdrawal throughout pregnancy than methadone at the maintenance therapy doses prescribed in this study.

4.4.4. Direct drug effects

Direct drug effects as measured by VAS were not significantly different between methadone and buprenorphine maintained groups with the exceptions of drug liking. AUC scores for drug liking were significantly higher for the buprenorphine group throughout pregnancy and in the second trimester alone compared to the methadone group. This is in support of the work by Johnson and colleagues (2001) who also reported maternal liking of buprenorphine, and reflects results observed in the general maintenance therapy population of patient acceptance of buprenorphine (Eder et al., 1998; Fischer et al., 1999). In addition, direct drug effects did not change significantly across pregnancy for either methadone or buprenorphine maintained women, with the exception of feelings of normality for buprenorphine maintained women that was significantly higher in the second trimester.

When asked to report the best and worst aspects of being on their respective maintenance pharmacotherapies none of the best aspects of the maintenance therapy reported were significantly different between the methadone and buprenorphine groups. However 36% of women in the buprenorphine group reported that buprenorphine was better than being on methadone whilst no women in the methadone group reported the reciprocal, despite reports of methadone maintained women previously receiving buprenorphine (Table 2-7). When asked to report the worst aspects of the drug, significantly more women in the methadone group reported that they just did not like the drug or being on it compared to the buprenorphine group. Following on from this, 32% of women in the methadone group also reported that they felt chained down or held back by the drug, whereas none of the women in the buprenorphine group reported this. While no differences in maintenance therapy side

effects were found between the methadone and buprenorphine groups when assessing VAS scores, significantly more women in the buprenorphine group reported the worst aspect of the drug to be the side effects.

4.4.5. Additional substance use

In general, additional substance use during pregnancy was significantly higher for both experimental groups compared to the control group. According to self-reports and urine analysis, significantly more methadone and buprenorphine maintained mothers used additional opioids, benzodiazepines and cannabis during pregnancy. With the exception of additional opioid use for both experimental groups and benzodiazepines for the buprenorphine maintained group, significantly more women in the experimental groups also used these substances in the 4 weeks prior to delivery. Despite this, the frequency of substance use, as measured by the percentage of days used in relation to the number of days enrolled in the study, was only significantly higher for the methadone and buprenorphine groups for additional opioids used during pregnancy and not for benzodiazepines or cannabis or for the three substances in the 4 weeks prior to delivery. Previous research has reported conflicting results in particular with relation to additional opioids consumed during pregnancy by mothers maintained on buprenorphine compared to methadone (Fischer et al., 2006; Jones et al., 2005). Results obtained from the current study indicate that methadone and buprenorphine when used during pregnancy have similar efficacies in preventing concomitant opioid use and are in contrast to previous reports by Fischer and colleagues (2006) who reported significantly higher rates of additional opioid use in buprenorphine maintained compared to methadone maintained women. However, in addition, and in accordance with Fischer and colleagues (2006) and Jones and colleagues (2005), benzodiazepine use was not significantly different between the two groups in the current study.

4.4.6. Symptom checklist

Overall, more women in the methadone group reported symptoms than women in the control group, and on several occasions this was significantly greater than the buprenorphine group. More women in the methadone group reported typical opioid symptoms previously discussed (Section 1.4.1.4) such as dry mouth, sweats, photophobia and watery eyes than women in the buprenorphine group.

Significantly more women in the methadone group experienced a loss of appetite during pregnancy compared to the control group. In addition, more women in both the methadone and buprenorphine groups experienced a loss of appetite in the third trimester alone compared to controls. This is in contrast to reports that opioids actually stimulate appetite (Glass et al., 1999). Significantly more women in both the methadone and buprenorphine groups also reported vomiting compared to the control group. A review of nausea and vomiting in pregnancy by Davis (2004), reports that 70-80% of pregnant women will experience nausea and or vomiting at some stage during their pregnancy that is also accompanied by food aversions. For the majority of women these symptoms have usually subsided by gestational week 14. However for up to 10% of women these symptoms can persist beyond the 22nd week of gestation. Hyperemesis gravidarum (severe nausea and vomiting) affects 0.5-2% of pregnancies and is the most common reason for hospitalisation in early pregnancy and only second to preterm labour throughout the whole of pregnancy (Davis, 2004). This occurred in one woman from the buprenorphine group but was not observed in any women from the methadone or control groups.

The increase in vomiting alone observed in methadone and buprenorphine maintained women in the current study, may have resulted in loss of appetite (or food aversion as discussed by Davis (2004)) experienced by these women, as a natural reluctance to

consume food would develop if the expectation is that the outcome would be vomiting. While mild or moderate nausea and vomiting during pregnancy have not been shown to have an effect on pregnancy outcome or low birth weight (Davis, 2004), as discussed by Finnegan and Kandall (Finnegan & Kandall, 1997) it is vital that during pregnancy women receive adequate nutrition to support themselves and the developing fetus. Therefore, it is important that maternal nutrition be closely monitored during pregnancy in these women, to ensure nutritional deficits do not occur as a result of loss of appetite in combination with increased vomiting.

Another consideration when assessing vomiting in methadone and buprenorphine maintained pregnant women is that of re-dosing. If vomiting occurs following maintenance therapy dosing, the issue often becomes whether or not to re-dose particularly in the case of methadone but is perhaps less relevant for buprenorphine maintained women. As previously mentioned in Section 1.4.2.2, buprenorphine undergoes first pass metabolism and has a low oral bioavailability and is therefore taken sublingually. If vomiting does occur following dosing, re-dosing is not necessary as buprenorphine has already been absorbed under the tongue and is not contained in the emptied stomach contents. This issue becomes far more complex with methadone as it is taken orally. If vomiting occurs following dosing, how long after dosing did it occur and is a full or partial dose re-administered? If a full dose is readministered and some of the original dose has already been absorbed, there is the risk of intoxication or overdose to the mother and therefore the fetus. Conversely, if it is believed that the original dose was absorbed and re-dosing is not undertaken there is a risk of maternal, and therefore fetal, withdrawal and the associated consequences. Therefore, buprenorphine may have an advantage over methadone when assessing its use as a maintenance therapy during pregnancy.

Depression was also reported by significantly more women in the methadone group during pregnancy compared to the control group, and by more women in both the methadone and buprenorphine groups in the third trimester compared to the control group. This is consistent with substance users suffering higher rates of psychiatric disorders and depression as discussed in Section 1.3.3.1 (Havard et al., 2006). Substance users and depressed individuals have also been shown to have poorer physical health states than the general population (Darke et al., 2003; Spitzer et al., 1995) which should be avoided during pregnancy to ensure the mother is healthy in order to promote fetal development. Most importantly, depression observed in the antenatal period is correlated with postnatal depression (Josefsson et al., 2001). Postnatal depression has been shown to result in disruptions to mother-infant bonding as well as reduced infant mental and motor development and reduced cognitive development (Lyons-Ruth et al., 1986; Moehler et al., 2006; Murray, 1992; Murray et al., 1991; Murray et al., 1996a; Murray et al., 1996b). Therefore, pregnant women on opioid maintenance therapies should be monitored closely for depression in order to prevent a decline in maternal health and also as an early warning system for increased chances of postnatal depression and its associated consequences.

4.5. Conclusion

In terms of maintenance therapy dosing, there was no significant change in either methadone or buprenorphine dose from the time of recruitment through to delivery. By the time of delivery both groups were also maintained on relatively low doses of maintenance therapy compared to the general maintenance therapy population. Women in the buprenorphine group in general experienced less withdrawal than women in the methadone group and also had higher scores for liking of the drug.

Additional substance use was higher for both methadone and buprenorphine maintained mothers compared to control mothers with the two experimental groups having similar rates of additional substance use.

In general, patterns of symptom complaints were higher in the methadone group than the control group with buprenorphine posing no greater pattern of symptom complaints than methadone, and if anything may result in slightly less.

Results from the current study highlight several important factors that need to be considered when caring for women on maintenance therapies that are less relevant in the non-pregnant maintenance therapy population. Firstly, that of increased reports of vomiting in the maintenance therapy populations in the current study compared to controls needs to be taken into consideration. This is important for reasons of ensuring adequate maternal nutrition is received to promote healthy fetal development, and also ensuring that if vomiting occurs following daily dosing, the appropriate measures are taken to ensure adequate re-dosing occurs preventing maternal intoxication or conversely withdrawal. Secondly, close attention should be paid to any signs of maternal depression in the

antenatal period, particularly in methadone maintained mothers of which more reported depression during pregnancy and not just in the third trimester alone. Not only do substance users suffer higher rates of depression in general, but the combination of substance use and depression may predispose the mother to poorer physical health and in combination with increased nausea, vomiting and loss of appetite, may lead to reduced fetal development. Additionally, depression in the antenatal period is highly correlated to postnatal depression and its associated consequences.

In conclusion, buprenorphine produced similar outcomes to methadone when used as a maintenance pharmacotherapy in the antenatal period. As hypothesised, buprenorphine did not produce significantly different direct drug effects, symptoms or adverse events, differences in treatment compliance or additional substance use compared to methadone. Buprenorphine may even have advantages over methadone when used in this period in regard to reducing maternal withdrawal severity and minimising issues associated with re-dosing when vomiting occurs. In addition, special attention needs to be paid to ensure pregnant opioid maintained women are closely monitored for nutritional and health status as well as depression.

5. LABOUR AND DELIVERY OUTCOMES

5.1. Introduction

Several studies reviewed in Section 1.5.4.1 of Chapter 1 have described the similarities and differences between methadone maintained (or in some cases opioid dependent women in general) and control women for parameters assessed during labour and delivery. In general, it has been observed that more women maintained on methadone are induced for IUGR, require more analgesia and anaesthesia (and therefore more assisted deliveries), and have infants that are delivered earlier, are smaller for gestational age and have decreased Apgar scores than control women and their infants. While infant parameters such as gestational age at delivery, infant size and Apgar scores have been reported for buprenorphine exposed infants, as yet they have not been compared to a control population. In addition, labour and delivery parameters that focus on maternal and fetal aspects have not been reported for buprenorphine maintained women. Furthermore, whilst several clinical studies have assessed the transfer of methadone across the placenta (Blinick et al., 1974; 1975; Doberczak et al., 1993; Mack et al., 1991) only one study has measured the concentration of buprenorphine in umbilical cord plasma obtained from 3 infants (Johnson et al., 2001). In addition, the transfer of the individual enantiomers of methadone across the placenta has also not been studied. The following chapter will present and discuss aims and hypotheses, methods used and results obtained during the labour and delivery period that relate to the mother, fetus, and the neonate for methadone maintained, buprenorphine maintained and control mothers and infants.

In the first instance aims and hypotheses relating specifically to the current chapter will be presented. Following this, general methods described in Chapter 2 that pertain to the

current chapter will be presented in more detail where required. Finally, results relating to the aims and hypotheses presented below will be separated and discussed under three main sections. The first section will focus on maternal and fetal outcomes during labour and delivery. The second section will discuss outcomes relating to the neonate. The third section will present result relating to transplacental transfer of both methadone and buprenorphine. Finally, a closing discussion will review all results obtained during labour and delivery.

5.1.1. Aims and hypotheses

As a result of previously published data and the physiology of transplacental transfer of drugs the following aims and hypotheses were developed.

5.1.1.1. Maternal and fetal outcomes

5.1.1.1.1. Hypotheses

- More women in both the methadone and buprenorphine groups will require analgesia and anaesthesia than women in the control group.
- Complications of labour will not be significantly different for women in either the methadone or buprenorphine groups compared to the control group.

5.1.1.2. Neonatal outcomes

5.1.1.2.1. Hypotheses

- Gestational age at delivery, Apgar score at 1 and 5 minutes after birth and fetal distress in neonates from the methadone and buprenorphine groups will not differ from those in the control group.
- Body weight, length and head circumference of infants at birth will be lower in both methadone and buprenorphine groups than in the control group, but will be greater in the buprenorphine group compared to the methadone group.

5.1.1.3. Placental transfer

5.1.1.3.1. Aim

- To test buprenorphine and methadone concentrations in maternal and umbilical cord plasma.

5.1.1.3.2. Hypotheses

- Buprenorphine concentrations will be lower in umbilical cord plasma than in maternal plasma, while methadone concentrations will be similar in both umbilical cord and maternal plasma at birth.

5.2. Methods of data collection

5.2.1. Maternal and neonatal outcomes

Maternal outcomes including duration of labour, type of delivery and presentation, requirement for anaesthesia and analgesia, placental weight and blood loss together with any complications during labour and delivery were recorded by the WCH delivery suite staff in maternal case notes and collected at a later date by the researcher. Fetal condition during labour and delivery was assessed using CTG to ensure the fetus was not experiencing stress during this period.

Neonatal outcomes including gestational age at delivery, body weight, length, head circumference and Apgar scores at 1 and 5 minutes after birth (Apgar, 1953) were also recorded by the WCH delivery suite staff in the infant's case notes and were collected at the same time as maternal labour and delivery outcomes.

5.2.2. Transplacental transfer of maintenance therapy

In order to determine the transplacental transfer of methadone and buprenorphine, 3 ml corresponding maternal and cord blood samples were collected at delivery. Due to the spontaneous nature of labour and delivery, not all delivery blood samples were collected at the same time post maternal maintenance therapy dose. Where possible, maternal and corresponding cord samples were collected in lithium heparin tubes within 30 min of each other, and delivery, by the WCH delivery suite staff and refrigerated. Once collected by the researcher from the delivery suite they were centrifuged at 3000 rpm for 10 min, the plasma removed and frozen at -20°C until the time of assay.

5.2.2.1. Sample analysis

Samples were analysed by Dr David Foster in the Discipline of Pharmacology, University of Adelaide in the laboratory of Professor Andrew Somogyi.

5.2.2.1.1. Methadone

Methadone samples were analysed in accordance with methods described by Foster and colleagues (Foster et al., 2006) with the lower limit of quantification (LLOQ) set at 0.50 $ng.ml^{-1}$.

5.2.2.1.2. Buprenorphine

Buprenorphine samples were analysed by liquid chromatography/mass spectrometry (LCMS) with the LLOQ set at 0.125 $ng.ml^{-1}$ with details provided by Dr Foster below. The LCMS system consisted of an LC-10AD pump (Shimadzu, Kyoto, Japan), a DGU-12A solvent degasser (Shimadzu), a SIL-10AD auto-injector (Shimadzu), a SPD-10A UV-VIS detector (Shimadzu), and an LCMS-2010A liquid chromatograph mass spectrometer (Shimadzu) with an Electrospray (ESI) probe (Shimadzu) in positive ionisation mode. The system was controlled using a SCL-10A system controller (Shimadzu), and LCMS solutions software (v2.04-H3, Shimadzu). High purity (99.99%) nitrogen gas (BOC Gases, Salisbury, Australia) was used for the nebulization and drying gas. The following ions were monitored in single ion monitoring mode: m/z 468.40 for buprenorphine; m/z 414.4 for norbuprenorphine; m/z; 472.40 for the $^{2}H_4$-buprenorphine internal standard; and m/z 417.40 for the $^{2}H_3$-norbuprenorphine internal standard. Optimal ionisation conditions were: a curved desolation line voltage of 20 V at 250°C, heating block of 200°C, Q-Array voltage of +25 V, detector gain voltage of 2.0 kV, 1.5 $L.min^{-1}$ nebulization gas and 2 $L.min^{-1}$ drying gas.

The analytical column was a C18(2) LUNA (150x2.0 mm I.D., Phenomenex, USA), the mobile phase comprised 0.1% formic acid in 44% methanol at a flow-rate of 0.2 $ml.min^{-1}$. Injection volume was set at 40 µl, and run time was 14 min per sample, with retention times of 3.1 and 4.5 min for norbuprenorphine and buprenorphine, respectively.

Briefly, plasma samples (1 ml) and internal standard (50 µL of 20 $ng.ml^{-1}$ d^3-norbuprenorphine and d^4-buprenorphine) were aliquoted into 10 ml tapered bottom plastic tubes, alkalinized (30 µl, 1 M NaOH pH 10) and extracted with 5 ml of 30:70 (v/v) diethyl ether:hexane for 20 min on a rotary mixer. Samples were then centrifuged (2000xg, 10 min) and the organic phase transferred to a clean 10 ml tapered bottom plastic tube containing 100 µl ml of 5mM HCl and vortexed for 1 min. Samples were then centrifuged (2000xg, 10 min), the organic phase aspirated to waste and 40 µl of the 5mM HCl was injected onto the chromatography system. In the case of calibration standards and quality control (QC) samples, 100 µl of an appropriate stock solution containing buprenorphine and norbuprenorphine was mixed with 900 µl of blank human plasma and extracted as outlined above.

Calibration curves consisting of 8 standards were constructed in blank plasma over the concentration range 0.125-10 $ng.ml^{-1}$ of each analyte. Low (LQC), medium (MQC) and high (HQC) quality control samples were also prepared in duplicate, with final concentrations of 0.35 $ng.ml^{-1}$, 2.5 $ng.ml^{-1}$ and 7 $ng.ml^{-1}$ for each analyte, respectively. The robustness of the analytical method was assessed by assaying 6 replicates of each QC sample and the lowest calibration standard (LLOQ) on a single day to determine the intra-assay accuracy and precision. Inter-assay accuracy and precision were determined by analysis of duplicates of each QC sample, and the LLOQ, on eight different assay days. Extraction recovery was approximately 80% for all analytes, without evidence of

differences between the unlabelled and stable-labelled compounds or concentration dependency. Peak areas of each compound of interest were converted into peak area ratios using the peak area of the internal standard. Linear regression analysis (GraphPad Prism v4.03, GraphPad Software, CA, USA), weighted $1/y^2$, of peak area ratios against nominal concentrations provided an estimate of slope, intercept and coefficient of determination (r^2). Accuracy was calculated as the mean (calculated concentration/nominal concentration) x100% for each individual sample, and the residual standard deviation of the mean (RSD) was taken as the precision.

There were no interfering peaks in the analysis of 6 blank plasma samples, or in the subjects' samples. Calibration curves for all analytes were linear over the 0.125-10 $ng.ml^{-1}$ concentration range, with r^2 values greater than 0.99 for all assays with no evidence of time related changes in slope values. The assay demonstrated excellent precision and accuracy over the entire calibration range, both within- and between days. Briefly, inter-assay accuracy and precision (accuracy ± RSD %) were 101 ± 5 (HQC), 105 ± 6 (MQC), 102 ± 8 (LQC), 101 ± 1 (LLOQ, 0.125 $ng.ml^{-1}$), for buprenorphine and 100 ± 7 (HQC), 107 ± 9 (MQC), 92 ± 14 (LQC), 101 ± 5 (LLOQ) for norbuprenorphine. Similarly, intra-assay accuracy and precision (accuracy ± RSD %) were 103 ± 2 (HQC), 107 ± 2 (MQC), 91 ± 2 (LQC), 101 ± 3 (LLOQ, 0.125 $ng.ml^{-1}$), for buprenorphine and 97 ± 1 (HQC), 105 ± 2 (MQC), 89 ± 10 (LQC), 104 ± 12 (LLOQ) for norbuprenorphine.

5.3. Results: maternal and fetal outcomes

5.3.1. Onset of labour

For women who did not undergo a Caesarean section there was no significant difference in the requirement for induction of labour versus the spontaneous onset of labour between the three groups (Figure 5-1).

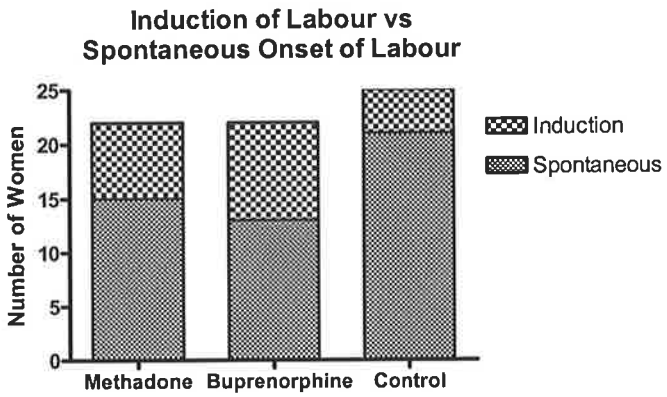

Figure 5-1 Type of labour onset for methadone maintained, buprenorphine maintained and control women.

