

Clinical Guidelines for the use of Buprenorphine in Pregnancy



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Steering Committee

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Executive summary

The safety of buprenorphine treatment for opiate dependence during pregnancy and breastfeeding has not yet been definitively established. There is a lack of controlled studies with adequate follow up periods demonstrating safety of the medication during pregnancy and during breastfeeding. Methadone maintenance remains the treatment of choice for pregnant and breastfeeding women.

All non-pregnant women of childbearing age who commence buprenorphine treatment should be warned of the lack of proven safety of buprenorphine in these situations and advised on appropriate contraception.

The Therapeutic Goods Administration approved buprenorphine in October 2000 for the treatment of opiate dependence. Both pregnancy and breastfeeding have been listed as contraindications (Reckitt Benckiser 2003). Any use of buprenorphine in either scenario is, therefore, 'off-label' use of the medication, placing a greater responsibility on the prescribing doctor to discuss the risks and benefits of the medication for the patient.

Due to the lack of comprehensive data on the safety of buprenorphine during pregnancy, pregnant women who conceive while on buprenorphine treatment are advised to transfer to methadone maintenance.

However, some pregnant women may decline to transfer to methadone treatment. Clinical situations may arise where it is less 'unsafe' for a pregnant woman to continue buprenorphine during pregnancy than to relapse to dependent heroin use. A consideration of the balance of risks for pregnant women who use heroin is, therefore, required. The risks of maintaining dependent opioid use, particularly illicit heroin use, during pregnancy may well be significantly greater than the risks of buprenorphine maintenance for these women and their babies. The substantial body of knowledge of the safety of methadone treatment during pregnancy must also be considered.

These guidelines detail clinical issues involved in managing pregnant women who are on buprenorphine during pregnancy.

The majority of research regarding the use of buprenorphine for pregnant and breastfeeding women has occurred in Europe. Published data currently exists on 288 buprenorphine maintained pregnancies (including one case comparison study only). This research is in a state of ongoing development. Data on the safety of buprenorphine during pregnancy and breastfeeding will evolve in the coming years. Clinicians are advised to check annually for updates.

Introduction

These guidelines are written for medical, nursing, midwifery, drug and alcohol clinicians and allied health staff involved in the management of opioid dependent women who are pregnant. They are intended as a guide for managing opioid dependent women who are on buprenorphine maintenance programs for heroin dependence and are pregnant or considering becoming pregnant.

The guidelines are consensus guidelines, based upon consultation with experts in the field of addiction medicine, obstetrics and neonatology. Consensus was reached regarding recommendations in the guidelines. The body of evidence from the research literature regarding the use of buprenorphine in pregnancy is small but rapidly evolving. Clinical guidelines should be used as a guide to clinical management; clinicians must always consider the pregnant woman they are managing as an individual, and apply the guidelines appropriately.

Evidence on the safety of buprenorphine during pregnancy and lactation are currently emerging. These guidelines have been written in 2003. It is anticipated that new evidence will emerge in the coming years regarding buprenorphine in pregnancy and breastfeeding.

Medico-legal issues

These guidelines discuss the clinical management of pregnant and breastfeeding women. They do not aim to discuss medico-legal situations of the management of opioid dependent women using buprenorphine in pregnancy.

Opioid dependence and pregnancy

Different patterns of opioid use occur amongst heroin users. Non-dependent patterns include experimental heroin use, recreational or occasional heroin use and abuse of heroin.

Opioid dependence is a chronic relapsing clinical syndrome defined by tolerance, withdrawal, loss of control and relapse. DSM IV (American Psychiatric Association 1994) defines dependence where 3 or more criteria are seen in a twelve-month period:

- Tolerance
- Withdrawal
- Opioids taken in larger amounts or longer than intended.
- Persistent desire or unsuccessful attempts to cut down or control use
- A great deal of time is spent in activities necessary to obtain opioids, use opioids, or recover from their effects.
- Important social, occupational, or recreational activities are given up or reduced because of opioid use.
- The opioid use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.

Practically, opioid dependence is usually ascertained by assessment of a history of dependence in combination with supportive clinical findings (e.g. evidence of acute and chronic injection). A drug consumption history provided by a patient is usually accurate unless there are significant reasons for a person to under-report substance use (e.g. fear of reporting to a child protection agency). Objective evidence (e.g. urine toxicology) and/or collateral history (e.g. from partner/relative) may provide valuable additional information.

Opioid use during pregnancy

Pregnancy outcomes

Heroin use during pregnancy, particularly dependent heroin use, is associated with a range of problems, affecting both obstetric and neonatal health and pregnancy outcomes.

Proximal risks

Significant adverse health outcomes for pregnant women who use heroin include:

- Reduction on foetal growth resulting in low birthweight
- Prematurity
- Foetal and neonatal death

Heroin use during pregnancy is associated with low birth weight (Glantz JC and Woods JR Jr 1993) (Hulse GK, Milne E et al. 1997), prematurity (Finnegan LP 1988) (Ellwood DA, Sutherland P et al. 1987) and neonatal death (Hulse GK, Milne E et al. 1998) (Finnegan LP 1988). In turn the above risk factors are associated with a wide range of other obstetric and neonatal problems including: respiratory distress syndrome, IUGR, intracranial haemorrhage, asphyxia neonatorum, meconium aspiration, placental abruption and other conditions.