5.3.1.1. Reasons for induction of labour

There was no significant difference in the number of women induced due to fetal IUGR for reasons of small for gestational age between the three groups (Figure 5-2). Other reasons for induction in the methadone group were preeclampsia (M13) and fetal CTG abnormalities (M22). Other reasons for induction in the buprenorphine group included DVT (B5), postmaturity (B11, B12 and B26), fetal CTG abnormalities (B19) and social reasons (B24). Other reasons for induction of labour in the control group were postmaturity (C5 and C21) and fetal CTG abnormalities (C20).

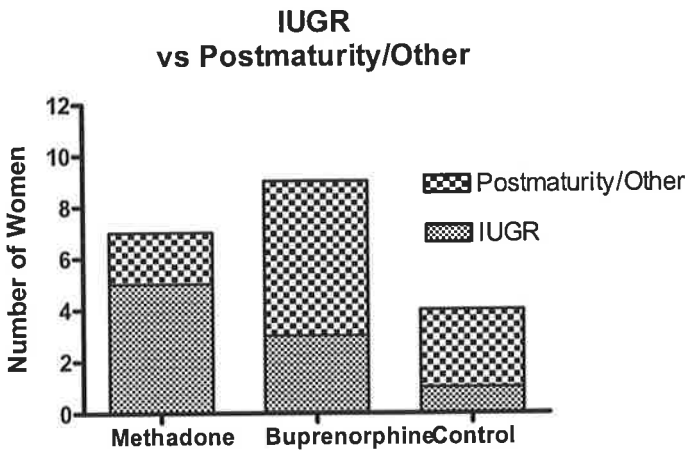

Figure 5-2 Reasons for induction of labour in methadone, buprenorphine maintained and control women.

5.3.2. Type of delivery

There was no significant difference between each of the three groups of women as to whether they delivered via vaginal delivery or underwent a Caesarean section (Figure 5-3).

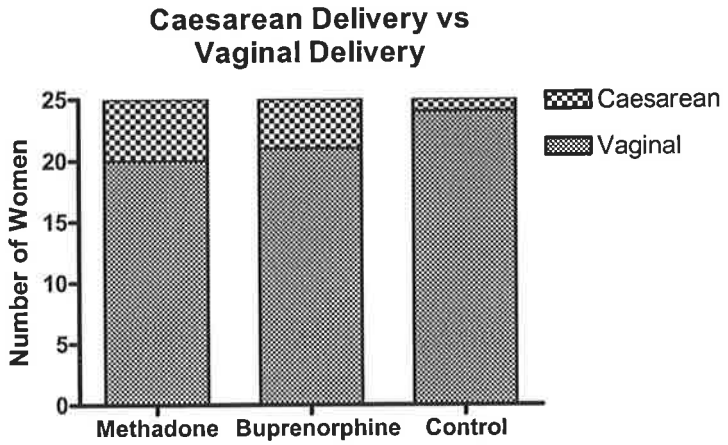

Figure 5-3 Type of delivery in methadone maintained, buprenorphine maintained and control women.

5.3.2.1. Emergency Caesarean section

The requirement of an emergency Caesarean section due to complications was not significantly different between the three groups (Figure 5-4).

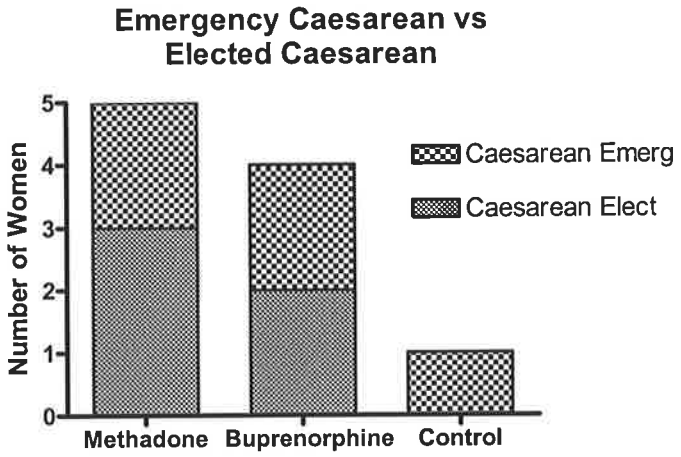

Figure 5-4 Type of Caesarean section in methadone maintained, buprenorphine maintained and control women.

An emergency Caesarean section was performed on one woman from each of the methadone (M22) and buprenorphine (B11) groups for fetal CTG irregularities/fetal stress, one woman from each of the methadone (M19) and control (C01) groups for failure to progress in the first stage of labour, and one woman in the buprenorphine (B15) group for antepartum haemorrhage (previously mentioned in Antenatal and Gynecology Ward admissions in Section 3.3.3.4.2) combined with fetal bradycardia.

5.3.2.2. Type of vaginal delivery

There was no significant difference in the number of women who required an assisted vaginal delivery compared to a normal vaginal delivery between each of the three groups (Figure 5-5). Assisted vaginal deliveries included Ventouse (vacuum extraction), forceps and breech presentations where manual assistance was required for infant removal.

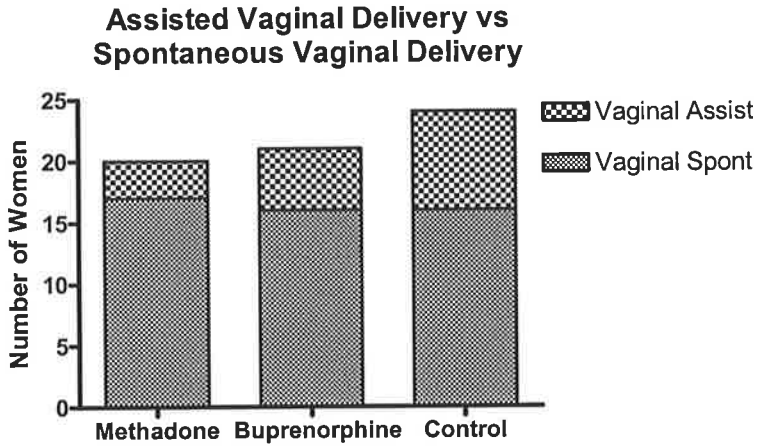

Figure 5-5 Type of vaginal delivery in methadone maintained, buprenorphine maintained and control women.

5.3.3. Anaesthesia and analgesia

Results for both the requirement of anaesthesia and analgesia presented below are for those women who did not undergo a Caesarean section. There was no significant difference in the requirement for anaesthesia or analgesia during labour between each of the three groups of women (Figure 5-6).

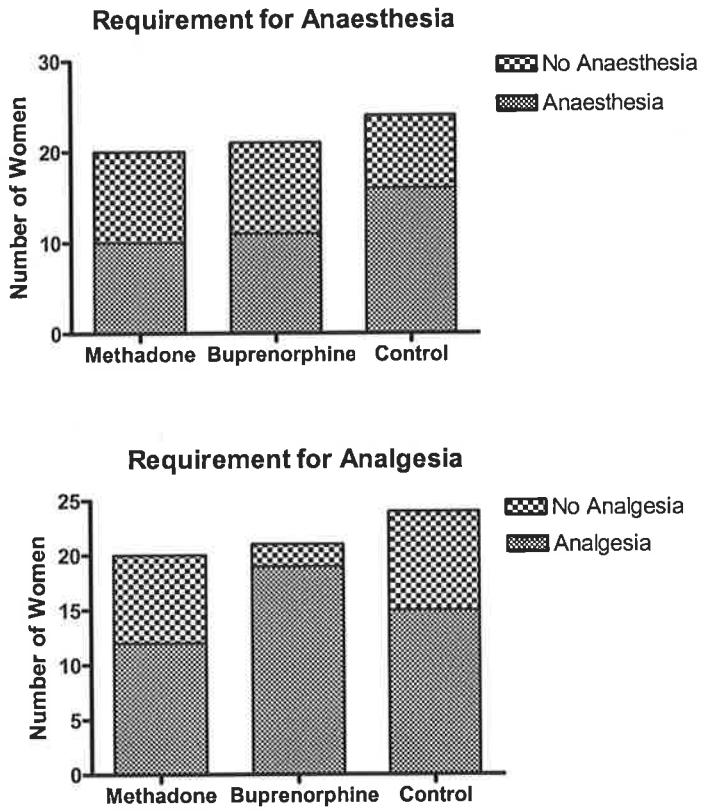

Figure 5-6 The number of women who required analgesia and anaesthesia during labour and delivery in methadone maintained, buprenorphine maintained and control women.

5.3.4. Complications of labour

There was no significant difference in the number of women who had suffered from any complications of labour or delivery throughout the birthing process between each of the three groups (Figure 5-7). Any complications of labour and delivery included instrumental deliveries, emergency Caesarean sections and other complications not previously discussed. For the methadone group the latter included abruption and oligohydramnios discovered at delivery (renal tract malformations in the fetus that prevent fetal urination) (M4) and the requirement of an episiotomy (M11). Other complications in the buprenorphine group were pyrexia (fever) in labour (B12), antepartum haemorrhage and placenta praevia (B17), the requirement of an episiotomy (B26), manual removal of the placenta (B31) and the need for general anaesthesia due to inadequate analgesia during a Caesarean section (B32). Other complications not previously discussed in the control group included the requirement of an episiotomy (C11, C24) and post-partum haemorrhage (C14).

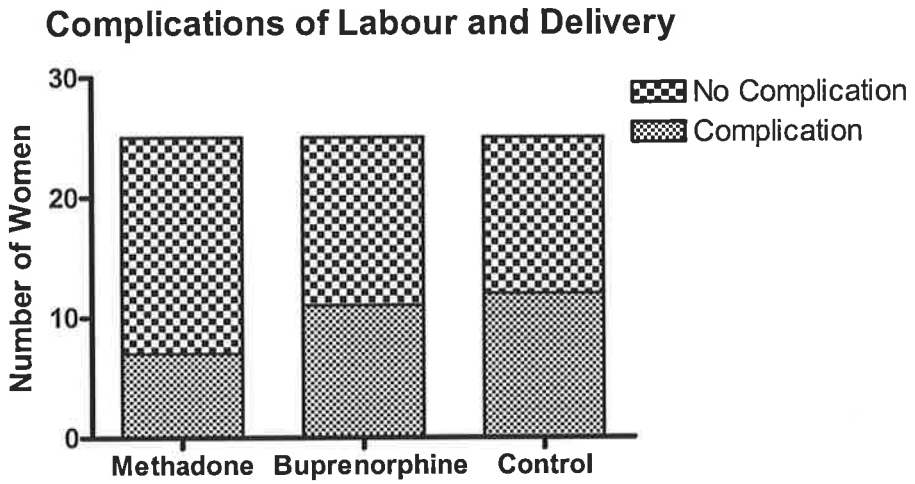

Figure 5-7 The number of women who experienced a complication during labour or delivery in methadone maintained, buprenorphine maintained and control women.

5.3.5. Duration of labour

Control women had a significantly longer duration of labour overall than women in the methadone group (methadone 5.33 ± 0.58 hours, control 8.55 ± 0.83; $p<0.05$). There was no significant difference between women in the buprenorphine group and the remaining two groups. When analysing the three stages of labour individually, control women also had a significantly longer first stage of labour than women in the methadone group (methadone 4.54 ± 0.54 hours, control 7.37 ± 0.82; $p<0.05$). The first stage of labour for women in the buprenorphine group was not significantly different to the remaining two groups. The second and third stages of labour were not significantly different between each of the three groups (Figure 5-8).

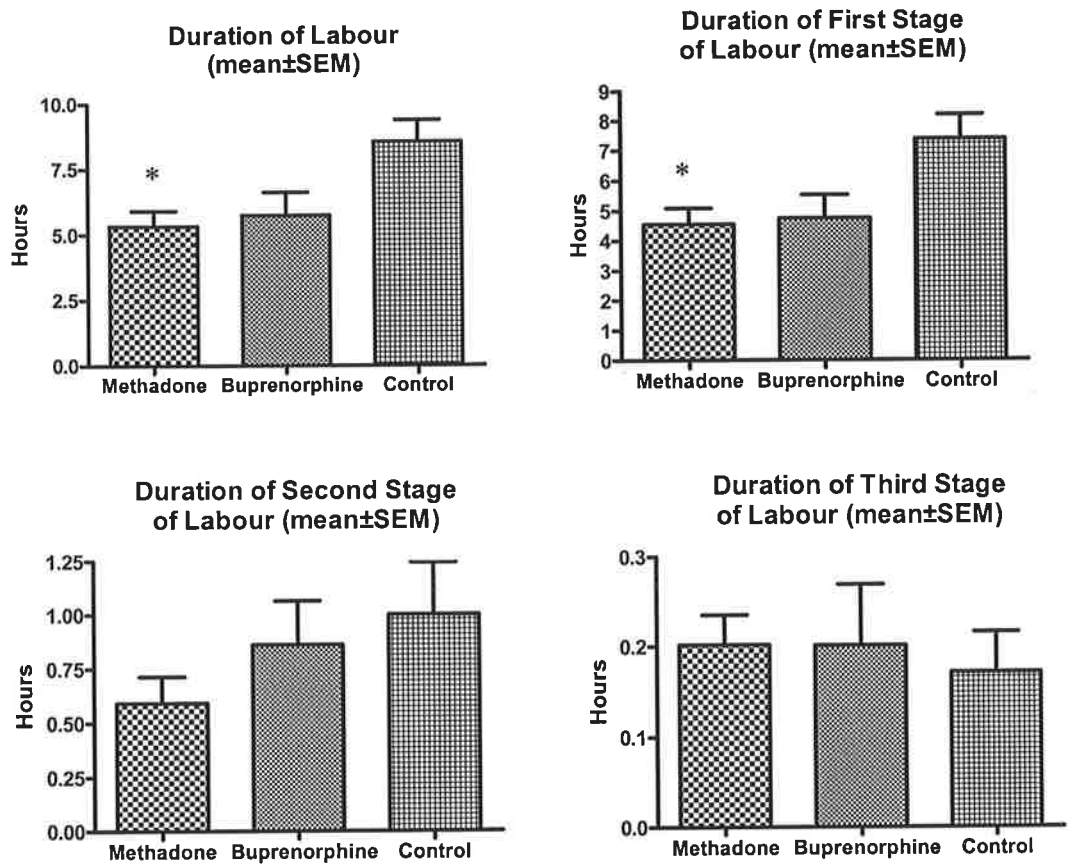

Figure 5-8 Duration of labour overall and for the three individual stages of labour in methadone maintained, buprenorphine maintained and control women. *p<0.05 compared to control women.

5.3.6. Blood loss and placental weight

Women in the buprenorphine group lost significantly more blood during delivery than women in the methadone group (methadone 184.8 ± 18.97 ml, buprenorphine 312.0 ± 54.1 ml; $p<0.05$). There was no significant difference in maternal blood loss between women in the control group and women in either of the two remaining groups. Placental weight was not significantly different between the three groups (Figure 5-9).

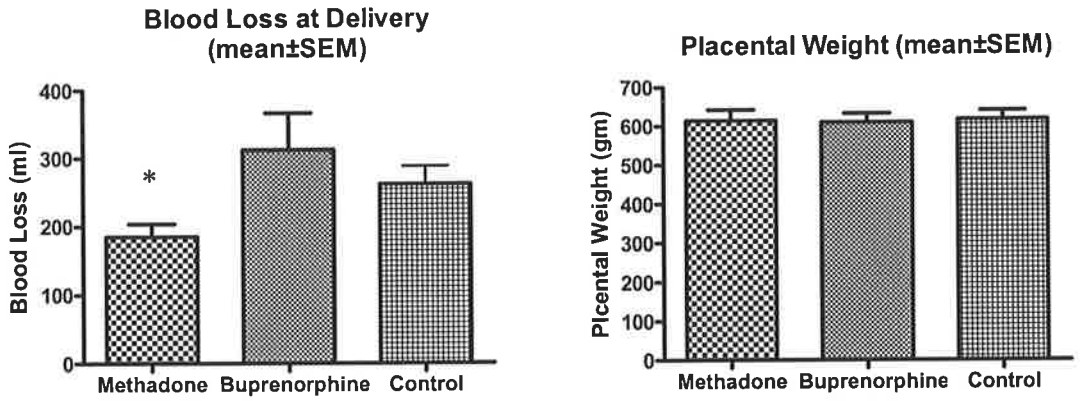

Figure 5-9 Blood loss during delivery and placental weight in methadone maintained, buprenorphine maintained and control women. *p<0.05 compared to buprenorphine.

5.4. Results: neonatal outcomes

5.4.1. Gestational age at delivery

There was no significant difference in gestational age at delivery between each of the three groups of infants (Figure 5-10).

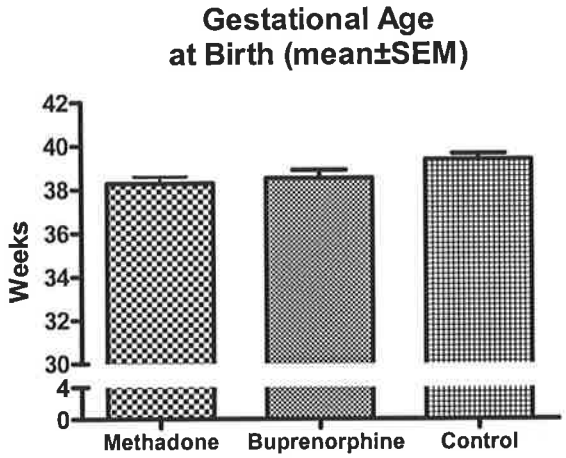

Figure 5-10 Gestational age at delivery for methadone exposed, buprenorphine exposed and control infants.

There was no significant difference between each of the three groups for the number of infants who were classified as being preterm (Figure 5-11).

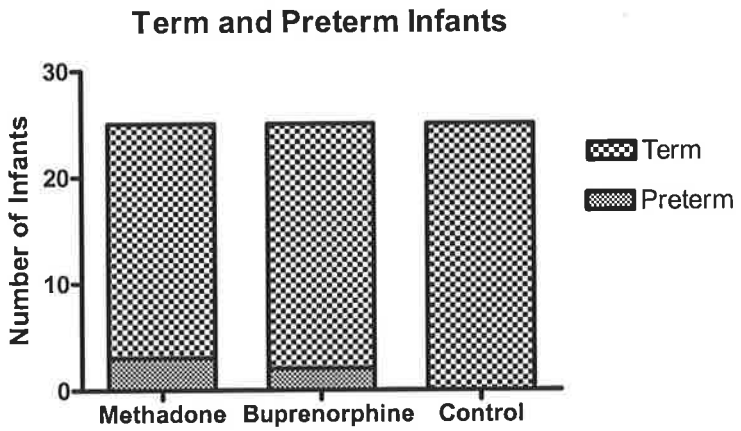

Figure 5-11 Number of term and preterm infants in methadone exposed, buprenorphine exposed and control infants.

5.4.2. Apgar scores

There was no significant difference in Apgar scores between each of the three groups of infants at either 1 or 5 minutes post delivery (Figure 5-12).