However, the association is complex and a number of other factors are likely to impact on the health of heroin dependent pregnant women and their infants. Pregnant women who are dependent to heroin are at particularly high risk of experiencing complications during pregnancy, due to a variety of factors. These may include:

- inadequate antenatal care;
- a range of biological (e.g. inadequate nutrition, blood borne virus exposure, overdose) psychological (depression, other mental health problems) and social problems (including abuse and violence, financial problems, accommodation problems, relationship problems, legal problems),
- other substance use including tobacco, cannabis and other drug use;
- repeated cycles of opioid intoxication and withdrawal due to heroin dependence that are dangerous to the foetus.

from (Finnegan LP 1988) (Finnegan LP 1991).

A number of confounding factors must be considered in understanding the relationship between heroin and pregnancy and the effects of methadone. Tobacco has a profound effect both on birthweight and pregnancy. Other drug use (including ongoing heroin use, alcohol and benzodiazepine use) may additionally have an effect. Stressors related to the 'lifestyle' associated with heroin use may have a profound impact on maternal and neonatal health. Poor antenatal care attendance may have a significant negative impact on obstetric and neonatal health.

Regardless of the exact nature of the association between heroin and pregnancy, methadone is associated with improvements in obstetric and neonatal health. Methadone is associated with improvements in neonatal mortality and morbidity including prematurity and low birth weights (Finnegan LP and Kandall SR 1997) (Ward J, Mattick R et al. 1998). Methadone maintenance avoids cycles of opiate intoxication and withdrawal; this may stabilise the inter-uterine environment. The beneficial effects of methadone maintenance may also, in part, be due to the capacity for methadone maintenance to increase antenatal clinic attendance, care and monitoring.

A significant positive effect on birth outcomes of infants born to heroin dependent women has been reported since data was collected in the 1960s and 1970s (Finnegan LP 1988). This may be due to several factor including: a marked capacity to manage premature, low and very low birthweight neonates as well as the development of specific alcohol and drug and obstetric services.

Summary of risks to pregnant women who use heroin

Pregnancy risks

- miscarriage, premature labour
- growth restriction, small for gestational age, low birth weights
- foetal distress, foetal death in utero, stillbirth
- other (as a result of the above problems e.g. asphyxia, intracranial haemorrhage, hypoglycaemia, septicaemia, hyperbilirubinaemia)

Maternal (& foetal) risks

- overdose
- blood borne viruses (Hepatitis C, B and HIV)
- local/systemic infections etc.

Neonatal

- neonatal abstinence syndrome

Neonatal abstinence

A variety of substances can result in an abstinence syndrome in neonates. These include:

- alcohol
- amphetamines
- barbiturates
- benzodiazepines
- diphenhydramine
- tricyclic antidepressants
- opioids

(Finnegan LP and Kandall SR 1997).

In addition, nicotine dependence, even at moderate to low levels, may be associated with a neonatal abstinence syndrome (Law, Stroud et al. 2003). Use of other substances by pregnant women can potentially complicate a neonatal abstinence syndrome. Consideration of use of all of these substances is important in managing pregnant women who use psychoactive substances as well as their neonates.

Dependent opioid use is associated with the opiate neonatal abstinence (or withdrawal) syndrome (NAS). This syndrome is characterised by the following symptoms in the neonate: gastrointestinal dysfunction, respiratory distress, sneeze, yawn, mottling, fever, feeding problems, tremors, high-pitched cry and increased muscle tone. The syndrome usually commences within 72 hours of birth and can last for up to several weeks. Severe neonatal withdrawal is an indication for pharmacological management of NAS (Finnegan 1980).

The Neonatal Abstinence Score (or Finnegan Score, see Appendix 3) was developed to monitor the progress of infants experiencing neonatal abstinence due to opioid exposure in utero. It can be used as a trigger for pharmacological treatment of neonatal abstinence (see section on Management of Neonatal Abstinence). Provided that neonatal abstinence is appropriately managed, it is not associated with long-term health problems.

Opioid substitution in pregnancy

Objectives of opioid substitution

Methadone maintenance for the management of heroin dependence is an intervention with a robust evidence base. The Australian National Policy on Methadone Treatment lists the following objectives of methadone treatment (National Drug Strategy 1997):

- to reduce harmful opioid and other drug use;
- to improve the health of clients;
- to help reduce the spread of blood-borne communicable diseases associated with injecting opioid use;
- to reduce deaths associated with opioid use;
- to reduce crime associated with opioid use; and
- to facilitate an improvement in social functioning.

These outcomes are associated with adequate maintenance doses of methadone (60 to 80 mg and above in the literature (Ward J, Mattick R et al. 1998)). Sub-therapeutic doses of methadone are not associated with significant reductions in heroin use nor other harm reduction objectives identified above.