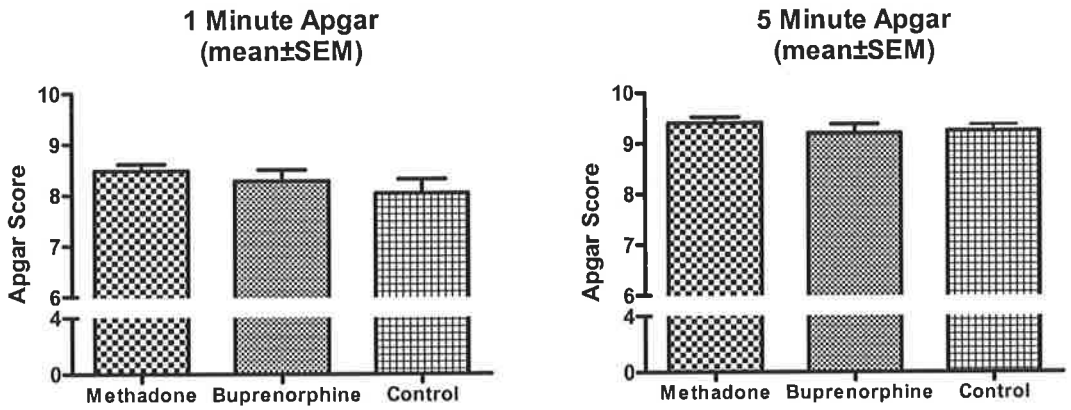

Figure 5-12 Apgar scores at 1 and 5 minutes for methadone exposed, buprenorphine exposed and control infants.

5.4.3. Birth weight and infant size

Methadone exposed infants weighed significantly less at birth compared to control infants (methadone 2854 ± 75.85 g, control 3312 ± 77.65 g; $p<0.01$). There was no significant difference in the birth weight of buprenorphine exposed infants compared to methadone exposed or control infants (Figure 5-13).

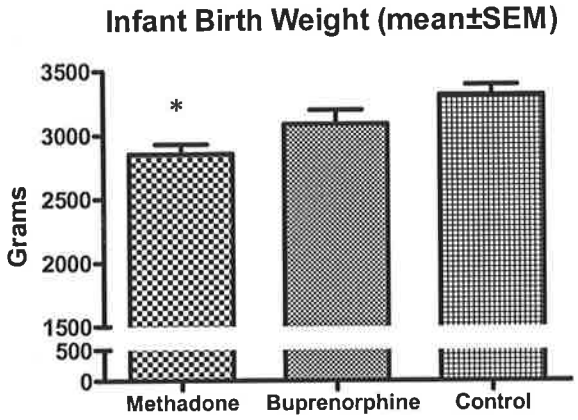

Figure 5-13 Infant birth weight for methadone exposed, buprenorphine exposed and control infants. *p<0.05 compared to control infants.

There was no significant difference in the number of infants who were classified as low birth weight between each of the three groups (Figure 5-14).

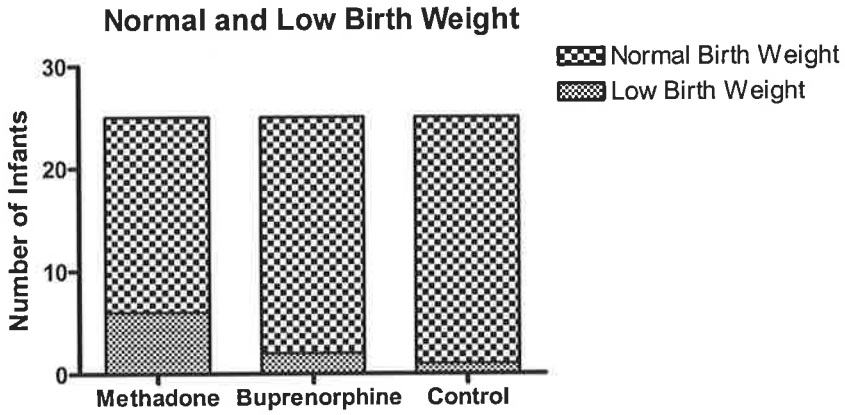

Figure 5-14 The number of infants in each group that were of normal or low birth weight for methadone exposed, buprenorphine exposed and control infants.

The body length of methadone exposed infants was significantly shorter compared to control infants (methadone 46.7 ± 0.41 cm, control 49.38 ± 0.37 cm; $p<0.001$). There was no significant difference in the body length of buprenorphine exposed infants compared methadone exposed or control infants. The head circumference of methadone exposed infants was also significantly smaller than control infants (methadone 32.81 ± 0.27 cm, control 34.11 ± 0.30 cm; $p<0.05$) (Figure 5-15).

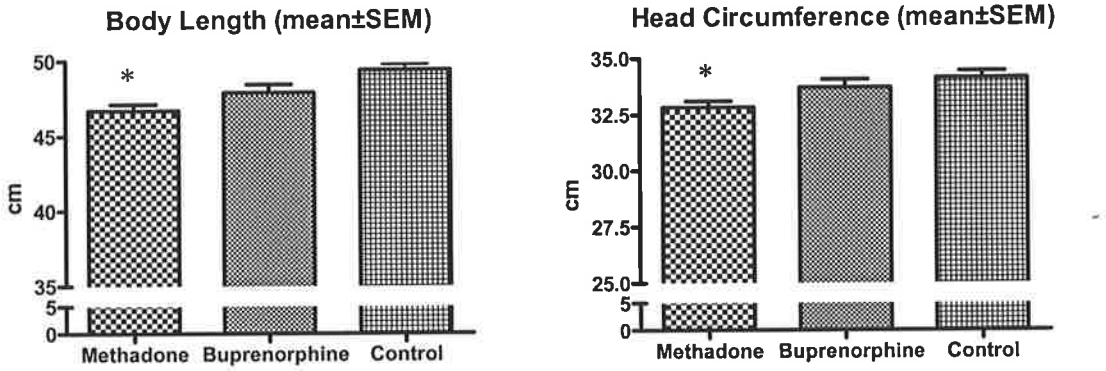

Figure 5-15 Body length and head circumference for methadone exposed, buprenorphine exposed and control infants. *p<0.05 compared to control infants.

5.5. Results: transplacental transfer of methadone and buprenorphine

As discussed in Section 5.2.2, maternal and cord blood samples were not collected at specific time intervals following maternal dosing. Mothers were also maintained on a wide range of maintenance therapy doses and differing dosing regimes as previously discussed in Section 4.3.1. Therefore, while maternal and cord plasma concentration means and ranges are presented, statistical analysis was not performed on this data due to the variability in the timing of both maternal and cord sample collection post maternal dosing within groups. Such analysis would not provide a true indication of the process of maternal transfer of maintenance therapy medication. As a result, in order to provide a more meaningful measure of exposure of the unborn infant to the drug relative to the mother, cord to maternal plasma drug concentration ratios were analysed and presented.

5.5.1. Methadone

Maternal and umbilical cord plasma samples were only able to be collected from 15 mother/infant dyads. Methadone was able to be detected and analysed in all samples collected. Maternal and cord plasma R(-)- and S(+)-methadone concentrations are displayed below in Table 5-1.

Table 5-1 Maternal and cord plasma R(-)- and S(+)-methadone concentrations.

Plasma concentration ng.ml^{-1} Mean ± SEM (range)	**Methadone**	**Cord**
R(-)-methadone	73.08 ± 11.30 (25.11-159.77)	27.83 ± 4.83 (10.59-71.23)
S(+)-methadone	70.39 ± 13.31 (20.57-197.71)	21.09 ± 3.65 (7.42-51.05)

Maternal and cord plasma concentration ratios are presented below in Table 5-2. Ratios of R(-)- to S(+)-methadone in cord plasma were significantly higher than R(-)- to S(+)-methadone concentration ratios in the mother ($p<0.0001$) and is a reflection of each cord R(-)- to S(+)-methadone concentration ratio being higher than the corresponding maternal R(-)- to S(+)- methadone concentration ratio.

Table 5-2 Maternal and cord plasma R(-)- and S(+)-methadone concentration ratios.

Plasma concentration ratio	Mean ± SEM	Range
Cord : maternal R(-)-methadone	0.40 ± 0.03	0.18-0.56
Cord : maternal S(+)-methadone	0.33 ± 0.03	0.15-0.53
R(-)- : S(+)-methadone maternal	1.12 ± 0.05	0.81-1.38
R(-)- : S(+)-methadone cord	1.36 ± 0.06 ***	0.95-1.67

***p<0.001 compared to maternal

5.5.2. Buprenorphine

Maternal and umbilical cord plasma samples were able to be collected from 18 buprenorphine mother/infant dyads and an additional 4 cord samples were collected that did not have corresponding maternal samples. Maternal plasma buprenorphine concentrations were able to be determined in 17 of the mothers samples as the remaining sample was below the LOQ. Cord plasma buprenorphine concentrations were only able to be determined for 11 of the cord samples as 11 were below the LOQ. Maternal plasma norbuprenorphine concentrations were not able to be determined in 2 mothers as they were below the LOQ. Cord plasma norbuprenorphine concentrations were not able to be determined from 4 cord samples as these were below the LOQ. For both buprenorphine and norbuprenorphine, if the maternal sample was below the LOQ then the corresponding infant sample was also below the LOQ. Similarly, if the maternal sample was never below the LOQ if either were detected in the cord. Maternal and cord plasma buprenorphine and norbuprenorphine concentrations for those samples that were able to be analysed are presented below in Table 5-3.

Table 5-3 Maternal and cord plasma buprenorphine and norbuprenorphine concentrations.

Plasma concentration ng.ml^{-1} Mean ± SEM (range)	**Maternal**	**Cord**
Buprenorphine	0.80 ± 0.19 (0.14-3.43)	0.40 ± 0.09 (0.13-1.12)
Norbuprenorphine	0.91 ± 0.16 (0.30-2.75)	0.50 ± 0.07 (0.15-1.49)

As a result of the maternal and cord samples that were below the LOQ and the additional 4 cord samples that did not have corresponding maternal samples, only 9 cord to maternal plasma concentration ratios were able to be determined. As a result of the maternal and cord samples that were below the LOQ and the additional 4 cord samples that did not have corresponding maternal samples, only 16 cord to maternal plasma concentration ratios were able to be determined for norbuprenorphine. Maternal and cord plasma concentration ratios are presented below in Table 5-4.

Table 5-4 Maternal and cord plasma buprenorphine and norbuprenorphine concentration ratios.

Plasma concentration ratio	Mean ± SEM	Range
Cord : maternal buprenorphine	0.34 ± 0.03	0.14-0.47
Cord : maternal norbuprenorphine	0.55 ± 0.04	0.24-0.91

5.6. Discussion

The current chapter presented results obtained during the labour and delivery period that compared methadone and buprenorphine as maintenance pharmacotherapies and their safety of use when assessing labour and delivery parameters compared to control mothers and infants. From the results presented in this chapter it is apparent that buprenorphine is at least as safe as a maintenance pharmacotherapy compared to methadone when assessing labour and delivery outcomes. In contrast to the hypothesis and previous research, there was no significant difference in the number of women in each group who required analgesia or anaesthesia during labour and delivery. Complications during labour and delivery were not significantly different between the three groups as predicted. As hypothesised, gestational age at delivery, Apgar score at 1 and 5 minutes after birth and fetal distress in neonates in the methadone and buprenorphine groups did not differ from those in the control group. Methadone exposed infants were significantly smaller compared to control infants as expected, however, there was no significant difference between buprenorphine exposed infants and methadone or control infants. Results were presented for the first time assessing the transfer of the individual enantiomers of methadone across the placenta. Methadone concentrations were able to be measured in all samples collected, whereas buprenorphine was below the limit of quantification and not able to be measured in all samples, suggesting decreased transfer of buprenorphine across the placenta as hypothesised.

5.6.1. Maternal and fetal outcomes

Maternal and fetal outcomes during labour and delivery were not significantly different as a whole between the three groups. Onset of labour, whether it was spontaneous or induced,

was not significantly different between the three groups, nor was the reason for induction whether it be induction due to fetal IUGR or for other reasons.

Induction due to fetal IUGR also relates to fetal growth as measured by fundal height discussed in Section 3.4.3. As mentioned in this section the need for induction due to fetal IUGR is an indicator of fetal growth. Results in the current chapter reported a lack of significance in the requirement for induction due to fetal IUGR. This is an indication that fetal growth was not significantly different between the three groups. Despite this, as discussed in Section 3.4.3, fetal growth was significantly slower for the treatment groups compared to controls throughout pregnancy, but did not significantly differ for the third trimester. As there was no significant difference in the requirement for induction due to IUGR between the three groups, the improved fetal growth in the third trimester is likely to be as a result of improved antenatal care in the treatment groups as pregnancy progressed.

One woman from each group was induced due to abnormal fetal CTG results. Of these one woman (from the methadone group) required an emergency Caesarean section for continuing fetal CTG irregularities, while women from the buprenorphine and control groups progressed to normal vaginal deliveries. Two women in the buprenorphine group required an emergency Caesarean section due to fetal CTG abnormalities. In these women the indication for induction of labour were postmaturity in one woman and antepartum haemorrhage in another. The current results, displaying similar numbers of women in each of the three groups requiring induction and emergency Caesarean sections due to fetal CTG abnormalities, indicate that buprenorphine poses no greater risk than methadone in increasing fetal stress during pregnancy or throughout labour and delivery as hypothesised.

There was no significant difference between the three groups for the type of delivery whether it was vaginal or Caesarean nor was there any difference between the three groups in the requirement of an assisted delivery or emergency Caesarean due to complications in labour or delivery. In addition, there was also no significant increase in the requirement for analgesia or anaesthesia for opioid maintained women compared to controls as previously reported in other studies (Cassidy & Cyna, 2004; Silver et al., 1987). This may have accounted for the similar rates of assisted vaginal deliveries in each of the three groups as increased analgesia and anaesthesia can result in the increased chance of an assisted delivery due to decreased maternal sensation (Finnegan & Kandall, 1997). However the type of anaesthesia and analgesia used or its effectiveness during labour and delivery was not specifically assessed in the current study.

When all complications during labour and delivery were considered, there was no significant difference between the three groups as to whether or not women had suffered from any complications, with complication rates being similar between the three groups. Women in the buprenorphine group did experience significantly more blood loss than women in the methadone group, however this was not significantly different to women in the control group. Furthermore, as increased blood loss during labour and delivery has not previously been reported in buprenorphine maintained women, or during surgery in the general buprenorphine maintenance therapy population, this appears to be an incidental finding that is unlikely to be directly related to the maintenance therapy.

There was a decrease in the duration of labour in the methadone group compared to the control group not only for the first stage of labour, but also the entire duration of labour. This was unexpected, as all three groups had been matched for parity which can affect the duration of labour (Vahratian et al., 2006). However, while not significantly different, more

women in the methadone group were induced compared to the control group. Induction of labour can affect the duration of labour. If induction occurs with an unfavourable cervix this can lead to extended labour compared with spontaneous onset. However if the cervix has already softened, then the duration of labour can actually be shorter than with spontaneous onset (Vahratian et al., 2005). Therefore, if more women in the methadone group were induced with a favourable cervix this may have resulted in a shortened duration of labour in this group compared to controls.

5.6.2. Neonatal outcomes

The gestational age at which infants were born was not significantly different between the three groups of infants. In addition, the number of preterm infants that are classified as being born before the 36th completed week of pregnancy (Llewellyn-Jones, 1999) was not significantly different between the three groups. Previous studies have debated whether Apgar scores are depressed following delivery in opioid exposed infants, (Blinick et al., 1973; Doberczak et al., 1993) however scores at 1 and 5 minutes after birth were not significantly different between the three groups in the present study. In the other two comparative studies performed in this area (Fischer et al., 2006; Jones et al., 2005) gestational age at delivery and Apgar scores also did not differ significantly between methadone and buprenorphine exposed infants.

As has previously been shown (Blinick et al., 1973; Kaltenbach & Finnegan, 1987; Kandall et al., 1976; Wouldes et al., 2004) methadone exposed infants were significantly smaller than control infants in the present study. Birth weight, body length and head circumference were all significantly smaller than control infants. This is important, as low birth weight and small head circumference has been shown to result in increased morbidity and learning difficulties later in life (Connaughton et al., 1977; Hack, 2006; Peterson et al., 2006).

Buprenorphine exposed infants were not significantly different to controls or methadone exposed infants as was also observed by Jones and colleagues (2005) and Fischer and colleagues (2006). Despite methadone exposed infants being significantly smaller than control infants, there was no significant difference in the number of infants in each group that were classified as low birth weight (i.e. below 2500 g) (Llewellyn-Jones, 1999). In addition, average birth weights for all three groups were above 2500 g.

5.6.3. Transplacental transfer outcomes

Firstly methadone was able to be detected in all maternal and cord samples collected, whereas buprenorphine was below the LOQ of the assay used to assess buprenorphine concentration and was unable to be detected in approximately one third of samples collected. This is not a reflection of the quality of the assay used to detect buprenorphine in the current study, but provides an indication that the transfer of buprenorphine across the placenta may be minimal, and may result in a reduced NAS in buprenorphine exposed infants.

It was not possible to compare average maternal and cord R(-)- and S(+)-methadone concentrations to assess placental transfer due to differing times of maternal dosing and sample collection. Despite this, every cord R(-)- to S(+)-methadone concentration ratio was higher than the corresponding maternal R(-)- to S(+)-methadone concentration ratio, and may indicate that the time of maternal dosing and the time of sample collection does not necessarily reflect differences in cord R(-)- to S(+)-methadone concentration ratio compared to maternal R(-)- to S(+)- methadone concentration ratio.

Not being able to compare maternal and cord concentrations directly and the fact that earlier studies have not previously investigated the transfer of the individual enantiomers of

methadone across the placenta makes it difficult to compare the current findings to previous research. However, the cord to maternal plasma R(-)-methadone concentration of 0.40 gives an indication that the transfer of the active enantiomer of methadone across the placenta is approximately 40%. In addition, comparing the ratios of R(-)- to S(+)-methadone concentration in the cord and the mother raised several interesting findings. This significantly higher cord R(-)- to S(+)-methadone concentration ratios compared to maternal R(-)- to S(+)-methadone concentration ratios may be accounted for by several different mechanisms that may effect the transplacental transfer of methadone. This significant difference could be the result of: a) more R(-)-methadone transferred from the mother to the cord; or b) less S(+)-methadone transferred from the mother to the cord. This again may be due to mechanisms such as stereoselectivity in metabolism or stereoselectivity by drug transporters. As yet no work has been performed assessing the stereoselective metabolism of R(-)- and S(+)-methadone by CYP19 (aromatase) in the placenta. With regard to the effect of drug transport, the drug transporter P-gp does not stereoselectively transport the individual enantiomers of methadone (Coller, 2004) and is therefore not likely to affect the differing concentration ratios. However, the role of other drug transporters should be investigated.

In those samples where buprenorphine could be detected, due to the differing times of maternal dosing and blood sample collection, average maternal and cord plasma buprenorphine concentrations could not be compared. However, the average cord to maternal buprenorphine concentration ratio of 0.34 from samples where buprenorphine could be detected, gives an indication that the transplacental transfer of buprenorphine is approximately 34%, which appears to be higher than that observed *in vitro* by Nanovskaya and colleagues of 10% (2002).

When it came to comparing the current data to previous clinical research, Johnson and colleagues (2001) provide data from the only study to have previously reported buprenorphine concentrations in umbilical cord plasma. Cord plasma concentrations between 101-137 $ng.l^{-1}$ (0.101-0.137 $ng.ml^{-1}$) were reported in cord plasma obtained from 3 infants at delivery. These concentrations appear to be lower than those obtained in the current study of 0.13-1.12 $ng.ml^{-1}$. However, maternal samples from the same study collected post-delivery had concentrations ranging from 115-798 $ng.l^{-1}$ (0.115-0.798 $ng.ml^{-1}$) also appeared to be lower than the current study (0.14-3.43 $ng.ml^{-1}$). These differences in maternal plasma concentrations may be a reflection of differing times of sample collection. Maternal samples obtained by Johnson and colleagues (2001) were obtained at times of assumed trough concentration. As maternal samples obtained in the current study were collected at delivery and not at a specific times in relation to time of dosing (i.e. peak or trough) this may have accounted for lower buprenorphine concentrations observed by Johnson and colleagues (Johnson et al., 2001) compared to those obtained in the current study.

5.7. Conclusion

Data from the current chapter assessed differences between buprenorphine maintained, methadone maintained and control women during the labour and delivery period. Maternal and fetal outcomes were not significantly different between the three groups in terms of complications during labour and delivery or in the requirement for analgesia and anaesthesia. While buprenorphine maintained women did experience significantly greater blood loss than methadone maintained women, this was not significantly different to controls and has not been previously reported elsewhere. Buprenorphine and control infants did not differ significantly in size, however methadone exposed infants were significantly smaller than controls as has previously been reported. Other neonatal outcomes such as gestational age at delivery and Apgar scores were not significantly different between the three groups. In addition, it appears that relatively less buprenorphine than methadone is transferred from the mother to the fetus.

6. POSTNATAL OUTCOMES

6.1. Introduction

As discussed in Section 1.5.5 of Chapter 1, there is an increase in the amount of research investigating the effects of buprenorphine exposure on the incidence and severity of NAS. The outcomes of research presented to date indicates that infant exposure to buprenorphine *in utero* produces a mild NAS that is of short duration and often does not require treatment (Fischer et al., 1998; Fischer et al., 1999; Johnson et al., 2003b; Johnson et al., 2001; Kayemba-Kay's & Laclyde, 2003; Lacroix et al., 2004; Marquet et al., 1997). Despite this, comparison studies with methadone appear to be inconclusive as to whether its use during pregnancy results in a milder NAS compared to methadone, as measured by the percentage of infants who require pharmacological treatment and the amount of treatment administered (Fischer et al., 2006; Jones et al., 2005). Outcomes of infants exposed to buprenorphine have also not been compared to a control infant population. In addition, there is still controversy as to whether maternal maintenance therapy medication or breast-feeding, in either methadone or buprenorphine maintained women, affects the severity of NAS in the neonate.

The following chapter will present and discuss aims and hypotheses, methods used and results obtained during the postnatal period that relate to the infant and the effects of maternal dose at delivery on infant withdrawal as well as the effects of breast-feeding on infant withdrawal.

In the first instance aims and hypotheses relating specifically to the current chapter will be presented. Following this, general methods described in Chapter 2 that pertain to the

current chapter will be presented in more detail. Finally, results relating to the aims and hypotheses presented below will be separated and discussed under three main sections. The first section will focus on NAS and treatment to control NAS. The second section will discuss outcomes relating to maternal dose at delivery and infant withdrawal and treatment. The third section will present results relating to breast-feeding and the effects on infant withdrawal and subsequently infant treatment. Finally, a closing discussion will review all results obtained during the postnatal period.

6.1.1. Aims and hypotheses

As a result of the incomplete research to date assessing NAS resulting from buprenorphine exposure and the effects of maternal dose and breast-feeding on NAS, the following hypotheses were developed.

6.1.1.1. NAS and treatment

6.1.1.1.1. Hypotheses

- The severity of NAS will be less in infants from the control group than methadone or buprenorphine maintained groups
- The severity of NAS will be less in infants whose mothers are maintained on buprenorphine during pregnancy compared with infants whose mothers are maintained on methadone
- Infants whose mothers are maintained on buprenorphine during pregnancy will spend fewer postnatal days in hospital compared with those from mothers maintained on methadone

- Pharmacological treatment to control NAS will be required in fewer infants whose mothers were maintained on buprenorphine compared to infants whose mothers were maintained on methadone
- In those infants treated, the total amount of morphine sulphate received to control NAS will be lower in infants whose mothers are maintained on buprenorphine compared with mothers who are maintained on methadone

6.1.1.2. Maternal dose and plasma concentration

6.1.1.2.1. Hypotheses

- There will be no correlation between maternal methadone/buprenorphine dose and infant withdrawal
- There will be a positive correlation between the severity of NAS and maternal plasma methadone/buprenorphine concentration from samples collected at delivery
- There will be a positive correlation between the severity of NAS and umbilical cord plasma buprenorphine/methadone concentrations.

6.1.1.3. Breast-feeding

6.1.1.3.1. Hypotheses

- Breastfeeding will not effect the requirement for pharmacological treatment in either methadone or buprenorphine exposed infants

6.2. Methods of data collection

6.2.1. NAS and treatment

As previously mentioned in Section 2.4.4.1 NAS onset and severity were assessed using a modified Finnegan Withdrawal Scale (Finnegan & Kandall, 1997) from the NSW MMT Clinical Practice Guidelines (used with permission) in all three groups of infants (Appendix 4). This is an 18-item scale arranged into three sub-sections according to withdrawal symptoms shown by the infant: 1) CNS Disturbances, 2) Metabolic Vasomotor and Respiratory Disturbances and 3) Gastrointestinal Disturbances. The maximum score of 41 indicated severe NAS and the minimum score of 0 indicated the absence of NAS. The scale was administered by hospital midwives every 4 hours after birth (if the infant was awake) until hospital discharge. If at any time the infant's score was 8 or greater, more frequent scoring sessions were initiated and continued for 24 hours from the last total score of 8 or greater. If more frequent scoring continued to produce scores of 7 or less for 24 hours, scoring was returned to 4 hourly intervals. Modified Finnegan Withdrawal scores were recorded in the infant's case notes and collected by the researcher at a later date. Following hospital discharge the modified Finnegan Withdrawal Scale was administered and recorded by the researcher once per week during the 4 week postnatal follow up period.

Once infant withdrawal scores had been collected, data was standardised such that the time of each withdrawal score was determined relative to the time of birth. Scores for each infant were then entered into a spread-sheet of 2 hourly time periods. Each infant's withdrawal scores were then averaged over 24 hour periods to give an average daily withdrawal score. The AUC of Finnegan Score versus time was then calculated for each

group to give a measure of total infant withdrawal over the 4 week postnatal follow up period.

The requirement and amount of pharmacological treatment used to control NAS was also recorded. Treatment was initiated with oral morphine sulphate (1 $mg.ml^{-1}$) when Finnegan scores of 8 were observed on three consecutive scoring sessions, when the average of any 3 consecutive scores was 8 or greater, or if deemed necessary by the treating neonatologist. While in hospital, treatment requirements were recorded in the infant's case notes and the data collected at a later date. Following hospital discharge, and if still continuing treatment, the dose of infant morphine was recorded by the researcher at the weekly follow up visits along with any missed doses. This dose was then checked against the outpatient prescription in the infant's case notes.

6.2.2. Length of hospital stay

The length of infant hospital stay was also used as a primary outcome measure. This was recorded in the infant's case notes and collected by the researcher at a later date.

6.2.3. Breast-feeding

Whether or not infants were breast-fed during their hospital stay was recorded in the infant's case notes and collected by the researcher at a later date. Whether or not infants were breast-fed at each of the 4 postnatal weekly visits was recorded by the researcher.

6.3. Results

6.3.1. Infant withdrawal

Average daily Modified Finnegan Scores are presented in Figure 6-1.

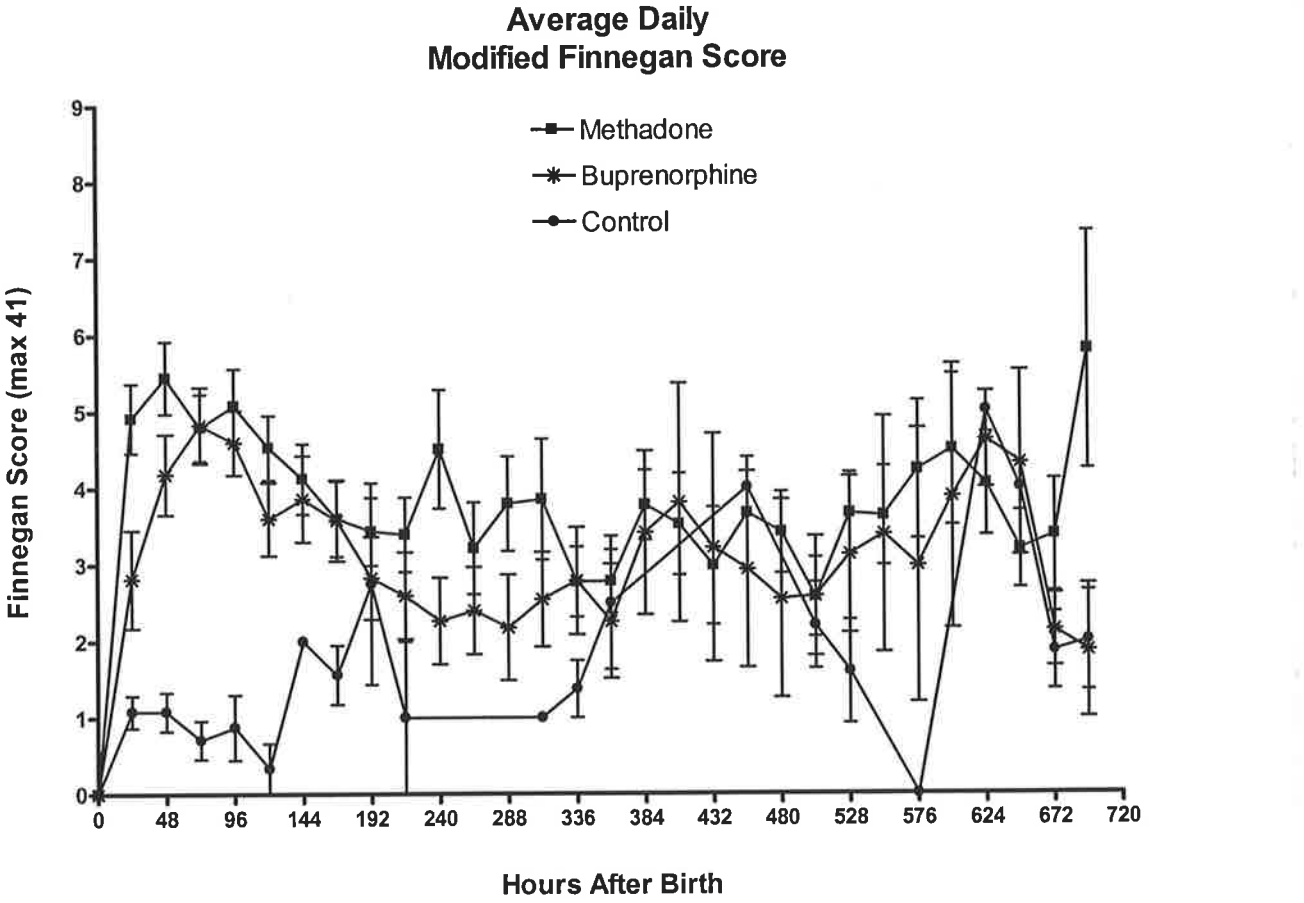

Figure 6-1 Average daily modified Finnegan scores for the 4 week postnatal follow up period for methadone exposed, buprenorphine exposed and control infants.

The AUC of Finnegan Score versus time for the 4 week postnatal follow up period was significantly larger for methadone exposed compared to control infants (methadone: 2311 ± 181.4, control: 1121 ± 152.4; $p<0.001$). There was no significant difference in AUC between buprenorphine exposed and methadone exposed or control infants (Figure 6-2).

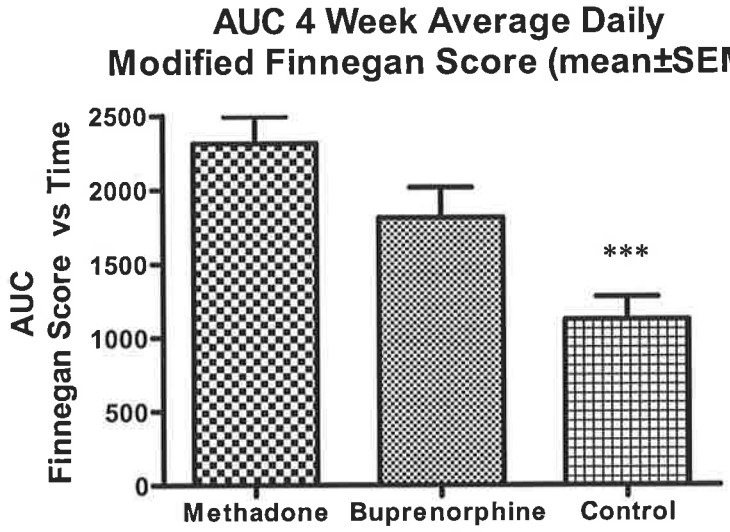

Figure 6-2 AUC Average daily modified Finnegan scores for the 4 weeks postnatal follow up period for methadone exposed, buprenorphine exposed and control infants. ***p<0.001 compared to methadone.

The average peak modified Finnegan score achieved at any one time was significantly higher for both the methadone and buprenorphine groups compared to the control group (methadone: 12.21 ± 0.68, buprenorphine: 10.42 ± 0.77, control: 4.12 ± 0.34; $p<0.001$). There was no significant difference in peak scores between the methadone and buprenorphine groups (Figure 6-3).

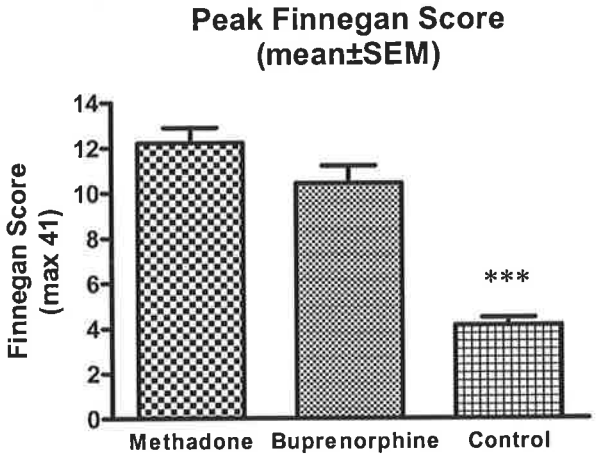

Figure 6-3 Peak Finnegan score achieved in the 4 week postnatal follow up period for methadone exposed, buprenorphine exposed and control infants. ***p<0.001 compared to methadone and buprenorphine.

The time at which the peak score occurred was not significantly different between the three groups (Figure 6-4).

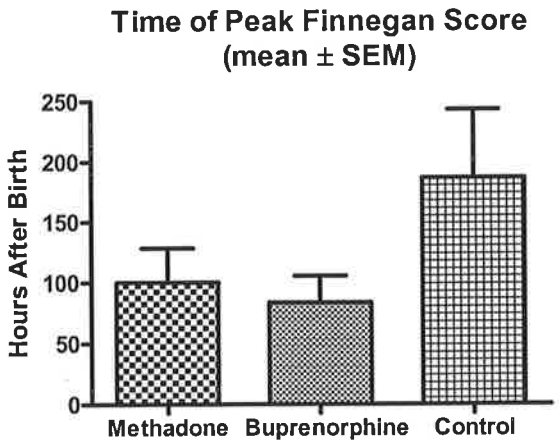

Figure 6-4 Time from birth to peak Finnegan score achieved for methadone exposed, buprenorphine exposed and control infants.

6.3.2. Infant treatment

The number of infants who required pharmacological treatment to control NAS was not significantly different between the methadone and buprenorphine groups with 60% of methadone exposed infants, and 48% of buprenorphine exposed infants requiring pharmacological treatment (Figure 6-5).

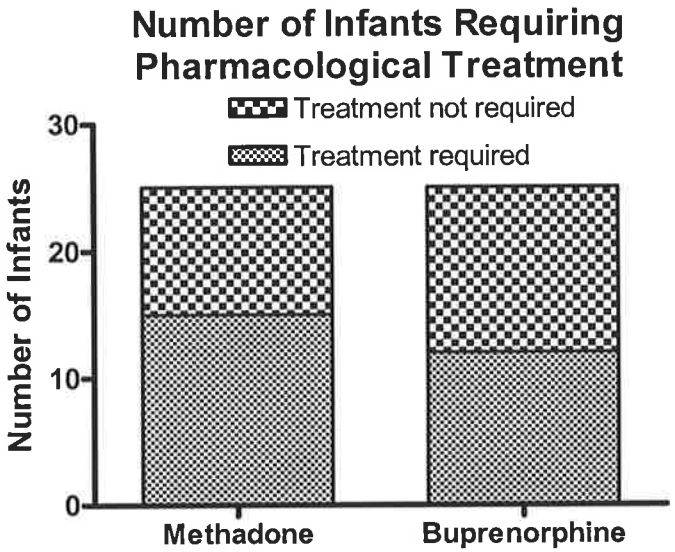

Figure 6-5 Number of infants in the methadone and buprenorphine groups who required pharmacological treatment to control NAS.

In addition to treatment with morphine sulphate one infant from each of the methadone and buprenorphine groups required treatment with phenobarbitone on one occasion each in the follow up period due a reported lack of NAS improvement from morphine treatment alone. The infant from the methadone group (M13A) was treated on day 2 of life with 20 mg phenobarbitone. The infant from the buprenorphine group (B16A) was treated on day 28 of life with 9 mg phenobarbitone.

One infant from the buprenorphine group (B14A) was treated primarily with phenobarbitone as distinct from morphine sulphate. This was no reflection on the severity of withdrawal, but rather a communication breakdown between hospital staff and the

infant's mother. The mother believed that if treatment were to be with morphine it would be intravenous as distinct from oral and refused to give consent for the infant to be treated with morphine. A second infant in the methadone group (M04A) received both morphine sulphate and phenobarbitone for the majority of the 4 week follow up period. As a result of the differing treatment regimes in these 2 respective infants, their withdrawal scores were not included in infant withdrawal scores presented above in Section 6.3.1.

For those infants who required pharmacological treatment, the time to treatment initiation was not significantly different between the two groups (Figure 6-6).

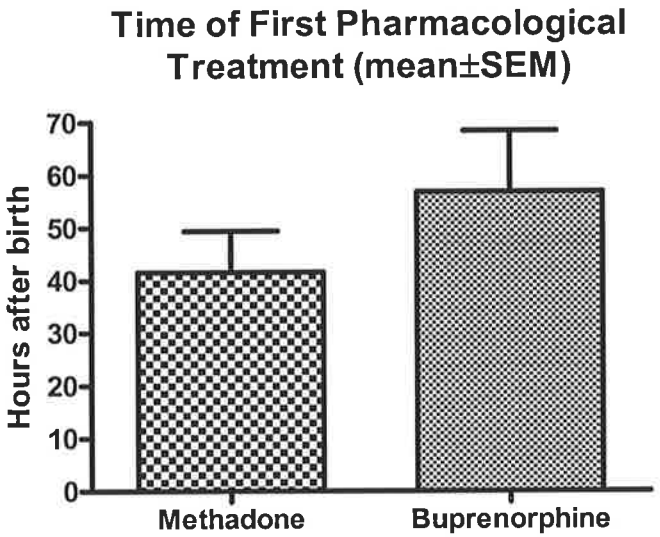

Figure 6-6 Time of initiation of pharmacological treatment in methadone and buprenorphine exposed infants.

The initial dose of morphine sulphate used to control NAS was not significantly different between methadone and buprenorphine exposed infants (Figure 6-7).

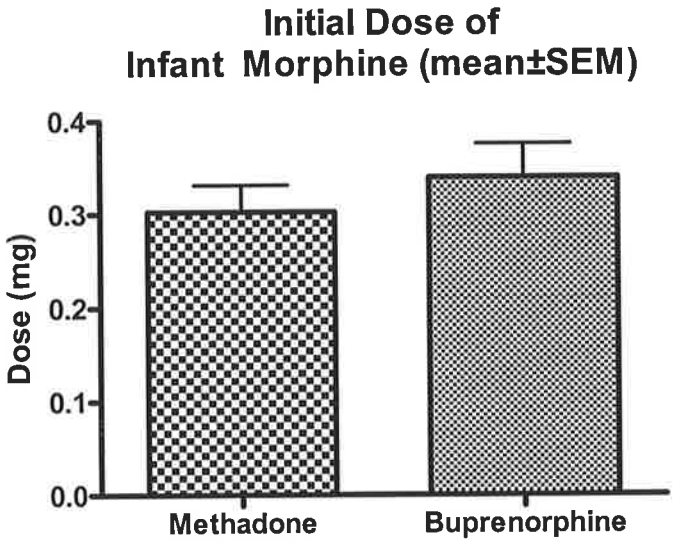

Figure 6-7 Initial dose of morphine used to treat methadone and buprenorphine exposed infants.