However, some patients can effectively be maintained on lower doses of methadone if there is cessation of heroin use. Clinical dose titration is the mainstay of how to identify an adequate dose of methadone for an individual patient. It should also be noted that effective doses change dynamically over time depending on patients' lifestyles, exposure to heroin and other illicit opioids and other factors.

For additional information regarding methadone maintenance see the Victorian Methadone Prescribing Guidelines (Department of Human Services Victoria 2000) and the Australian National Policy on Methadone (National Drug Strategy 1997).

Opioid substitution during pregnancy

Methadone maintenance treatment has been demonstrated to significantly improve pregnancy outcomes for opioid dependent women. Methadone maintenance:

- enables stabilisation of drug use and lifestyle,
- reduces or eliminates illicit drug use and can help stabilise the in utero environment,
- facilitates access to comprehensive antenatal and postnatal care,
- does not increase the risk of congenital abnormalities in the foetus.

Methadone itself may not be responsible for all the above benefits, but it may be that the additional care associated with methadone treatment may provide some of these benefits. Increasing access to ante-natal care and monitoring improves both maternal and neonatal outcomes (Finnegan LP and Kandall SR 1997) (Ward J, Mattick R et al. 1998).

In Victoria, pregnant opioid dependent women have high priority for access to methadone maintenance programs in order to minimise the risk of complications (Department of Human Services Victoria 2000). Consideration should be given for priority access for the partners of pregnant opioid dependant women to methadone maintenance.

There is strong evidence suggesting that significant improvement in the health of pregnant opioid dependent women and their babies occurs if they are monitored by specialist obstetric units with expertise in managing substance use (Ward J, Mattick R et al. 1998) (Finnegan LP and Kandall SR 1997). Ante-natal care should, therefore, be managed in collaboration with obstetric services that specialise in the management of drug dependence during pregnancy.

Objectives of opioid substitution in pregnancy

The objectives of treating pregnant women with methadone during pregnancy include the above National Objectives of methadone treatment and the following objectives:

- to prevent drug related harms occurring to pregnant women and their babies;
- to assist the establishment of bonding between the mother and child.
- to improve health and development outcomes for the infant

Methadone maintenance should be commenced as soon as possible after a confirmed diagnosis of pregnancy or continued for women already on methadone programs. The overall aim should be to maintain the pregnant woman on methadone for the duration of the pregnancy.

Withdrawal from methadone treatment is strongly discouraged due to the risk of miscarriage in the first trimester, premature labour and foetal death in utero in the third trimester and return to dependent opioid use with its' many associated harms.

Objectives of opiate substitution treatment during pregnancy

- to reduce harmful opioid and other drug use;
- to improve the health of clients;
- to help reduce the spread of blood-borne communicable diseases associated with injecting opioid use;
- to reduce maternal and infant deaths associated with opioid use;
- to reduce crime associated with opioid use;
- to facilitate an improvement in social functioning;
- to prevent drug related harms occurring to pregnant women and their babies;
- to assist the establishment of bonding between the mother and child;
- to improve health and development outcomes for the infant

Management of opioid substitution during pregnancy and perinatally

Methadone maintenance is the mainstay of management of opioid dependence in pregnancy

Assessment of pregnant women

Pregnant women who present for commencement of methadone maintenance should be assessed on a priority basis. Delayed commencement of methadone for those women that have decided they want to commence methadone may result in ongoing harms to the women and their babies.

- Opioid antagonist (e.g. naloxone) challenge **should not** under any circumstances be used in pregnant women because this may precipitate miscarriage or premature labour or foetal death in utero. (Finnegan 1980)
- Consideration should be given to facilitated access for the opioid dependent partners of pregnant women to methadone or buprenorphine maintenance treatment.

There are several complications of methadone treatment during pregnancy. Methadone treatment during pregnancy is associated with:

- increased risk of the neonatal withdrawal syndrome; possibly both in severity and duration;
- increased requirement for admission to neonatal special care units, and increased likelihood of the neonate requiring pharmacological treatment for the neonatal withdrawal syndrome;
- greater neonatal weight loss;
- longer periods of hospital admission;
- the potential for problems with breastfeeding.

However, the advantages of treatment with methadone for pregnant women outweigh the disadvantages. Neonatal withdrawal, when managed by experienced and expert staff, is not life threatening; can be successfully managed by specialist neonatal units and is not associated with long term dangers to the newborn. In contrast, heroin use throughout pregnancy is associated with increased neonatal mortality as well as increased morbidity.

Pregnant women should be adequately informed of the advantages and disadvantages of methadone treatment during pregnancy in order to make an informed decision regarding methadone maintenance.

Maintenance treatment

Methadone treatment should comprise:

- Comprehensive assessment for suitability for methadone treatment;
- Regular medical reviews and follow up;
- Supervised methadone dosing at a community pharmacy or other dispensing point;
- Appropriate psycho-social services where indicated;
- Co-ordination of care between obstetric and methadone services.
- Monitoring and documentation of drug use during the pregnancy

Obstetric and drug treatment reviews should occur on a regular and frequent basis throughout the pregnancy. For stable clients this should occur as frequently as clinically indicated. This will vary from patient to patient but would normally be more frequent than for non-pregnant methadone patient and would usually be from weekly to monthly. Many clinics would review pregnant patients on a fortnightly basis and weekly in late pregnancy.

Once stabilised, pregnant patients on methadone should be reviewed as frequently as clinically indicated.

The general principles of methadone treatment during pregnancy are:

- Stabilisation of the patient on an appropriate dose sufficient to cease illicit drug use.
- Maintenance at a level that keeps the woman comfortable, and avoids drug withdrawal during pregnancy. Dose reduction is not encouraged and dose increases may be required.
- Keeping the patient on a maintenance dose for a minimum of two to three months postpartum before any dose reduction.
- A consideration of the need to address other substance abuse problems (smoking, alcohol, benzodiazepines) that have adverse effects on pregnancy outcomes.

Methadone doses should be titrated against patient needs. Doses should be increased until there is cessation of heroin use. This will vary from patient to patient. Usually, doses of 60 to 80 mg are required to achieve abstinence from heroin use.

Methadone dose increments may be required throughout the pregnancy, especially during the third trimester. Particularly dose increments may be expected due to several factors during pregnancy including:

- Physiological factors including:
 - increased volume of distribution.
 - increased liver metabolism.
 - increased GFR resulting in increased metabolite excretion.
 - increased narcotic metabolism by placenta and foetus
- Psychosocial factors including:
 - Level of support from partner, family and friends
 - Exposure to substance use including partner's use of or abstinence from drugs
 - Stability of accommodation and overall environment
 - Other problems e.g. legal, financial etc.

Split dosing of methadone may also be required during pregnancy, especially during the third trimester, due to the factors described above. The usual approach is to trail a 50/50 split of the dose in morning and evening and adjust the ratio where required clinically.

Breastfeeding

As a general principle, breastfeeding should be encouraged for pregnant opiate dependent women maintained on methadone.

The amounts of methadone secreted in breast milk are minimal and are unlikely to have any adverse effects on neonates.

Contra-indications to breastfeeding include ongoing illicit/unsanctioned substance use and HIV positive status. Hepatitis C positivity is generally not a contraindication to breast-feeding.

Other management approaches for the treatment of heroin dependence during pregnancy

Withdrawal from illicit heroin, or withdrawal from methadone maintenance, is not encouraged due to the high risk of relapse to dependent opioid use and the many associated harms. In particular, withdrawal during pregnancy can result in:

- miscarriage during the first trimester;
- premature labour during the third trimester;
- high risk of return to dependent illicit opioid use with associated harms.

If a patient wants to reduce their methadone dose during pregnancy, the second trimester appears to be the period associated with least risk.

In the context where a patient is adamant about reducing their methadone dose, and is aware of the potential dangers associated, gradual reductions (e.g. by no more than 5 mg at a time) may be considered during this period. Such patients should be monitored intensively during and after withdrawal. Re-stabilisation on methadone should occur in the event of relapse. For a more detailed discussion of the risks of withdrawal off methadone during pregnancy, clinicians are referred to (Finnegan LP 1991) (Finnegan 1980).

The evidence base behind management approaches other than methadone maintenance (e.g. substance withdrawal, accelerated withdrawal, naltrexone maintenance) during pregnancy is limited. Consideration should always be given to the balance of risks and benefits for pregnant women when considering all drug treatment interventions during pregnancy.

The use of naltrexone as a maintenance agent is strongly advised against during pregnancy due to:

- **the modest effectiveness of naltrexone in reducing heroin use,**
- **the lack of clinical data on safety of the medication in pregnancy and**
- **the risk of withdrawal if resumption of heroin use occurs and subsequent potential for harm during pregnancy.**

Practitioners should consult with an addiction medicine specialist to discuss the management of such cases. This can be done (in Victoria) by contacting the Drug and Alcohol Clinical Advisory Service on 1800 812 804.

Buprenorphine

Registration and listing of buprenorphine

The following italicised sections are taken from the Buprenorphine Product Information (Reckitt Benckiser 2003)

Registration

The Therapeutic Goods Administration registered Buprenorphine for use in Australia in April 2001.

Indications

Buprenorphine is indicated for: *"Treatment of opiate dependence, including maintenance and detoxification, within a framework of medical, social and psychological treatment."*

Contraindications

- *Hypersensitivity to buprenorphine or any other component of the tablet.*
- *Children less than 16 years of age.*
- *Severe respiratory or hepatic insufficiency.*
- *Acute intoxication with alcohol or other CNS depressant.*
- *Pregnant Women.*
- *Breast-feeding.*

Pregnancy Listing

The Australian Drug Evaluation Committee lists Buprenorphine as category C medication. Category C drugs are:

"Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details"

Use in Pregnancy

Category C. Treatment with buprenorphine during pregnancy was associated with difficult parturition and fetotoxicity, including post-implantation loss and decreased post-natal survival, in rats and rabbits at systemic exposures similar to the maximum anticipated human exposure (32 mg/day). Evidence for teratology was not evident in animal studies.

Maternal oral administration at high doses (80mg/kg/day) during gestation and lactation resulted in a delayed postnatal development of some neurological functions (surface righting reflex and startle response) in neonatal rats with a NOEL of 8mg/kg/day PO (representing a systemic exposure of ~30% of the maximum anticipated clinical exposure).