The total morphine received over the 4 week postnatal follow up period to control NAS was significantly less for buprenorphine exposed compared to methadone exposed infants (methadone: 40.07 ± 3.95 mg, n=15; buprenorphine: 22.77 ± 4.29 mg, n=12; $p<0.05$) (Figure 6-8).

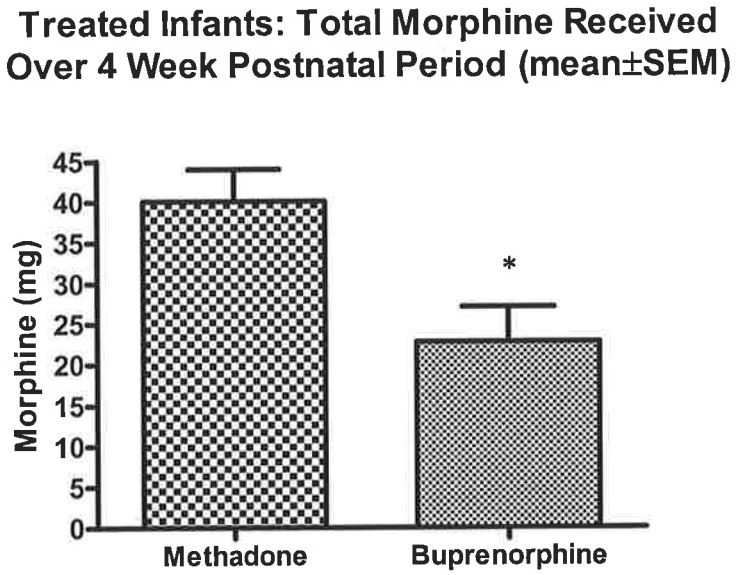

Figure 6-8 Total morphine received over the 4 week postnatal follow up period in methadone and buprenorphine exposed infants. *p<0.05 compared to methadone.

When assessed on a weekly basis, total morphine received over the 4 week postnatal follow up period to control NAS was significantly less for buprenorphine compared to methadone exposed infants exposed for each of the 4 postnatal follow up weeks with the exception of the fourth week (Figure 6-9). There was no significant change over the 4 weeks in total morphine received to control NAS in either methadone or buprenorphine exposed infants.

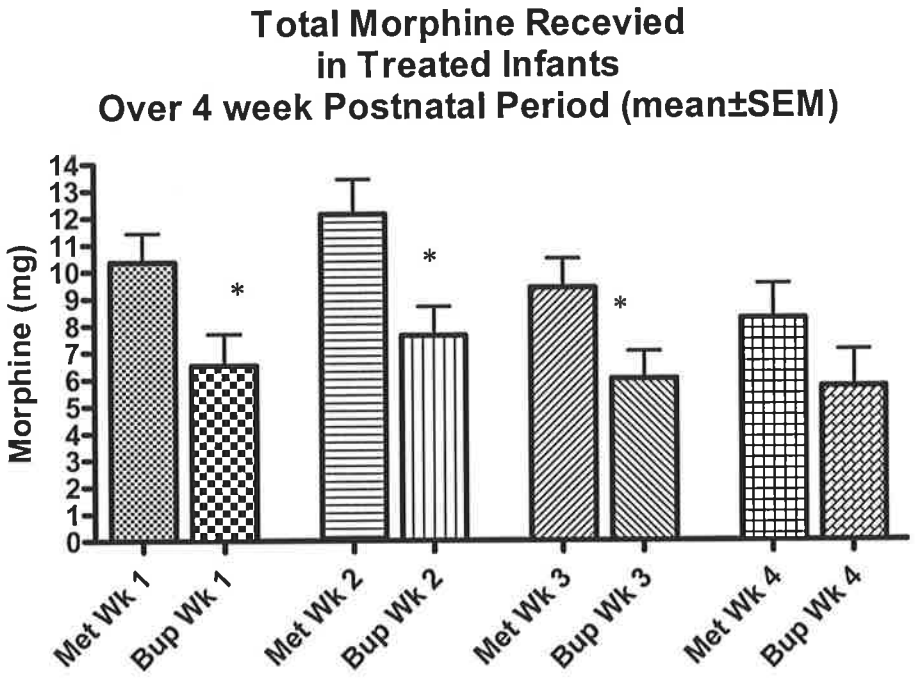

Figure 6-9 Total morphine received over the 4 week postnatal follow up period in methadone and buprenorphine exposed infants. *p<0.05 compared to corresponding methadone week. Met=methadone, Bup=buprenorphine, Wk=week.

6.3.3. Length of infant hospital stay

The length of infant hospital stay was significantly longer for both methadone and buprenorphine exposed infants compared to control infants (methadone: 18.17 ± 2.45 days, buprenorphine: 14.04 ± 2.55, control: 3.04 ± 0.21 days; $p<0.001$). There was no significant difference in the length of infant hospital stay between methadone and buprenorphine exposed infants (Figure 6-10).

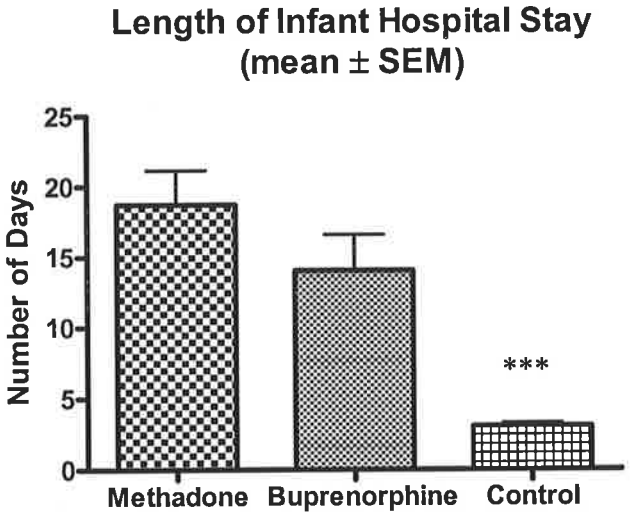

Figure 6-10 Length of infant hospital stay for methadone exposed, buprenorphine exposed and control infants. ***p<0.001 compared to methadone and buprenorphine.

6.3.4. Maternal dose and infant withdrawal outcomes

There was no significant correlation between peak Finnegan score achieved and maternal dose of methadone or buprenorphine at delivery. For those infants who received morphine, there was no significant correlation between the maximum dose of morphine administered or total morphine administered and maternal dose at delivery for either the methadone or buprenorphine groups.

There was, however, a significant correlation ($p<0.05$, $r=0.49$) between maternal methadone dose at delivery and AUC of infant withdrawal score versus time for the 4 week postnatal follow up period. This correlation was not significant for maternal buprenorphine dose at delivery and AUC of infant Finnegan withdrawal score versus time for the same period (Figure 6-11).

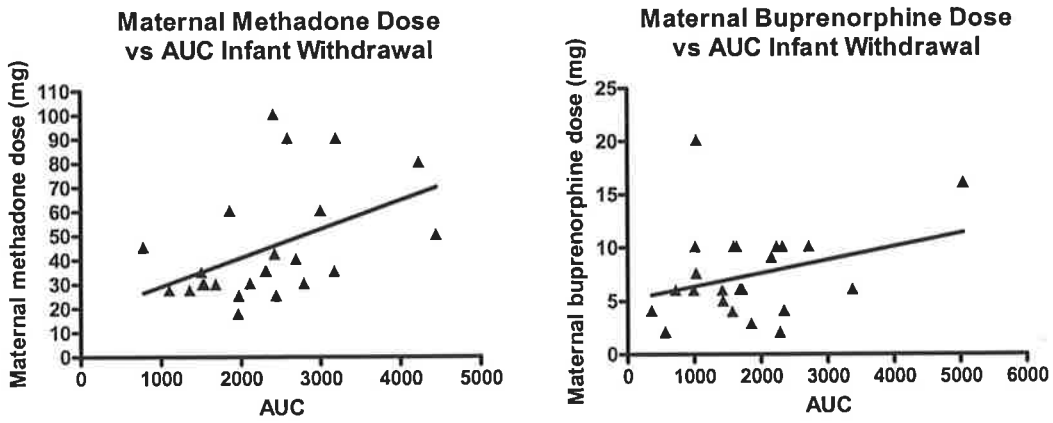

Figure 6-11 Correlation of maternal maintenance therapy dose at delivery and infant Finnegan withdrawal score for methadone and buprenorphine exposed infants.

6.3.5. Plasma concentration and NAS

There was no significant correlation between AUC infant withdrawal score versus time over the 4 week postnatal follow up period and maternal or cord plasma R(-)-methadone concentration or cord plasma S(+)-methadone concentration. There was a significant correlation between AUC infant withdrawal score versus time over the 4 week postnatal follow up period and maternal plasma S(+)-methadone concentration ($p<0.05$, $r=0.53$, $n=14$) (Figure 6-12).

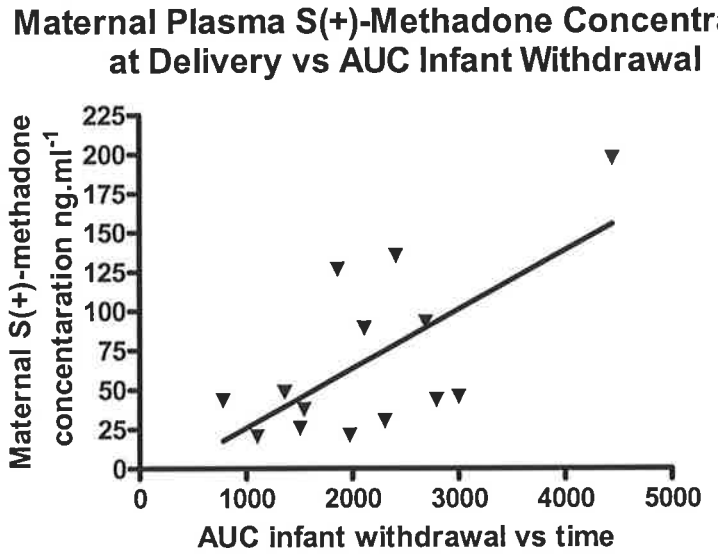

Figure 6-12 Correlation of maternal plasma S(+)-methadone concentration at delivery and AUC infant withdrawal score versus time over the 4 week postnatal follow up period. $p<0.05$, $r=0.53$.

There was no significant correlation between AUC infant withdrawal score versus time over the 4 week postnatal follow up period and maternal or cord plasma buprenorphine or norbuprenorphine concentration at delivery.

6.3.5.1. Plasma concentration and NAS treatment

There was no significant correlation between total morphine received in treated infants and maternal or cord plasma R(-)- or S(+)-methadone concentrations.

There was no significant correlation between total morphine received in treated infants and cord plasma buprenorphine and norbuprenorphine concentrations. There was a significant correlation between total morphine received in treated infants and maternal plasma buprenorphine ($p<0.01$, $r=0.93$, $n=7$) and norbuprenorphine ($p<0.05$, $r=0.86$, $n=7$) concentrations Figure 6-13.

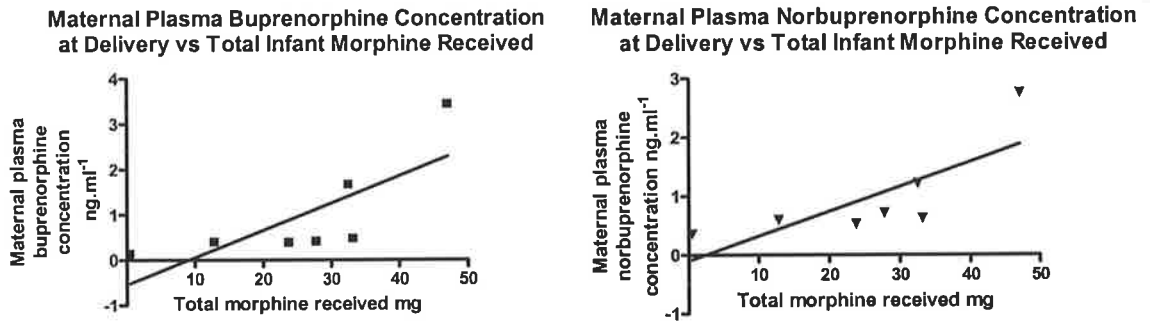

Figure 6-13 Correlation of total infant morphine received in treated infants and maternal plasma buprenorphine ($p<0.01$, $r=0.93$, $n=7$) and norbuprenorphine ($p<0.05$, $r=0.86$, $n=7$) concentrations.

6.3.6. Breast-feeding outcomes

Due to missing data as a result of mothers being unable to attend some weekly follow up visits, for the same number of infants percentages may vary between groups and between time points in the same group.

6.3.6.1. Number of infants breast-fed

Table 6-1 presents the number of infants who were breast-fed at each of the 4 weekly postnatal follow up visits. Data includes infants who were either fully or partially breast-fed. There were no significant differences between the three groups in the number of infants who were being breast-fed at each of the 4 weekly postnatal follow up visits.

Table 6-1 Number of infants breast-fed in methadone exposed, buprenorphine exposed and control infants.

	Postnatal Week			
	Week 1 (n,(%))	Week 2 (n,(%))	Week 3 (n,(%))	Week 4 (n,(%))
Methadone	18 (75)	16 (67)	15 (65)	13 (57)
Buprenorphine	21 (84)	19 (76)	16 (64)	15 (60)
Control	20 (83)	18 (75)	17 (71)	16 (64)

6.3.6.2. Breast-feeding and requirement for pharmacological treatment

Breast-feeding in the first week did not affect the requirement for pharmacological treatment in either methadone or buprenorphine exposed infants. For methadone exposed infants 61% of breast-fed, and 67% of non-breast-fed infants required treatment and for buprenorphine exposed infants 48% of breast-fed, and 50% of non-breast-fed infants required treatment (Figure 6-14). In addition there was no significant difference between methadone and buprenorphine exposed infants in the number of infants who were breast-fed and treated in each group.

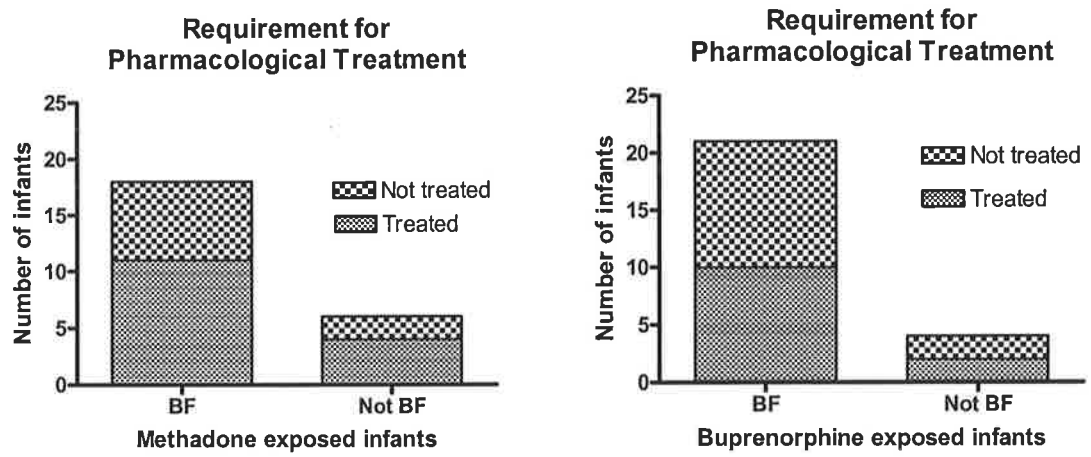

Figure 6-14 Requirement for pharmacological treatment in breast-fed and non-breast-fed infant for methadone and buprenorphine exposed infants. BF=breast-fed.

6.3.6.3. Breast-feeding and time of pharmacological treatment

For those infants who required pharmacological treatment, there was no significant difference in the time of treatment initiation between breast-fed and non-breast-fed infants for either methadone or buprenorphine exposed infants (Figure 6-15). In addition, the time to pharmacological treatment initiation was not significantly different between breast-fed methadone or buprenorphine exposed infants.

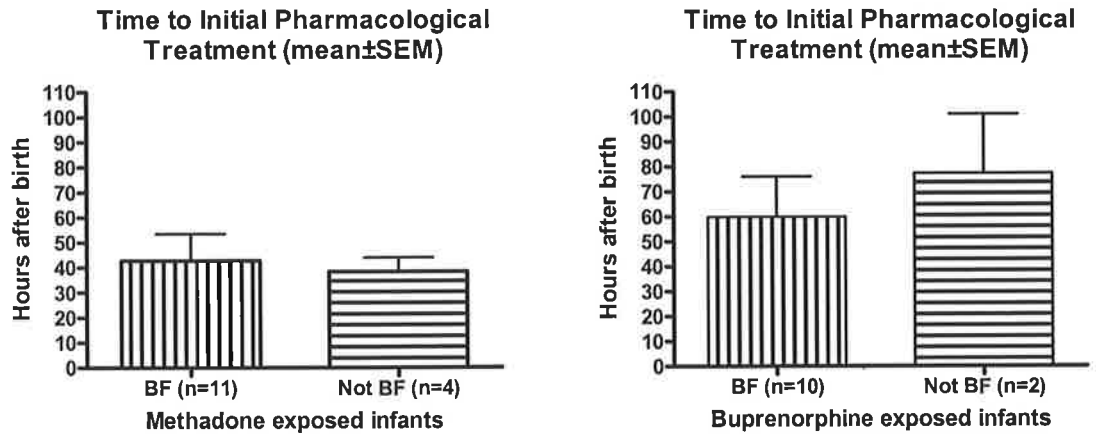

Figure 6-15 Time to pharmacological treatment initiation in treated breast-fed and non-breast-fed infants for methadone and buprenorphine exposed infants. BF=breast-fed.

6.3.6.4. Breast-feeding and initial dose of morphine

There was no significant difference in the initial dose of morphine required to control NAS between breast-fed and non-breast-fed infants in either methadone or buprenorphine exposed infants (Figure 6-16). All non-breast-fed buprenorphine exposed infants received the same initial dose of morphine to control NAS. Therefore, a Wilcoxon rank sum test was performed in order to assess significant differences in initial morphine dose between breast-fed and non-breast-fed infants. It should be noted that initial morphine concentrations are only presented for n=11 in the buprenorphine group due to the infant in the from this group who was treated with phenobarbitone. In addition, there was no significant difference in the initial dose of morphine required to control NAS in breast-fed infants between methadone and buprenorphine exposed infants.

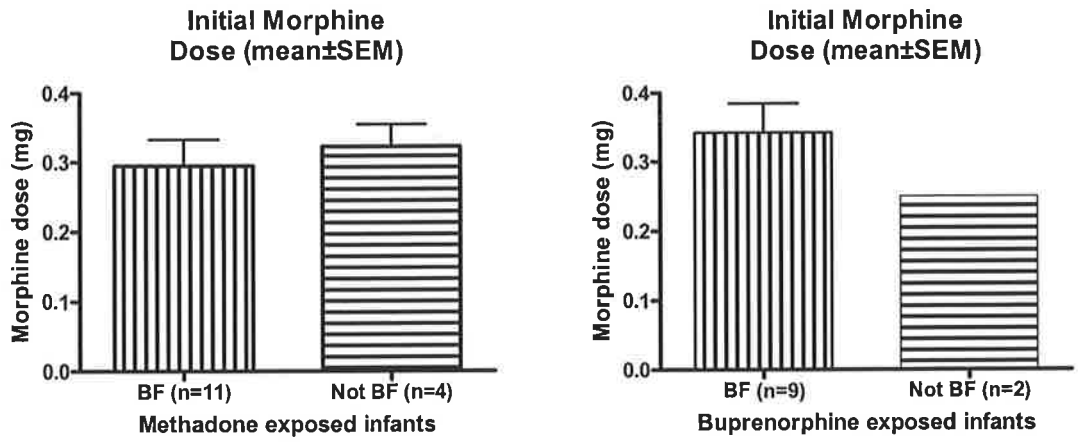

Figure 6-16 Initial dose of morphine in treated breast-fed and non-breast fed infants for methadone and buprenorphine exposed infants. BF=breast-fed.