Continued use of heroin during pregnancy is associated with significant risk to the mother and the foetus and neonate.

There are no adequate and well controlled studies of Subutex in pregnant women. Buprenorphine readily crosses the placental barrier, and may cause respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates. Subutex is contraindicated in pregnant women (see contraindications).

Use in Lactation

Animal studies indicate buprenorphine has the potential to inhibit lactation or milk production. Decreases in postnatal survival, growth and development were also observed in animals treated with buprenorphine during lactation. Because buprenorphine passes into the mother's milk, Subutex should not be used in breast-feeding women.

Precautions

Neonatal Abstinence Syndrome: Neonatal withdrawal has been reported in the infants of women treated with Subutex during pregnancy. Time to onset of withdrawal symptoms ranged from Day 1 to Day 8 of life with most (69%) occurring on Day 1. Adverse events associated with neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus. There have been rare reports of convulsions and in one case, apnoea and bradycardia were also reported. In many cases the withdrawal was serious and required treatment (see Use in Pregnancy).

Literature summary: clinical studies of buprenorphine and pregnancy

Thirty human studies involving the use of buprenorphine in pregnancy, published in English or translated to English have been identified using the Medline database: keywords buprenorphine, methadone and pregnancy (search January 1970 to January 2003); hand searching; information from Reckitt Benckiser manufacturers of buprenorphine and from experts in the field.

From these 30 papers, twelve original papers have been reviewed. Inclusion criteria for review were papers providing information on pregnancy and birth including two or more of the following outcomes: methadone and buprenorphine doses and period of treatment, gestational age at delivery and birthweight, foetal or neonatal death, foetal adverse events, neonatal abstinence syndrome (NAS): incidence, severity and number requiring medical treatment. For two papers, translation from either French or Italian was obtained. Seven papers were from France, two from Italy, two from Austria and one from the USA published from 1995 to 2003. Eleven papers are case reports or case series, and one is a case comparison study of methadone and buprenorphine.

Table 1 Clinical studies of buprenorphine pregnancies

Authors	Year	Country	n	N retro spec tive	N pros pecti ve	N live births	NAS	% NAS	% NAS requiring Rx
Herve, F	1998	France	1	1		1	1	100	100
Regini, P.	1998	Italy	1	1		1	1	100	NR
Schindler, SD	2003	Austria	2		2	2	2	100	0
Johnson, R. E.	2001	USA	3		3	3	3	100	0
Reisinger, M.	1995	Italy	4	4		4	1	25	0
Marquet, P.	1998	France	6	6		6	4	67	NR
Loustauneau, A.,	2000	France	18	18		14	8	57	36
Fischer, G.	2000	Austria	15		15	15	7	47	20
Jernite, M.	1999	France	24	13	11	24	16	67	NR
Noblett, C.	2000	France	27	27		27	18	67	67
Lacroix, I	2002	France	34		34	31	13	38	26
Lejune, C	2001	France	153		153	153	100	65	52
TOTALS			288	70	63	281	72	57	

(NR: not reported)

Eight of these papers provide some limited data on neonatal abstinence of neonates born to pregnant women treated with buprenorphine. They include either the following: single case reports (Herve and Quenum 1998) (Regini, Cutrone et al. 1998), or case series (n=4 to 34) (Reisinger M 1995) (Marquet P, Lavignasse P et al. 1998) (Loustauneau, Auriacombe et al. 2000) (Jernite, Viville et al. 1999) (Noblett, Burtin et al. 2000) (Lacroix, Berrebi et al. 2002) and are either abstracts only, brief reports or original papers. Of the 115 total cases in these 8 papers, the majority are retrospective. In these studies, the only consistent outcome reported was the prevalence of the neonatal abstinence syndrome from buprenorphine, 7 studies also reporting on numbers requiring pharmacotherapy for neonatal withdrawal. Some studies reported on maternal risk factors, and foetal or neonatal outcomes and intermittent reporting of inclusion criteria.

Pooling of these data, (with the inherent errors of this method in pooling case reports and series without clear inclusion/exclusion criteria) results in a prevalence of 62/108 (57%) of (live born)

neonates experiencing neonatal abstinence syndrome after buprenorphine maintained pregnancies. Proportion of neonatal abstinence requiring pharmacological treatment was not reported in all papers, but in those that did, the proportion varied from 0 to 100%, with the larger case series showing 26% to 67% infants requiring pharmacotherapy for neonatal abstinence.

Four deaths not related to planned terminations were reported among these papers. (Loustauneau, Auriacombe et al. 2000) report 2 ‘involuntary interruptions’ and 2 ‘voluntary interruptions’ (terminations) among their case series and (Lacroix, Berrebi et al. 2002) report on 1 stillbirth, 1 spontaneous abortion and 1 voluntary termination. No comment has been made by either group of authors on the details of the foetal loss or on any association between buprenorphine and the spontaneous abortions. (Lacroix, Berrebi et al. 2002) also report of 2 malformations: a tragus appendage in a neonate exposed to sulphamethoxazole and trimethoprim (category C in pregnancy), lamivudine and zidovudine (category B3 in pregnancy) for HIV therapy in utero, and a premature ductus arteriosus closure in a neonate exposed to aspirin and cannabis.

(Regini, Cutrone et al. 1998) report on a single case of cerebral palsy. The authors comment that maternal epilepsy, with possible other drug use (alcohol, heroin, amphetamines and cocaine are raised), problems with compliance with buprenorphine treatment, neonatal narcosis, naloxone reversal and possible hypoxia may all have been associated; more so than exposure to buprenorphine. Two studies, (Fischer, Peternell et al. 2000; Johnson, Jones et al. 2001) and (Jernite, Viville et al. 1999) report on intrauterine growth restriction: n=1 and n=7 respectively. This may have occurred across other studies and been under-reported as an overall prevalence of IUGR 8 from 126 (6.8%) births of a group of opiate dependent women is low.

Three prospective studies report in detail on their case series including history, progress and outcome data (Fischer, Peternell et al. 2000; Johnson, Jones et al. 2001; Schindler SD, Eder H et al. 2003), n=15, 3 and 2 respectively. These case series report on maternal age, other drug use, buprenorphine doses, gestational age at exposure to buprenorphine, foetal adverse events, neonatal abstinence syndrome (prevalence treatment, duration), birth outcome (gestational age at delivery, Apgar scores, birthweight, length and head circumference).

Table 2 Detailed case series, buprenorphine pregnancies, and birth outcomes

Author, year	N	Site	Bup doses (mg) range or mean, SD	Other drug use	Gest. age on bup induction (weeks) mean, SD	Gest age at delivery (weeks) mean, SD	Birth weight (gm) mean, SD	Length, (cm) mean, SD	head circum, (cm) mean, SD	Apgar (1,5,10 min) Mean	Foetal AE
Johnson, R. E. 2001	3	In-patient ¹	8-12	Nicotine	25 (±1)	39.3 (±0.6)	3183 (±337)	50.7 (±1.1)	34.3 (±1.9)	² 8, 9, NR ³	Nil reported
Fischer, G. 2000	15	Out-Patient	1-10	Nicotine, cannabis	27.8 (±5.4)	39.6 (±1.5)	3049 (±349)	34.1 (±1.8),	49.78 (±1.9)	8.9, 9.9, 10	1 infant IUGR
Schindler S.D. 2003	2	Out-patient	9 (±4.2)	Nicotine	Concept-ion	39.5 (±2.1)	3115 (±445)	50 (±1.4)	34 (±1.4)	9, 10, 10	Nil reported

¹ 2 of 3 cases

² n=2, 3rd case data not recorded

³ 10 minute Apgar scores not reported

Johnson reports on 3 cases, 2 treated as hospital inpatients for the duration of the pregnancies. The women were all Afro-American: except for from tobacco there was no evidence of other drug use (from urine screening). Buprenorphine doses of 8-12 mg sublingual tablets were used; mean gestational age of induction onto buprenorphine treatment was 25 weeks. One delivered by caesarean section, the others without intervention. Birth outcomes are reported in table 2. Neonatal abstinence syndrome was observed in all 3 cases; none required pharmacotherapy for neonatal withdrawal. Neonatal withdrawal onset occurred within 12 hours of birth, peaked by 72 hours, and returned to below 12 hour levels by 120 hours. The most prevalent withdrawal signs were: tremors, hyperactive Moro reflex and sleeping < 3 hours after feeds. Pharmacokinetic data from the 3 women and neonates showed buprenorphine to plasma ratio of approximately 1.0.

Fischer reports on 15 cases of buprenorphine maintained pregnancies. Fourteen were transferred from either methadone or long acting morphine and one inducted from street heroin onto buprenorphine. Induction occurred as a 3 day inpatient admission without any report of foetal adverse event by the authors. Details of the transfer have not been provided in this paper. One woman was HIV positive; all women were nicotine and cannabis dependent on entry. Other drug use does not appear to have been highly significant with 9% of urine drug screens were positive for opiates, and other drug use including alcohol not observed. Flexible dosing of buprenorphine 1-10 mg sublingual tablets were used. Birth outcomes are reported above in table 2. Neonatal abstinence syndrome was observed in 7/15 cases (47%), of a mean duration of 1.1 days (\pm 2.5, range 0-9). Three (20%) required pharmacotherapy for NAS. There was no correlation between buprenorphine dose and presence of NAS ($r=-0.136$, $p=0.630$).

Schindler reports on 2 women who conceived whilst taking buprenorphine. Both women had participated in a previous study involving transfer to buprenorphine during pregnancy (Fischer G, Johnson RE et al. 2000), previously delivering well infants experiencing neonatal withdrawal but not requiring pharmacotherapy for NAS. During the second pregnancies on buprenorphine discussed in this paper, one patient was maintained on 6 mg buprenorphine, the other 12 mg. Pregnancies progressed uneventfully, one woman requiring a caesarean section for poor progression of labour. Both women again delivered well infants, both experiencing NAS but again, neither requiring pharmacotherapy for NAS.