6.3.6.5. Breast-feeding and total morphine received

For those infants who were treated, there was no significant difference in the total morphine received between breast-fed and non-breast-fed infants during each of the four weekly postnatal follow up periods for either methadone or buprenorphine exposed infants. Nor was there any significant difference in the total morphine received in breast-fed infants alone between weeks 1-4 for either methadone or buprenorphine exposed infants (Figure 6-17).

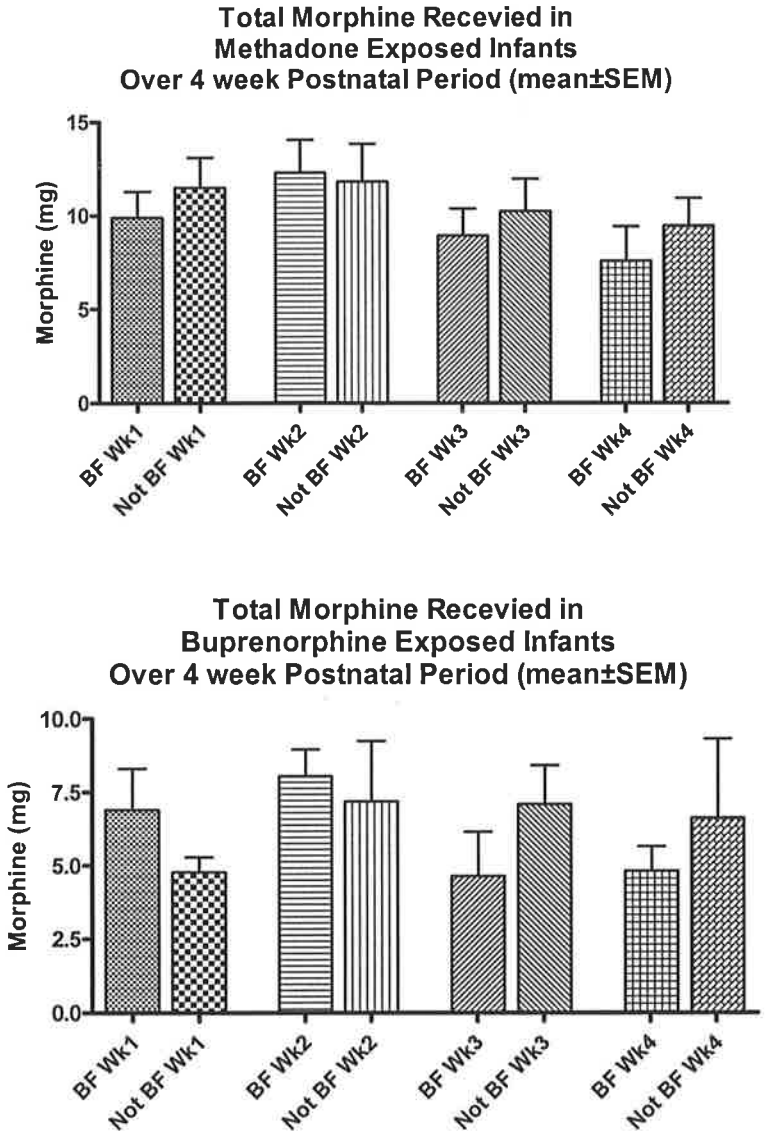

Figure 6-17 Total morphine received in treated breast-fed and non-breast-fed infants for methadone and buprenorphine exposed infants over the 4 week postnatal follow up period. Met=methadone, Bup=buprenorphine, Wk=week, BF=breast-fed.

6.3.6.6. Breast-feeding and maternal maintenance therapy dose

For those infants who were breast-fed, there was no significant difference in maternal maintenance therapy dose between treated infants and infants who were not treated for either methadone or buprenorphine exposed infants at each of the 4 weekly postnatal follow up visits (Figure 6-18). Maternal maintenance therapy doses for methadone and buprenorphine did not change significantly over the 4 weeks for breast-fed treated infants.

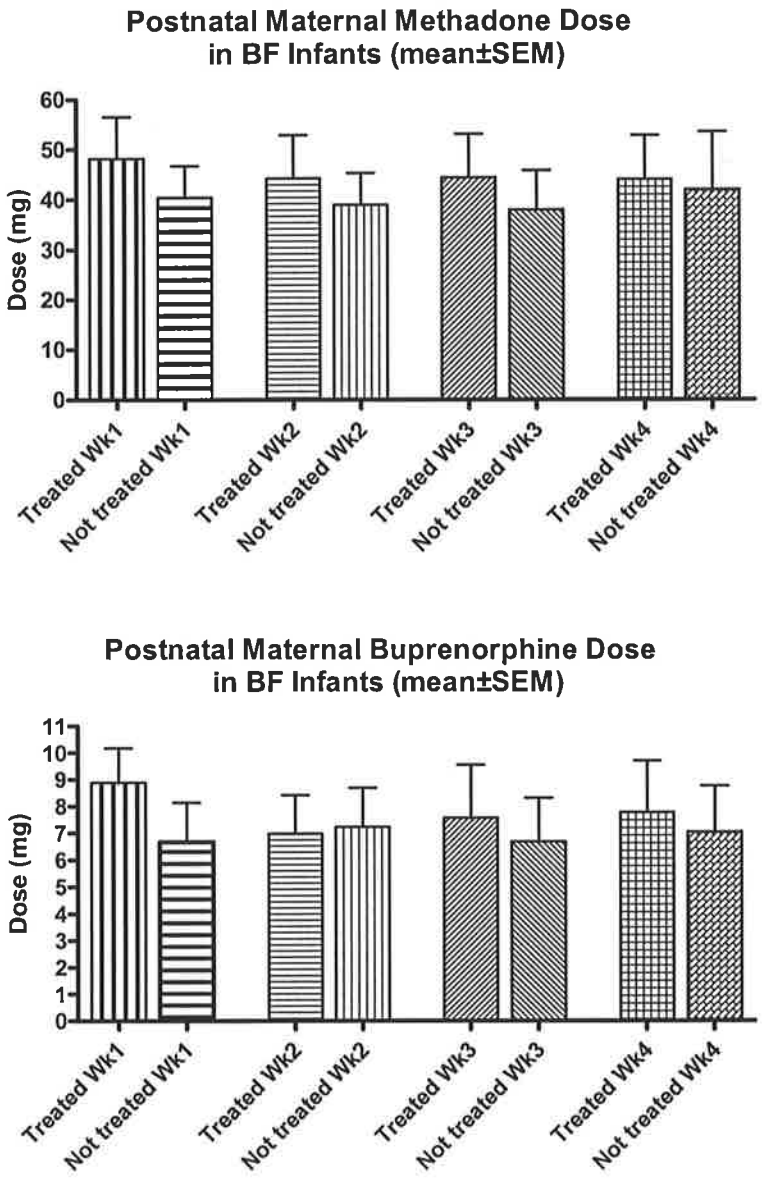

Figure 6-18 Maternal maintenance therapy dose in treated and non treated infants for breast-fed methadone and buprenorphine exposed infants over the 4 week postnatal follow up period. Wk=week, BF=breast-fed.

6.4. Discussion

The current chapter presented results obtained during the postnatal period that compared methadone and buprenorphine maintenance pharmacotherapies and focussed on their effect on NAS compared to control infants, which has not previously been performed. Furthermore the effect of maternal maintenance therapy dose, maternal and umbilical cord plasma concentration and breast-feeding on NAS were also assessed. From the results presented in this chapter it is apparent that buprenorphine is at least as safe as a maintenance pharmacotherapy compared to methadone when assessing postnatal outcomes. When assessing infant withdrawal scores, it first appeared that buprenorphine produced a NAS of intermediate severity compared to methadone exposed and control infants as was originally broadly hypothesised. However, despite the frequency of infants requiring treatment to control NAS being similar in both buprenorphine and methadone exposed infants, as well as a similar duration of hospital stay, significantly less morphine was required to control NAS in buprenorphine exposed infants as was predicted. In addition, morphine administration in the two treatment groups provided an indication of the pattern of NAS in methadone and buprenorphine exposed infants. There was no clinical correlation between maternal methadone or buprenorphine dose at delivery and infant withdrawal score, with maternal plasma concentrations at delivery tending to be more indicative of infant withdrawal severity. Finally breast-feeding while maintained on methadone or buprenorphine did not appear to effect the requirement for pharmacological treatment in the current study as was hypothesised.

6.4.1. NAS and pharmacological treatment

When analysing infant withdrawal data alone it appeared that buprenorphine produced a NAS that was of intermediate severity compared to methadone exposed and control infants. While AUC of infant withdrawal scores over the 4 week postnatal follow up period versus

time were significantly higher for methadone exposed infants compared to controls, buprenorphine scores were not significantly different to methadone or controls. Peak withdrawal scores were significantly higher for both methadone and buprenorphine exposed infants compared to controls but were not significantly different between treatment groups. Furthermore, the time at which peak scores were achieved was not significantly different between the three groups. Therefore, when analysing withdrawal score alone, the pattern of NAS onset appeared to be similar for both methadone and buprenorphine exposed infants. Observed withdrawal scores in control infants may have been due to non-specific symptoms as well as due to the presence of mild tobacco withdrawal. Finnegan withdrawal scores have been shown to be significantly higher in infants exposed to maternal tobacco use compared to control infants (Godding et al., 2004; Law et al., 2003). Infants exposed to tobacco *in utero* tend to be more excitable and hypertonic, require more handling and show more stress/abstinence signs, specifically in the CNS, gastrointestinal, and visual areas (Law et al., 2003). Since all three groups were matched for approximate comparability which included smoking of tobacco, all except for 4 mothers in the control group were current smokers and therefore some withdrawal could be expected.

When treatment for NAS was analysed in methadone and buprenorphine exposed infants, it appears that NAS as a result of buprenorphine exposure is less severe compared to the NAS produced as a result of methadone exposure. Pharmacological treatment to control NAS is a more definitive and absolute measure of the severity of NAS, as distinct from infant withdrawal score alone. Withdrawal score is a pharmacodynamic objective measurement and reflects both withdrawal itself and the effect of treatment with morphine. In contrast, total morphine received is a direct measure of how much medication is actually required to bind to opioid receptors to alleviate opioid withdrawal. The percentage of

infants who required treatment to control NAS was not significantly different between the two experimental groups. Furthermore nor was the initial dose of morphine received or the time of initial administration. This indicates that the onset of NAS is similar in both its timing and severity in both methadone and buprenorphine exposed infants. Had the initial dose been higher in one group this may have been indicative of a more severe onset and similarly had the initial timing of dose administration been earlier, this may have been indicative of a more rapid onset. Nevertheless, the total amount of morphine required to treat NAS was significantly less for buprenorphine compared to methadone exposed infants, and was so for each postnatal follow up week with the exception of the fourth week.

These results also give an indication to the pattern of NAS observed in treated methadone and buprenorphine exposed infants. Firstly the onset appears to be similar in both groups as observed by similar initial doses used to control NAS as well as similar times of treatment initiation. Following this, while there was no significant change in the total amount of morphine administered between weeks for either methadone or buprenorphine exposed infants there was a trend towards higher total morphine received in the second week by methadone exposed infants. It therefore appears that the severity of NAS in methadone exposed infants continued to rise beyond that of buprenorphine during the first week, peak in the second week and then gradually decline to a similar severity to that of buprenorphine exposed infants by the fourth week.

While only a handful of studies have compared NAS as a result of methadone and buprenorphine exposure, the current findings confirm trends observed by Jones and colleagues (Jones et al., 2005) who observed an indication towards fewer buprenorphine exposed infants requiring treatment to control NAS, in addition to less overall

pharmacological treatment than methadone exposed infants. The time to NAS onset, as measured by the time to treatment initiation from birth, was not significantly different between the two groups in the current study. Fischer and colleagues (Fischer et al., 2006) also observed a similar time of NAS onset in methadone and buprenorphine exposed infants, as measured by the time of infant treatment initiation from the time of last maternal dose prior to delivery. In addition to confirming a reduced NAS severity in buprenorphine compared to methadone exposed infants, the current study was able to observe patterns of withdrawal in treated infants as indicated by weekly totals of morphine administration, which has not previously been shown.

Length of infant hospital stay, which has also been used as a measure of NAS severity, was longer for methadone and buprenorphine exposed infants compared to controls but was not significantly different between the two treatment groups. Jones and colleagues (2005) reported longer infant hospital stays in methadone compared to buprenorphine exposed infants. Length of infant hospital stay can be influenced by several factors, and while it may provide an indication of the severity of NAS, results should be interpreted taking into consideration the following factors. Firstly NAS itself can affect the length of infant hospital stay. Different health care systems have different rules and regulations concerning pharmacological treatment for NAS and infant discharge from hospital. Many facilities do not allow infants to be discharged until they are completely weaned from their NAS medication. Infants treated for NAS in the study conducted by Jones and colleagues (2005) were only able to be discharged following a period of 24 hrs with no medication and if scores decreased to 8 or less on the Finnegan scale. Infants in the current study were able to be discharged home while still receiving pharmacological treatment to control NAS at the discretion of the treating neonatologist and following an initial weaning period. Other factors that may also influence the length of infant hospital stay include other

complications of pregnancy as a result of antenatal substance exposure in either the mother or infant, or other unfavourable social circumstances that may not enable the infants to be discharged home with the mother (Johnson et al., 2003a). This may therefore account for differences in the length of hospital stay between the two studies and account for the variability between methadone and buprenorphine exposed infants between the two studies.

Reasons for increased NAS in methadone compared to buprenorphine exposed infants in the current study cannot be attributed to other influential maternal factors such as differences in additional substance use during pregnancy. There was no significant difference in additional opioid, benzodiazepine or cannabis use between methadone and buprenorphine maintained women and therefore this would be unlikely to contribute to significant differences in NAS severity between the 2 groups (Section 4.3.4). Doberczak and colleagues (1991) also observed that signs and symptoms of prematurity can also be confused with withdrawal. However, there was no significant difference between the three groups for the number of infants born preterm (Section 5.4.1) and therefore this is unlikely to contribute to differing severities of NAS between methadone and buprenorphine exposed infants.

The variation observed in NAS in the current study may be due to differences in the transfer of methadone and buprenorphine across the placenta. Although difficult to measure statistically, a trend was observed towards less placental transfer of buprenorphine than the active enantiomer of methadone from the mother to the fetus with 34% (in samples with measurable concentrations of buprenorphine) and 40% transfer, respectively.

6.4.2. Maternal dose correlation and NAS

Previous research has debated as to whether maternal methadone dose at delivery affects the severity of NAS (Section 1.5.4.1.5.1) which previously lead to the recommendation that women's daily doses be reduced down over the course of pregnancy to achieve a target dose of less than 20 $mg.day^{-1}$ methadone. While the current study did observe a significant correlation between maternal methadone dose and AUC infant withdrawal versus time curve, this may have been more clinically relevant had maternal dose been correlated with total morphine received. In addition, there was no significant correlation between maternal buprenorphine dose at delivery and infant withdrawal. The most recent study by Fischer and colleagues (Fischer et al., 2006) also did not observe a correlation between maternal methadone or buprenorphine dose at the time of delivery and infant withdrawal. Since the current study observed that maternal maintenance therapy dose does not predict infant withdrawal severity, this highlights the importance of ensuring that women are maintained on adequate maintenance therapy doses to suppress their own withdrawal during pregnancy, without having a significant impact on infant outcome.

6.4.3. Plasma concentration correlation and NAS

While maternal maintenance therapy doses at delivery did not affect the severity of infant withdrawal, maternal plasma concentrations appear to provide a slightly better indicator as to the severity of NAS. While it would have been expected that maternal R(-)-methadone plasma concentration would have been correlated to infant withdrawal, this was not observed in the current study. Maternal plasma S(+)-methadone concentration was the only plasma methadone concentration related to infant withdrawal severity. There was a significant correlation between maternal plasma S(+)-methadone concentration and the AUC of infant withdrawal scores for methadone exposed infants. In a study observing the effects of methadone on subjective and physiological responses, Mitchell and colleagues

(2004) observed plasma S(+)-methadone concentration to be positively correlated to withdrawal in the general maintenance therapy population, whereas R(-)-methadone was not. However, it was suggested that these findings may be due to the effect of the S(+)-methadone enantiomer on the subjective effects of methadone withdrawal. As infant withdrawal is measured objectively, the observed correlation between maternal S(+)-methadone plasma concentration and infant withdrawal may simply be an incidental observation. Conversely, the lack of a significant correlation of maternal plasma R(-)-methadone concentration and infant withdrawal may not have been observed due to the small sample population from which plasma was collected from.

The positive correlation observed between maternal buprenorphine and norbuprenorphine concentrations and total infant morphine received was as hypothesised. This has not been assessed previously in buprenorphine exposed infants. This positive correlation indicates that the severity of infant withdrawal in buprenorphine exposed infants is directly related to the cut off of supply of buprenorphine in the maternal circulation. This indicates that morphine therapy in buprenorphine exposed infants is treating NAS and not other confounding symptoms. Knowing maternal plasma buprenorphine concentrations prior to delivery in particular, may therefore help predict withdrawal severity in the infant.

6.4.4. NAS and breast-feeding

Since both methadone and buprenorphine (although not yet norbuprenorphine) have been previously measured in breast milk (Section 1.5.7) it was important to determine whether breast-feeding affects NAS severity and treatment. As previous reports have suggested that infants breast-fed by mothers maintained on methadone are exposed to less than 5% of the maternal dosage (Begg et al., 2001), and the low oral bioavailability of buprenorphine in

adults, despite high concentrations of buprenorphine observed in breast milk, it was not expected that breast-feeding would affect NAS in the current study.

As hypothesised, breast-feeding did not appear to have an effect on the onset of NAS or the requirement for treatment in methadone or buprenorphine exposed infants. Whether or not infants were breast-fed did not affect the requirement for pharmacological treatment in either methadone or buprenorphine exposed infants. In those infants who were treated, breast-feeding did not affect the time of pharmacological initiation or the initial dose of morphine administered to control withdrawal in either methadone or buprenorphine exposed infants. In addition, breast-feeding did not affect the total amount of morphine administered to control withdrawal in either methadone or buprenorphine exposed infants.

For buprenorphine, this is in accordance with Marquet and colleagues (1997) and Schindler and colleagues (2003) who also did not observe breast-feeding to have an effect on NAS. In addition to the findings from the current study, Fischer and colleagues (2006) also did not observe an effect of breast-feeding on NAS in methadone or buprenorphine exposed infants. Results from the current study and the above mentioned prior research is in contrast to findings by Abdel-Latif and colleagues (2006) who observed considerably lower Finnegan scores in methadone exposed breast-fed, compared to non-breast fed infants. In addition, onset of withdrawal occurred significantly later in breast-fed compared to non-breast-fed infants. Breast-fed infants were also less likely to require pharmacological treatment as well as lower maximum doses of morphine. It should be noted that low numbers of non-breast-fed infants in both the methadone and buprenorphine groups in the current study, and low subjects numbers in the studies conducted by Marquet and colleagues (1997), Schindler and colleagues (2003) and Fischer and colleagues (2006)

would have resulted in low statistical power and therefore this area requires further investigation with a larger sample population of patients.