Table 3 Case-comparison study: buprenorphine c.f. methadone for pregnancy

Author, year	N	Site	Other drug use	On substitution Rx pre-pregnancy	Gest age at delivery (weeks) mean	Birth-weight (gm) mean	Foetal AE	NAS	NAS requiring Rx
Lejeune C. 2001	246 bup = 153 meth = 93	Multi-centre, outpatient	Heroin, hashish, nicotine, alcohol, cocaine	79%	38.7	2838	26 % foetal distress 32% IUGR	65%	50%

Only one study includes a comparison group. (Lejeune, Aubisson et al. 2001) is a multi-centre case-comparison study (the “Pregnancy and Addictions” GEGA study) comparing outcomes of 93 patients on methadone and 153 on buprenorphine. Mean age was 26.6 years, 23% were foreign nationals, and mean age of onset of dependence was 19.3 years. The methadone group were typically treated in a specialist treatment centre (78% vs. 37%), whereas the buprenorphine group

were more likely to be treated in general practice (office based) settings (79% vs. 50%, $p < 0.001$). Those on buprenorphine also tended to be on substitution treatment before pregnancy was diagnosed (85% vs. 71%, $p < 0.03$) and more likely to have a partner ($p < 0.02$). Five per cent overall were HIV positive. There were no other differences in demographic data. The groups were not matched on any parameter.

Significant drug use occurred in both groups including tobacco (96%), hashish (38%), alcohol (31%) benzodiazepines and/or antidepressants and/or analgesics (29%), heroin (19%) and cocaine (9 to 14%) with no statistically significant difference between groups. No neonatal deaths were seen across either group. There was no difference for attendance for antenatal care or rate of delivery intervention. There was no difference in mean birthweight, low head circumference or length, prevalence of foetal distress or IUGR. There was no difference in mean gestational age at delivery however there was a difference in the proportions of premature delivery (<37 weeks) in the methadone group (18% vs. 9%, $p < 0.04$). However all other outcomes measures including: successful establishment and prevalence of breastfeeding, development of the mother-child relationship and need for placement after birth were the same in both groups.

The prevalence of the neonatal abstinence syndrome was the same in both groups (65%), mean time to onset of the NAS, mean maximal withdrawal score, proportion requiring pharmacotherapy treatment (50%), mean duration of treatment, proportion requiring transfer to higher level of care setting and age at regaining birthweight was not significantly different between groups. A significant difference was seen in the age at maximum withdrawal scores (92 hours vs. 70 hrs, $p < 0.01$) and a trend for longer hospital stays were seen in the methadone group. The authors report some association between buprenorphine or methadone dose at delivery (doses for both substitution agents have been grouped) and intensity of neonatal withdrawal, however, there is a marked overlap of the data between groups.

These data on the safety and effectiveness of buprenorphine as a substitution maintenance treatment in pregnancy are encouraging. The fact that the buprenorphine group was not significantly worse than the methadone group on any of the above parameters is a positive outcome regarding the use of buprenorphine during pregnancy. The benefits of buprenorphine for neonatal abstinence appear equivalent to methadone in this study. However, extrapolation from a single case comparison study (with no factors controlled for) can only be done with great caution. The safety of buprenorphine from this study would therefore be not greater than approximately 1 in 50 risk (with 95% confidence) of foetal death and severe adverse outcomes during pregnancy and immediately after delivery. It is worth noting that the prevalence of NAS requiring pharmacological treatment is equal to methadone in this study. More studies are required to replicate these data. Controlled studies including thousands of pregnant women are required to more conclusively demonstrate safety in pregnancy and breastfeeding.

Data on the long term outcomes of children born to women taking buprenorphine during pregnancy is limited. (Reisinger 1997) reports of four children followed up to ages 3 to 5 years old; all are reported to be 'well'. One infant was breast fed while the mother was taking buprenorphine for 6 weeks with no reported adverse event. (Marquet, Chevrel et al. 1997) also reports on one infant breastfed while the mother was taking buprenorphine for 8 weeks post delivery. Breastfeeding was abruptly ceased (due to a chest infection) at 8 weeks; the infant did not develop a withdrawal syndrome. (Schindler SD, Eder H et al. 2003) reports on normal developmental assessment of 2 infants in that study at 6 and 12 months; one infant was breast fed for 6 months.

Concerns regarding the use of buprenorphine in pregnancy

There is a lack of adequately controlled prospective studies of the use of buprenorphine in pregnancy to establish the safety of the use of the medication.

Particular concern should be given to the following areas:

1. Babies born to women maintained on buprenorphine during their pregnancies may experience a neonatal withdrawal syndrome related to buprenorphine.

A growing body of evidence is being collected regarding the association between buprenorphine in pregnant women and the neonatal abstinence syndrome. There is insufficient data to comment on whether this is more or less likely with buprenorphine than methadone, if or how the severity and duration compare with methadone. The benefits of methadone maintenance treatment for both the mother and the baby strongly outweigh the risks from the neonatal withdrawal syndrome.