In addition, previous studies observing the effects of breast-feeding in methadone exposed infants have shown that breast-feeding cessation may lead to additional infant withdrawal (Malpas & Darlow, 1999). In contrast this was not observed in a single case study where breast-feeding was abruptly ceased in a buprenorphine exposed infant (Marquet et al., 1997). The effect of cessation of breast-feeding on NAS severity was also not assessed in the current study. Furthermore, as infants have been observed to have less biotransformation capacity than adults (Lacroix et al., 1997; Pelkonen et al., 1973; Shimada et al., 1994; Sonnier & Cresteil, 1998; Tateishi et al., 1997; Yang et al., 1994), it may be important to assess if cessation of breast-feeding results in a delayed withdrawal in infants due to increased concentrations of unmetabolised drug.

Maternal maintenance therapy doses of breast-feeding mothers also did not affect the requirement for pharmacological treatment in either methadone or buprenorphine exposed infants.

6.5. Conclusion

The current chapter presented the first results from a study comparing NAS as a result of methadone and buprenorphine exposure compared to non-opioid exposed control infants. Analysis of infant withdrawal scores indicated that buprenorphine produced NAS of intermediate severity between methadone exposed and control infants. However, when treatment for NAS was assessed it was possible to observe that NAS as a result of buprenorphine exposure is less severe than that produced as a result of methadone exposure as hypothesised. Importantly maternal maintenance therapy dose did not clinically correlate with infant withdrawal severity in either the methadone or buprenorphine group as predicted. This highlights the importance of ensuring mothers are adequately maintained to prevent their own withdrawal throughout pregnancy which may lead to premature labour. However, maternal buprenorphine plasma concentrations prior to delivery may provide an indication of severity of NAS. The current findings also observe that breast-feeding while maintained on methadone or buprenorphine does not affect the onset of NAS or requirement for treatment. However, since a large proportion of mothers in all three groups continued breast-feeding for longer than the 4 week observation period, the current study did not assess whether cessation of breast-feeding resulted in an increased NAS in either methadone or buprenorphine exposed infants or resulted in any other adverse events that may be related.

7. GENERAL SUMMARY AND DISCUSSION

7.1. Introduction

The primary aim of the current study was to assess the safety and efficacy of buprenorphine use during pregnancy and its effects on NAS, in comparison to methadone and a control population of pregnancies. This was the first study to present results comparing the effects of methadone and buprenorphine maintenance during and after pregnancy to a control population of pregnancies. In order to assess this, 25 women in each of the three groups of methadone maintained, buprenorphine maintained and non-opioid exposed control pregnancies, were recruited during pregnancy to participate in a non-randomised, open-label, flexible dosing study. Their infants were then followed up and assessed postnatally for NAS. The study was designed to assess differences in obstetric complications during pregnancy, as well as maintenance therapy outcomes in mothers including withdrawal and direct drug effects, and finally to assess NAS in methadone and buprenorphine exposed infants compared to non-opioid exposed control infants. The following discussion will begin by summarising the major findings of the study. Secondly, clinical implications of the current results will be discussed in relation to the use of methadone and buprenorphine as maintenance pharmacotherapies to be used during pregnancy. This will be followed by identifying future research directions regarding the use of methadone and buprenorphine for the treatment of opioid dependence during pregnancy and a final conclusion.

7.2. Summary of major findings

7.2.1. Antenatal obstetric outcomes

Previous research has observed that illicit opioid dependent women have higher rates of reported obstetric complications during pregnancy, but that these can be minimised to a level that is comparable to non-opioid exposed controls by a combination of methadone maintenance and increased prenatal care (Blinick et al., 1976; Doberczak et al., 1993; Silver et al., 1987; Strauss et al., 1974). It was therefore hypothesised in the current study that methadone and buprenorphine maintained women would suffer a similar rate of obstetric complications in the antenatal period as control women. This was measured by assessing the number of women from each group who attended services that were supplementary to their standard antenatal care, or were admitted to hospital in the antenatal period. Such measures and reasons for attendance/admission would provide an indication as to the frequency of potential or actual obstetric complications in the antenatal period. There was no significant difference between the three groups in attendances at additional services or admissions to hospital. In addition, if we assume admissions to the Antenatal and Gynecology Ward to represent the most serious of complications, these were again comparable in the buprenorphine group to those observed in the general population (Lacroix et al., 2004). This has not previously been assessed or reported. This study therefore confirms similar rates of obstetric complications in opioid maintained women as control women as was hypothesised for the current study, and observed in previous research for methadone maintenance.

The similar rate of obstetric complications in the antenatal period observed in opioid maintained women and controls in the current study, may be due to a similar number of

antenatal appointments attended by all three groups of women. This was in spite of methadone maintained women presenting significantly later for antenatal care than control women. Previous research has shown that increased antenatal care reduces obstetric complications (Berglund & Lindmark, 1998; Insler et al., 1986). As discussed in Section 1.5.4, prior research has also noted that opioid maintenance improves attendance rates for antenatal care. As previously mentioned (Section 3.4.1) similar rates of obstetric complications may also have been a reflection of the high level of care given to women who attend the high risk substance use antenatal clinic. If an individual woman presents late in her pregnancy for antenatal care, special attention is given to ensure that she in effect "catches up" on her antenatal care, attending the appropriate number of appointments and receiving adequate prenatal care. This may have also accounted for the improved fetal growth observed in the opioid maintenance therapy populations as pregnancy progressed, that was not significantly different to the control population and is in contrast to the proposed hypothesis.

Despite a lack of significant differences in other obstetric complications between the groups in the current study, it is important to note that three miscarriages were observed in the buprenorphine group and none in the methadone or control groups. Miscarriages have not previously been reported in prior studies assessing buprenorphine use during pregnancy and was therefore an unexpected outcome. While no miscarriages were observed in the methadone and control groups, those that were observed in the buprenorphine group were below what was predicted for the number of women recruited into the study in this group, based on miscarriage rates in the general population. Two of the women were already maintained on buprenorphine at the time of conception, while the third woman commenced BMT following conception. All three miscarriages occurred during the first trimester of pregnancy where there is an increased chance of miscarriage (Llewellyn-Jones, 1999). This

final aspect may have been why miscarriages were observed in the buprenorphine group alone compared to the methadone and control groups. No women from the control group were recruited in the first trimester which significantly decreased the chances of observing miscarriages in this group. In addition, significantly fewer women from the methadone group compared to the buprenorphine group were recruited in the first trimester which again decreased the chances of observing miscarriages in the methadone group compared to the buprenorphine group. Therefore, there was no difference in the frequency of obstetric complications, with the exception of the first trimester miscarriages, between methadone maintained, buprenorphine maintained or control women during pregnancy. Studies with a larger population of women observed during the first trimester may be required to further investigate whether the risk of miscarriage in buprenorphine maintained women is higher than the general population.

7.2.2. Maintenance therapy outcomes

Previous research in the area of methadone and buprenorphine use in pregnancy has focused primarily on infant outcomes with little data presented in the pregnant population comparing the two treatments for their maintenance efficacy. With known changes in methadone pharmacokinetic parameters as a result of pregnancy (Jarvis et al., 1999; Kreek, 1979; Pond et al., 1985; Swift et al., 1989; Wolff et al., 2005), it was vital that the two maintenance therapies be assessed and compared for their efficacy.

Maternal maintenance therapy doses did not increase significantly from the time of recruitment to the time of delivery in either methadone or buprenorphine maintained groups in the current study. The results presented in previous research are contradictory. Lacroix and colleagues (2004) reported that mothers wished to decrease their dose towards the end of pregnancy in order to prevent NAS in their infants. In contrast, Fischer and

colleagues (2006) observed a slight increase (although not reported as significant) in maintenance therapy doses in the third trimester in both methadone and buprenorphine maintained women. In the current study it is more likely that women simply refused to increase their doses towards the end of pregnancy in the belief that increasing their dose may increase the risk of NAS. On average maternal maintenance therapy doses were relatively low at the time of delivery for both methadone and buprenorphine maintained women and were below the average doses recommended to prevent illicit opioid use in the general maintenance therapy population. Inadequate dosing in the maintenance therapy population, as discussed previously, is one of the major factors contributing to discontinuation of maintenance therapy treatment and return to illicit opioid use (Section 1.4.3.6). However, treatment compliance did not appear to be affected by lower than average maintenance therapy doses in the current study, in either treatment group, as there was no significant difference between methadone and buprenorphine groups for the number of women who failed to continue maintenance therapy. Furthermore, an absence of increasing maternal maintenance therapy doses as pregnancy progressed, and below average doses at delivery, did not appear to affect maternal withdrawal or direct drug effects over the course of pregnancy in either maintenance therapy group. Maternal withdrawal scores or direct drug effects, such as craving for additional opioids, did not increase during pregnancy towards delivery. In light of the current results, clinical implications for maternal dosing will be discussed in further detail in a later section of the current chapter.

Despite a lack of change in maternal withdrawal and direct drug effects over the course of pregnancy in either treatment group, subjective measures of withdrawal were significantly higher during pregnancy for the methadone compared to the buprenorphine and control groups, with the buprenorphine group also not being significantly different to controls. In

addition, objective measures of maternal withdrawal were significantly higher for the methadone compared to the buprenorphine group, with controls not being significantly different to both groups. These results are in contrast to the proposed hypothesis that methadone and buprenorphine maintained women would experience similar withdrawal, and actually suggest that at doses observed in the current study (which were in the sub-therapeutic range), buprenorphine is more effective at preventing maternal withdrawal than methadone. Relatively low withdrawal scores in women maintained on buprenorphine are in accordance with those observed by Fischer and colleagues (1998; 2000) who reported absent or minimal maternal withdrawal in buprenorphine maintained mothers. However, when buprenorphine maintained women were compared to methadone maintained mothers there was no significant difference in maternal withdrawal (Fischer et al., 2006). A lack of difference in maternal withdrawal between methadone and buprenorphine maintained women observed by Fischer and colleagues (Fischer et al., 2006), may have been the result of increases in maternal maintenance therapy doses in the last trimester, resulting in women from both groups being maintained on doses that were above those recommended to prevent illicit opioid use in the general maintenance therapy population. Average doses of methadone and buprenorphine observed by Fischer and colleagues (Fischer et al., 2006) (53.5 $mg.day^{-1}$ and 14.0 $mg.day^{-1}$, respectively) were higher than those in the current study (48.4 $mg.day^{-1}$ and 7.5 $mg.day^{-1}$, respectively) and once again highlight the effectiveness of buprenorphine in the current study at minimising maternal withdrawal at sub-therapeutic doses.

Results obtained from the current study indicate that methadone and buprenorphine, when used during pregnancy, have similar efficacy in preventing additional opioid use. While significantly more women in the methadone and buprenorphine groups used additional opioids, benzodiazepines and cannabis compared to controls, there was no significant

difference between the two experimental groups in their use. With regard to additional opioid use, these results are as hypothesised and in accordance with work previously presented by Jones and colleagues (2005) who reported similar rates of additional substance use in methadone and buprenorphine maintained women. In contrast, Fischer and colleagues (2006) observed an increased use of additional opioids by buprenorphine maintained women during pregnancy. Differing results in additional substance use between the studies may be due to the small subject numbers used in the previous two studies (Fischer et al., 2006; Jones et al., 2005).

Patterns of symptom complaints were similar between methadone and buprenorphine maintained women as hypothesised, and for several symptoms buprenorphine maintained women reported the frequency to be significantly less than methadone maintained women. Typical opioid symptoms such as dry mouth, sweats, photophobia and watery eyes were reported by more women in the methadone group than the buprenorphine group. With the exception of dry mouth, these symptoms are indicative of withdrawal and once again highlight buprenorphine's effectiveness at minimising maternal withdrawal during pregnancy at below recommended doses.

Methadone and buprenorphine maintained women experienced significantly more symptoms overall than women in the control group; in particular loss of appetite, vomiting and depression. These three symptoms raised several issues of concern. Firstly, all three symptoms in combination may contribute to reduced fetal development due to poor maternal nutrition and physical health. As discussed in Section 4.4.6 loss of appetite due to vomiting may have obvious effects on nutritional intake in mothers. Furthermore, substances users are more likely to be depressed, and in combination with vomiting and reduced appetite, would contribute to poor physical maternal health (Darke et al., 2003;

Spitzer et al., 1995). Therefore all three symptoms should be closely monitored in order to prevent them from having an effect on fetal development.

Increased vomiting alone in opioid maintained pregnant women also raises issues of concern regarding re-dosing. If vomiting occurs following daily dosing administration, should re-dosing occur and if how much should be re-dosed? This is dependent on how long after administration vomiting occurred and would require careful consideration by the prescribing medical officer as to how much is re-dosed. This is less relevant for women maintained on buprenorphine due to its sublingual administration and absorption but more important for methadone maintained women as methadone is administered orally and may be regurgitated in the stomach contents.

The increased frequency of opioid maintained women reporting depression should also be closely monitored. As discussed in Section 4.4.6, depression in the antenatal period is correlated with postnatal depression. This has been shown to have an impact on maternal and infant bonding and lead to complications in later childhood (Lyons-Ruth et al., 1986; Moehler et al., 2006; Murray, 1992; Murray et al., 1991; Murray et al., 1996a; Murray et al., 1996b). Mothers and infants in the current study are already at an increased risk of having disruptions to maternal and infant bonding, as was observed with longer infant hospital stays for opioid exposed infants. Therefore, all efforts must be made to minimise depression in opioid maintained women during pregnancy so as not to compound issues with disruptions to mother and infant bonding.

7.2.3. Labour and delivery outcomes

Maternal and fetal outcomes during labour and delivery did not vary greatly between the three groups as hypothesised. There was no significant difference between the three groups

for the type of onset of labour or type of delivery. When assessing any complications of labour and delivery, there was also no significant difference between the three groups.

The increased number of opioid exposed women in previous studies who required analgesia and anaesthesia (Cassidy & Cyna, 2004; Silver et al., 1987) was not observed as hypothesised in the current study, with a similar number of women who had a vaginal delivery in each group requiring some form of analgesia and anaesthesia. Having observed these results, the current study did not actually assess whether or not women received adequate analgesia or anaesthesia during labour and delivery. While not statistically significant, trends observed in the number of women who did require anaesthesia and analgesia in the current study, suggest that an increasing number of women in the buprenorphine group require analgesia during labour and delivery than in the methadone or control groups. Furthermore one woman undergoing a Caesarean section from the buprenorphine group was actually placed under general anaesthesia due to reports of inadequate analgesia. Buprenorphine being a partial agonist at μ-opioid receptors means that if typical opioid analgesics are administered that have lower affinities at the μ-opioid receptors than buprenorphine, even in increasing doses these will not provide adequate, if any, analgesia. This, when coupled with previous reports observing hyperalgesia in opioid maintained individuals (Doverty et al., 2001) indicate that trends observed in the current study are not unexpected. Physicians often find it difficult to differentiate drug seeking behaviour and reports of inadequate analgesia in this patient population. Physicians are also hesitant to prescribe increasing amounts of opioid analgesia for fear of cognitive, respiratory, and psychomotor side effects (Alford et al., 2006; Mehta & Langford, 2006). Therefore opioid analgesics with higher affinities at μ-opioid receptors or other non-opioid forms of analgesia may be required in buprenorphine maintained women to provide

adequate analgesia (Alford et al., 2006; Mehta & Langford, 2006) during labour and delivery and requires further research.

When assessing infant outcomes immediately following labour and delivery, these were as hypothesised and were not significantly different between the three groups with the exception of infant size. Apgar scores at 1 and 5 min after birth were not significantly different between the three groups, which is in support of Doberczak and colleagues (1993) who observed median Apgar scores of opioid exposed infants to be within the normal range at birth. Gestational age at delivery was also not significantly different between the three groups. Methadone exposed infants were significantly smaller (with regard to birth weight, head circumference and body length) than control infants as shown in previous studies (Blinick et al., 1973; Kaltenbach & Finnegan, 1987; Kandall et al., 1976; Wouldes et al., 2004), with buprenorphine exposed infants not being significantly different to methadone exposed or control infants.

Infant parameters observed in the current study using a larger sample population, support the work of Jones and colleagues (2005) and Fischer and colleagues (2006) who did not observe significant differences in gestational age at delivery, Apgar scores, infant size including birth weight, body length and head circumference between methadone and buprenorphine exposed infants. Therefore, results from the current study support results from previous research that buprenorphine exposure produces similar infant outcomes immediately following labour and delivery as methadone.

Minimal clinical research has been performed in the area of transplacental transfer of opioids, and in particular, the transfer of the individual isomers of methadone, and buprenorphine and it's metabolite across the placenta. In the current study several

interesting findings were observed in relation to the timing of sample collection, the concentration ratio of R(-)- to S(+)-methadone in maternal and cord plasma and also buprenorphine samples that were below the limit of quantification. Firstly, the time of maternal dosing and the time of sample collection does not necessarily explain differences in cord R(-)- to S(+)-methadone concentration ratio compared to maternal R(-)- to S(+)-methadone concentration ratio as all cord R(-)- to S(+)-methadone concentration ratios were higher than the corresponding maternal ratio. Secondly, a significantly higher cord R(-)- to S(+)-methadone concentration ratio compared to maternal R(-)- to S(+)-methadone concentration ratio may be due to mechanisms such as stereoselectivity in metabolism or transport and requires further investigation to determine the mechanisms responsible. Thirdly, approximately 40% of the active R(-)- isomer of methadone is transported across the placenta compared to approximately 34% transfer of buprenorphine in samples that were able to be analysed. This appears to be greater than the 10% observed in previous *in vitro* studies (Nanovskaya et al., 2002). However, in contrast to methadone, buprenorphine was not able to be detected in one third of plasma samples collected from mothers and corresponding umbilical cords and may therefore indicate that significantly less buprenorphine is transferred across the placenta compared to methadone, and may result in a minimised NAS in buprenorphine exposed infants.

7.2.4. Postnatal outcomes

Results from the current study show that buprenorphine exposure results in a less severe NAS than methadone exposure as hypothesised. No significant differences were observed in the time or severity of onset between groups. There was no significant difference in the percentage of infants who required pharmacological treatment to control NAS between the two groups. However, significantly less total morphine was required in buprenorphine compared to methadone exposed infants to control NAS. While the time and amount of

morphine received were similar in both groups for the initial dose, the total amount of morphine received on a weekly basis was lower in buprenorphine compared to methadone exposed infants for the first three weeks of the 4 week follow up period. This suggests that the timing and severity of onset is similar in both groups with the severity continuing to increase in the methadone groups during the first and second week and returning to a similar severity as that produced by buprenorphine by the fourth week. This supports trends observed in small subject numbers by Jones and colleagues (2005) who reported similar numbers of methadone and buprenorphine exposed infants requiring treatment, with trends indicating less total morphine received in buprenorphine exposed infants.

In addition, differences in the severity of NAS between the two groups did not appear to be related to additional maternal substance use or infant prematurity, which was not significantly different between the two groups. Therefore, differences in NAS severity may have been related to differences in the placental transfer of the two medications. Furthermore as discussed in Section 1.4.3.5, as buprenorphine is a partial agonist, cessation of its use in the general adult maintenance therapy population results in a less severe withdrawal which may extend to infants, and therefore result in a less severe NAS as a result of buprenorphine exposure. Although not assessed in the current study, differences in fetal elimination of methadone and buprenorphine may also account for differences observed in the severity of NAS in the current study and would require a detailed study to investigate this.

The current study did not observe a clinical correlation between maternal methadone or buprenorphine dose at delivery and the severity of NAS. While a correlation was observed between maternal methadone dose at delivery and AUC infant withdrawal score versus time over the 4 week postnatal follow up period, the correlation did not extend to the more

pertinent outcome of total infant morphine received. Although the prior mentioned correlation should not be dismissed completely, it may have been more relevant had the correlation also been significant for total morphine received. This lack of correlation between maternal methadone dose at delivery with total morphine received, and in addition the lack of correlation between maternal buprenorphine dose at delivery and infant withdrawal, highlights the importance of focussing on ensuring mothers are maintained adequately during the antenatal period and treating NAS if and when it presents postnatally.

Correlations observed between maternal methadone and buprenorphine plasma concentration at delivery and infant withdrawal appear to be a more relevant indicator of clinical outcome. The correlation between maternal S(+)-methadone concentration and infant withdrawal may in itself have been an incidental finding considering a lack of correlation observed with maternal R(-)-methadone concentration. Similarly the lack of an observed correlation between R(-)-methadone concentration and maternal withdrawal may be due to the small sample size and may have been found had samples been obtained from all women in the study. However, the correlations that were observed show that while maternal maintenance dose is not a useful predictor of infant withdrawal, maternal plasma concentrations of maintenance therapy medication prior to delivery may be a useful factor for determining infant withdrawal and predicting its severity.

As methadone and buprenorphine have previously been detected in breast milk it was important to assess whether or not NAS was affected by breast-feeding. Breast-feeding did not affect the onset or requirement for NAS treatment in either group. Although the current study did not assess the transfer of either substance into breast milk or whether or not cessation of breast-feeding affected the severity of NAS, results from the current study

show that breast-feeding does not delay onset of NAS, does not reduce its severity and does not complicate its treatment and therefore suggests favourable outcomes for breast-feeding while maintained on methadone or buprenorphine. This is important and will aid with maternal and infant bonding in particular with relation to the longer infant hospital stays observed in the current study for infants in the methadone and buprenorphine groups compared to controls.

7.3. Clinical implications of current findings

Opioid dependence being the complex cognitive, behavioural and physiological condition that it is, often means that while one treatment may be effective in some individuals, it may not be as effective for others. Why then should this change simply because a woman is pregnant? Quite the contrary, the lack of effectiveness and acceptability of a particular maintenance therapy medication may even be exacerbated during pregnancy due to pharmacokinetic changes that have the potential to increases maternal withdrawal.

In the normal maintenance therapy population one of the primary aims is to minimise withdrawal over the inter-dosing interval, and for reasons previously mentioned, it is even more imperative to achieve this in pregnant women. However, the situation becomes far more complex during pregnancy, in that not only is it vital to minimise maternal withdrawal, but in addition, thought needs to be given to minimise, and if possible, prevent NAS.

The current findings suggest that buprenorphine is acceptable to pregnant women, minimises maternal withdrawal to some extent and most importantly reduces NAS in buprenorphine compared to methadone exposed infants. It appears that buprenorphine may even provide a better option as it alleviates withdrawal better than methadone at lower than recommended maintenance doses. However, methadone has been used for a considerable period of time during pregnancy and is the gold standard for treating illicit opioid dependence in the general maintenance therapy population. The current study has proven buprenorphine to be at least as effective as methadone at preventing maternal withdrawal, if not more superior at the doses used in this study, and demonstrates similar opioid effects and obstetric complications that were not significantly different to controls. Differences in

patient acceptance of both methadone and buprenorphine discussed in Section 1.4.3.4, highlight the need of matching a maintenance therapy to an individual. Furthermore, study design considerations discussed in Section 2.7.1 emphasise the need to not necessarily prove that one maintenance medication is better than the other, but to ensure that they are at least as effective as each other at maintaining women during pregnancy while reducing opioid side effects and obstetric complications at the same time as minimising NAS. Therefore, it is unlikely that observations from the current study will result in all pregnant opioid dependent women being induced onto buprenorphine. Nevertheless, findings from the current study may allow pregnant women, in consultation with their medical practitioner, more freedom of choice and flexibility as to which maintenance therapy is most effective for them and their unborn child. In addition, it may give pregnant illicit opioid users who are averse to being maintained on methadone and would not otherwise enter treatment, the opportunity to be maintained on buprenorphine throughout their pregnancy.

As discussed in Section 1.4 both the individual and maintenance therapy prescriber in the general maintenance therapy population need to view substitution maintenance therapy as a long-term commitment, as distinct from a short-term detoxification (Ling et al., 1994). Previous research has debated whether a correlation exists between maternal maintenance therapy dose at delivery and the severity of infant withdrawal. In the past this has often lead to women and medical prescribers decreasing maintenance therapy doses towards delivery (Section 1.5.4.1.5.1). The lack of a clinical correlation between maternal maintenance therapy dose at delivery and the severity of infant withdrawal in the current study highlights the need to ensure that women are maintained on adequate maintenance therapy doses during pregnancy in order to prevent their own withdrawal and its associated complications, without impacting the severity of NAS. Therefore, beliefs of both mothers

and medical prescribers need to be adjusted in order to ensure that as in the general maintenance therapy population, maintenance therapy use during pregnancy needs to be viewed as a long-term commitment as distinct form a short-term detoxification without significantly affecting NAS. In addition, for a population of women who prefer to be maintained on lower maintenance therapy doses, buprenorphine may be the treatment of choice as it provides superior alleviation of withdrawal compared to methadone in the lower dose range.

The benefits of breast-feeding have already been previously highlighted in Section 1.5.7 and include not only nutritional benefits for the infant, but most importantly positive psychological benefits for the mother and infant including boosting maternal self-esteem, and providing a greater opportunity for the mother and infant to bond. As these infants are already at a greater risk of maltreatment and neglect, often due to environmental factors that are associated with a substance using lifestyle, it is vital to maximise the opportunities for these mothers and infant to bond. As we have seen from this study this is made increasingly more difficult in this population, in that the length of infant hospital stay was significantly longer for methadone and buprenorphine exposed infants compared to control infants. In addition, debate has also risen regarding the effect of maternal dose and breast-feeding (Section 1.5.7) on NAS particularly in methadone exposed infants. However, the current study observed that the onset of, and requirement for treatment of NAS, was not affected by breast-feeding in methadone or buprenorphine exposed infants or by maternal maintenance therapy doses of breast-feeding mothers. The current study was however limited by small subject numbers of non-breast-fed infants and did not assess whether or not cessation of breast-feeding increased the severity of NAS. These results in conjunction with further research to assess the limitations of the current study, should allow these

infants to take advantage of the nutritional and health benefits associated with breast-feeding, as well as giving these mothers and infants a greater opportunity to bond.

7.4. Directions for future research

Despite the potential advantages shown in the current study for the use of buprenorphine during pregnancy it still leaves questions for future research to address. In demonstrating the efficacy of buprenorphine as a maintenance therapy during pregnancy evidenced by comparable outcomes to methadone and minimising NAS in newborn infants, the present study provides ethical justification for such studies to be undertaken. The following are areas as to where future research priorities should be directed.

Firstly, while changes in methadone pharmacokinetics have been assessed during pregnancy, these are yet to be assessed for buprenorphine. It is important that if any changes in $t_{1/2}$, C_{max}, volume of distribution, clearance or bioavailability occur, these are determined in order to give a better indication of the dosing requirements needed for these women to prevent withdrawal during pregnancy and the associated risks. For changes in buprenorphine pharmacokinetics to be determined this would involve conducting 24 hr dosing interval studies at various times throughout pregnancy and comparing them to dosing interval studies conducted postnatally. Following this, alternate daily dosing, that occurs in the general maintenance therapy population, should be assessed to determine if it is possible for this to occur during pregnancy. Therefore, again giving women the possibility of greater flexibility and choice in their maintenance therapy medication during pregnancy.

Secondly, the current study observed that more women in both treatment groups reported depression compared to control groups in the third trimester with significantly more women in the methadone group reporting depression during the remainder of the pregnancy compared to controls. Considering the deleterious effects depression may have on the

mother during the antenatal period, and consequently the developing fetus, as well as increasing the chances of postnatal depression, it is vital that depression be minimised during pregnancy. Previous research has debated whether or not buprenorphine itself may possess antidepressant activity. Dean and colleagues (2004) observed no difference between methadone and buprenorphine groups in improvement of depressive symptoms over a 3 month period. However, Pani and colleagues (2000) observed a more consistent improvement in depression in patients treated with methadone compared to those treated with buprenorphine. When studied alone, buprenorphine has been shown to be more effective in patients with depression when compared to patients without co-morbidities (Gerra et al., 2006). Furthermore, buprenorphine has even been shown to be effective in the treatment of refractory depression (Bodkin et al., 1995). The effect of buprenorphine on depression has been attributed to buprenorphine's κ-opioid receptor antagonistic properties. As binding at the κ-opioid receptor causes dysphoria (Section 1.3), the antagonist properties of buprenorphine at this receptor are thought to counteract dysphoria, negativism and anxiety (Gerra et al., 2006; Nunes et al., 2004). Therefore, future research could further investigate whether buprenorphine significantly improves depression when used to treat opioid dependence during pregnancy.

Thirdly, while the current study did not observe significant differences between the three groups in the percentage of women who required analgesia and anaesthesia during labour and delivery as observed in prior reports, trends indicated that significantly more women in the buprenorphine group may have required analgesia at this time. In addition, one woman from the buprenorphine group who underwent an elective Caesarean section was placed under general anaesthesia due to reports of inadequate analgesia. With previous reports of problematic pain management in opioid maintained individuals, not only in the general population but during labour and delivery, this area requires further research to ensure that

opioid maintained women, particularly those maintained on buprenorphine due to its pharmacology, are provided with adequate analgesia and anaesthesia during labour and delivery. This could be achieved by administration of pain assessment surveys as well as assessment of the type and amount of analgesia and anaesthesia used during labour and delivery.

Fourthly, several interesting findings were revealed in the current study in relation to the placental transfer of methadone and buprenorphine that require further investigation. This is the first clinical study to assess the placental transfer of the individual enantiomers of methadone and showed there to be some stereoselectivity in their transfer. The mechanisms for this are currently unknown, but may involve the enzymes responsible for placental metabolism of methadone or drug transporters. In addition, the transfer of buprenorphine across the placenta in the clinical setting appears to be higher than first observed in *in vitro* studies and therefore this area of placental transfer of methadone and buprenorphine requires further investigation.

Fifthly, the current study observed several correlations between maternal plasma concentration and NAS in both the methadone and buprenorphine groups that warrant further investigation. As maternal dose at delivery did not correlate clinically with NAS, this suggests that maternal plasma concentration of maintenance therapy towards delivery may give a better indication as to the severity of NAS as distinct from maternal dose. Due to the inability to collect samples at delivery from all women, or drug concentrations being below the limit of quantification, this resulted in significantly fewer samples being utilised than expected and therefore these findings should be confirmed with a larger sample population. Buprenorphine cord samples with plasma concentrations being below the limit of quantification is a finding in itself, as previously discussed, that suggests minimal transfer of buprenorphine across the placenta, which also requires further investigation.

Sixthly, determining how rapidly the infant can metabolize and eliminate drugs to which they are exposed, may provide a better understating as to the severity and time course of NAS. Analysis of plasma samples collected from the neonate at various stages postnatally could determine how fast methadone and buprenorphine are eliminated from the neonates' system and what relationship this may have to the severity of NAS. In addition, collection of infant urine samples for assessment of metabolite/parent drug ratios in comparison to maternal metabolite/parent drug ratio may provide evidence of the fetus' ability to accumulate and metabolize methadone and buprenorphine and confirm reports of reduced biotransformation capacity of the fetus and infant compared to the adult (Lacroix et al., 1997; Pelkonen et al., 1973; Shimada et al., 1994; Sonnier & Cresteil, 1998; Tateishi et al., 1997; Yang et al., 1994).

Seventhly, while the current study did not observe breast-feeding while maintained on buprenorphine to affect the onset or the requirement for treatment of NAS, these results were limited by small subject numbers of non-breast-fed infants and also did not assess if the cessation of breast-feeding affected the severity of NAS. In addition, only 2 previous studies have investigated the concentration of buprenorphine in breast milk. It is therefore important to confirm results observed in the current study as well as assess the effect of breast-feeding cessation on NAS severity or recurrence and determine the exposure of these infants to buprenorphine via breast milk. This would involve determining the concentration of buprenorphine in both colostrum and breast milk in relation to maternal plasma and could be achieved by collecting corresponding colostrum/milk samples with maternal plasma samples to determine the milk to plasma ratio and subsequent infant exposure.

Lastly, several safety aspects, including side effects of buprenorphine use during pregnancy, were assessed in the current study population. However, based on the sample size in the present study (n=25), it is difficult to make projections regarding safety, particularly the occurrence of rare events, in a wider population. Therefore further research to assess buprenorphine's safety is required in a larger population of patients.

7.5. Conclusion

The primary outcome measures to be assessed in the current study were the efficacy and safety of buprenorphine use during pregnancy and the resultant NAS compared to methadone and a non-opioid exposed control population. This study was the first study to compare results between methadone and buprenorphine maintenance and exposure to a control population of non-opioid exposed control pregnancies and their infants. While previous research has focussed on infant outcomes and NAS, there is a lack of published information concerning buprenorphine's efficacy as a maintenance pharmacotherapy or its effects on obstetric outcomes during pregnancy.

With the exception of the miscarriages observed in the buprenorphine group, which were below the level of those predicted and were within the limits of those experienced in the general population, the frequency of women who experienced obstetric complications in the antenatal period was similar between the three groups as hypothesised. Fetal growth was also comparable between the three groups by the third trimester and is in contrast to the hypothesis of slowest fetal growth in the methadone group.

At the sub-therapeutic doses observed in the current study buprenorphine may actually be more effective at preventing maternal withdrawal than methadone in contrast to the proposed hypothesis of similar withdrawal experiences in the two treatment groups. Additional substance use was significantly higher in both treatment groups compared to controls but was not significantly different to each other as hypothesised. Patterns of reporting of symptom complaints was also significantly higher but no different to each other in both treatment groups compared to controls and raised several maternal management issues including maternal health and nutrition, re-dosing and depression.

Complications of labour and delivery were similar between all three groups as hypothesised. In contrast to the proposed hypothesis the frequency of women requiring analgesia and anaesthesia during labour and delivery was similar between all three groups. Infant outcomes immediately following labour and delivery were similar between all three groups as predicted with the exception of smaller infants observed in the methadone group compared to controls, and no significant difference to buprenorphine exposed infants.

In terms of infant postnatal outcomes, time of NAS onset and severity was not significantly different between methadone and buprenorphine exposed infants nor was the percentage of infants who required treatment to control NAS. However, significantly less morphine was required to control NAS in buprenorphine compared to methadone exposed infants and may be due to less buprenorphine transport across the placenta.

Therefore, results from the current study report the first observations comparing methadone and buprenorphine for opioid maintenance therapy during pregnancy in comparison to a control population. The control population enabled a comparison to be made for obstetric outcomes and provided a baseline for assessment of maternal and infant withdrawal. The current study observed buprenorphine to have several advantages over methadone including improved maternal withdrawal at below recommended maintenance doses, possible reduction of re-dosing complications if vomiting occurs following dosing and minimisation of NAS severity. In addition, as it is vital that maintenance therapies be matched to the individual to maximise retention in treatment, results from the current research will help to extend choices and improve treatments available to opioid maintained women during pregnancy, consequently improving health outcomes for both the mother and the infant.

Appendices

Appendix 1 Maintenance therapy assessment

Subject initials: ☐☐☐ **Subject code:** ☐☐☐☐☐

Date today: ☐☐/☐☐/☐☐ ***BUP*renorphine/*MET*hadone:** ☐☐☐

Date previous visit: ☐☐/☐☐/☐☐ **Gestational age (weeks):** ☐☐

All questions in this questionnaire are about what has happened to you since your last visit. Any information you give here is completely confidential. Please answer all questions honestly and accurately.

Please make a vertical line across each line below to show what you think about your current maintenance therapy.

Office Use only

A1. How well has this drug been holding you?

too low — too high ☐

A2. How much of a "buzz" does this drug give you?

none — a lot ☐

A3. How many side effects do you feel from this drug?

none — a lot ☐

A4. How much do side effects from this drug bother you?

not at all — a lot ☐

A5. How much do you like this drug?

not at all — a lot ☐

A6. Does this drug make you feel more "normal"?

definitely no — definitely yes ☐

A7. How much do you crave heroin while on this drug?

not at all — a lot ☐

A8. What are the best things about this drug?

_____

A9. What are the worst things about this drug?

_____

Appendix 2 Additional substance use

Subject initials: ☐☐☐ **Subject code:** ☐☐☐☐☐

Date today: ☐☐-☐☐-☐☐ ***CON*trol/*BUP*renorphine/ *MET*hadone:** ☐☐☐

Date previous visit: ☐☐-☐☐-☐☐ **Gestational age (weeks):** ☐☐

All questions in this questionnaire are about what has happened to you since your last visit. Any information you give here is completely confidential. Please answer all questions honestly and accurately.

Buprenorphine/methadone only	**Dose:**
Heroin	Yes/No
Number of days used since last visit	
Other opioids	Yes/No
Substance (morphine, pethidine, oxycodone, codeine etc)	
Number of days used since last visit	
Marijuana	Yes/No
Number of days used since last visit	
Benzodiazepines	Yes/No
Substance (diazepam, temazepam, oxazepam etc)	
Number of days used since last visit	

Appendix 3 Symptom checklist

Subject initials: ☐☐☐ **Subject code:** ☐☐☐☐☐

Date today: ☐☐-☐☐-☐☐ ***BUP*renorphine/*MET*hadone/ *CON*trol:** ☐☐☐

Date previous visit: ☐☐-☐☐-☐☐ **Gestational age (weeks):** ☐☐

Patient Information: ***All questions in this questionnaire are about what has happened to you since your last visit. Please answer all questions honestly and accurately regarding any symptoms you have experienced as the result of your maintenance therapy (methadone and buprenorphine subjects only) or pregnancy (all subjects).***

	Yes	No
Body as a Whole		
Fatigue		
Chills		
Fever		
Headache		
Pain		
Pain abdominal		
Pain back		
Digestive System		
Loss of appetite		
Constipation		
Diarrhoea		
Dry mouth		
Indigestion		
Nausea		
Nausea +vomit		
Vomit		
Musculo-skeletal System		
Joint pain		
Muscle Pain		
Bone pain		
Nervous System		
Agitation		
Anxiety		
Depression		
Abnormal or vivid dreams		
Muscle tension		
Insomnia		
Nervousness		

Somnolence		
Tremor		
Twitch		
Dizzy spells		
Respiratory System		
Shortness of breath		
Hiccup		
Sniffily nose		
Skin and Appendages		
Acne		
Dermatitis		
Rash		
Sweat		
Special Senses		
Dry eye		
Watery eyes		
Photophobia		
Strange tastes		
Reduced libido		
Other		

OFFICE USE ONLY
Reporting of any repeated serious adverse events

Appendix 4 Modified Finnegan Withdrawal Scale

Modified Finnegan Withdrawal Scale

WARD

MRN

SURNAME

OTHER NAMES

DOB/SEX

NEONATAL WITHDRAWAL SCORING CHART (TERM INFANTS)

SYSTEM	SIGNS & SYMPTOMS	SCORE	DATE AND TIME IN HOURS									
CENTRAL NERVOUS SYSTEM DISTURBANCES	High-Pitched Cry	2										
	Continuous High-Pitched Cry	3										
	Sleeps <1 hour after feeding	3										
	Sleeps <2 hours after feeding	2										
	Sleeps<3 hours after feeding	1										
	Mild Tremors Disturbed	1										
	Mod-Severe Tremors Disturbed	2										
	Mild Tremors Undisturbed	3										
	Mod-severe Tremors Undisturbed	4										
	Increased Muscle Tone	2										
	Excoriation (Specify area) _____	1										
	Myoclonic jerks	3										
	Generalised Convulsions	5										
METABOLIC/VASOMOTOR/ RESPIRATORY DISTURBANCES	Fever (37.3°C-38.3°C)	1										
	Fever (38.4°C and higher)	2										
	Frequent Yawning (>3-4 times)	1										
	Nasal Stuffiness	1										
	Sneezing (>3-4 times)	1										
	Nasal Flaring	2										
	Respiratory Rate >60/min	1										
	Respiratory Rate >60/min with Retractions	2										
GASTROINTESTINAL DISTURBANCES	Excessive Sucking	1										
	Poor Feeding	2										
	Regurgitation	2										
	Projectile Vomiting	3										
	Loose Stools	2										
	Watery Stools	3										
	Max. Score= 41 TOTAL SCORE											
	SCORER'S INITIALS											

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