2. Respiratory depression in the newborn may also be associated with maternal use of buprenorphine.

Buprenorphine crosses the placenta in amounts that may be reduced compared to maternal circulation (Nanovskaya, Deshmukh et al. 2002). Buprenorphine may, therefore, cause respiratory depression in the newborn infant. There are inadequate clinical data to describe this risk. Respiratory depression may also be associated with methadone maintenance during pregnancy (Maas U, Kattner E et al. 1990).

Respiratory depression in neonates can usually be managed easily with respiratory support provided that it is diagnosed promptly.

THE USE OF OPIATE ANTAGONISTS (E.G. NALOXONE) IS STRONGLY CONTRA-INDICATED AND CAN RESULT IN SEIZURES IN NEONATES.

3. The protective effects of buprenorphine on obstetric and neonatal outcomes for heroin dependent pregnant women may not be as great as seen in methadone.

Obstetric complications including miscarriage, premature labour, low birth weight, foetal growth restriction and foetal death are strongly associated with heroin use during pregnancy and decrease with stabilisation on methadone during pregnancy (Finnegan LP and Kandall SR 1997) (Ward J, Mattick R et al. 1998) (Hulse GK, Milne E et al. 1998) (Hulse GK, Milne E et al. 1997).

The impact of buprenorphine maintenance on these conditions has not yet been established. Buprenorphine maintenance may be associated with a reduction in all the above risks, however, this reduction *may not be* as great as is seen with methadone.

4. The effectiveness of buprenorphine, as a maintenance substitution agent for heroin dependence, while being of the same order of magnitude as methadone, has not yet been demonstrated to be as effective as high dose methadone.

The effectiveness of buprenorphine has been compared to methadone in a number of large scale controlled studies (Johnson RE, Jaffe JH et al. 1992; Mattick, Ali et al. 2003); (Kosten TR, Schottenfeld R et al. 1993; Strain, Stitzer et al. 1994; Ling W, Wesson DR et al. 1996; Schottenfeld, Pakes et al. 1997; Fischer, Gombas et al. 1999; Johnson, Chutuape et al. 2000; Petitjean, Stohler et al. 2001), several review articles (Ritter 2001; Farre, Mas et al. 2002; Ling and Wesson 2003) two meta analyses, (West, O'Neal et al. 2000; Barnett, Rodgers et al. 2001) and a Cochrane review (Mattick, Kimber et al. 2003).

While the effectiveness of buprenorphine maintenance is similar to methadone, when using the outcome measures of heroin use and retention in treatment, high dose methadone has superior outcomes to moderate to high dose buprenorphine (Barnett, Rodgers et al. 2001; Mattick, Kimber et al. 2003). Sixteen mg and above doses of buprenorphine have not been compared to high dose methadone in a controlled trial.

As high dose buprenorphine maintenance may not be as effective as high dose methadone maintenance treatment, overall, pregnant women who require high dose opiate substitution maintenance may have better outcomes in relation to heroin use and retention in treatment on methadone than on buprenorphine. Controlled clinical trials have not yet been conducted to establish these the effectiveness of opiate substitution treatment for pregnant women.

5. Buprenorphine does not appear to be associated with malformations from either animal models or current data from babies born to women maintained on buprenorphine during pregnancy, however a lack of association with malformations or other obstetric/neonatal problems has not yet been absolutely proved.

Definitive data on the safety of buprenorphine in pregnancy can only be obtained by large numbers of pregnant women having taken buprenorphine during pregnancy and been adequately followed up. This may require many more cases (e.g. thousands) to be studied.

Monitoring of women for pregnancy while on buprenorphine programs

The National Clinical Guidelines and Procedures for the use of Buprenorphine in the Treatment of Heroin Dependence (Lintzeris N, Clark N et al. 2001) recommend:

"Women wanting to become pregnant are better advised to consider methadone maintenance, or alternative forms of treatment for the management of heroin dependence" (pg 50).

Advice regarding the lack of data on the safety of buprenorphine during pregnancy and breast-feeding should be given to all women before commencing buprenorphine programs, for maintenance or withdrawal treatment.

Contraception advice should be offered to all women commencing opioid substitution programs and reliable forms of contraception should be recommended to women not wishing to become pregnant

As part of the routine clinical assessment of all women of childbearing age commencing opioid substitution maintenance, clinicians should assess pregnancy status. Women on buprenorphine should be encouraged to have regular monitoring for pregnancy during their period of treatment on buprenorphine.

Use of buprenorphine in pregnancy

The National Clinical Guidelines and Procedures for the use of Buprenorphine in the Treatment of Heroin Dependence discuss the following (Lintzeris N, Clark N et al. 2001) :

"In rare circumstances, discontinuation of buprenorphine treatment may pose a greater risk to mother and baby than continuing. In particular, the woman who refuses to transfer to methadone should be given the option of continuing her buprenorphine treatment after the risks to the foetus and baby and the concerns about breast-feeding whilst in buprenorphine treatment, have been explained to her. The woman must be capable of giving informed consent." (pg. 51)

Continuation of treatment with buprenorphine for pregnant women should only be considered if, after discussion of the risks of ongoing treatment with buprenorphine during pregnancy the mother:

- **does not want to transfer back to methadone;**
- **is capable of providing informed consent.**

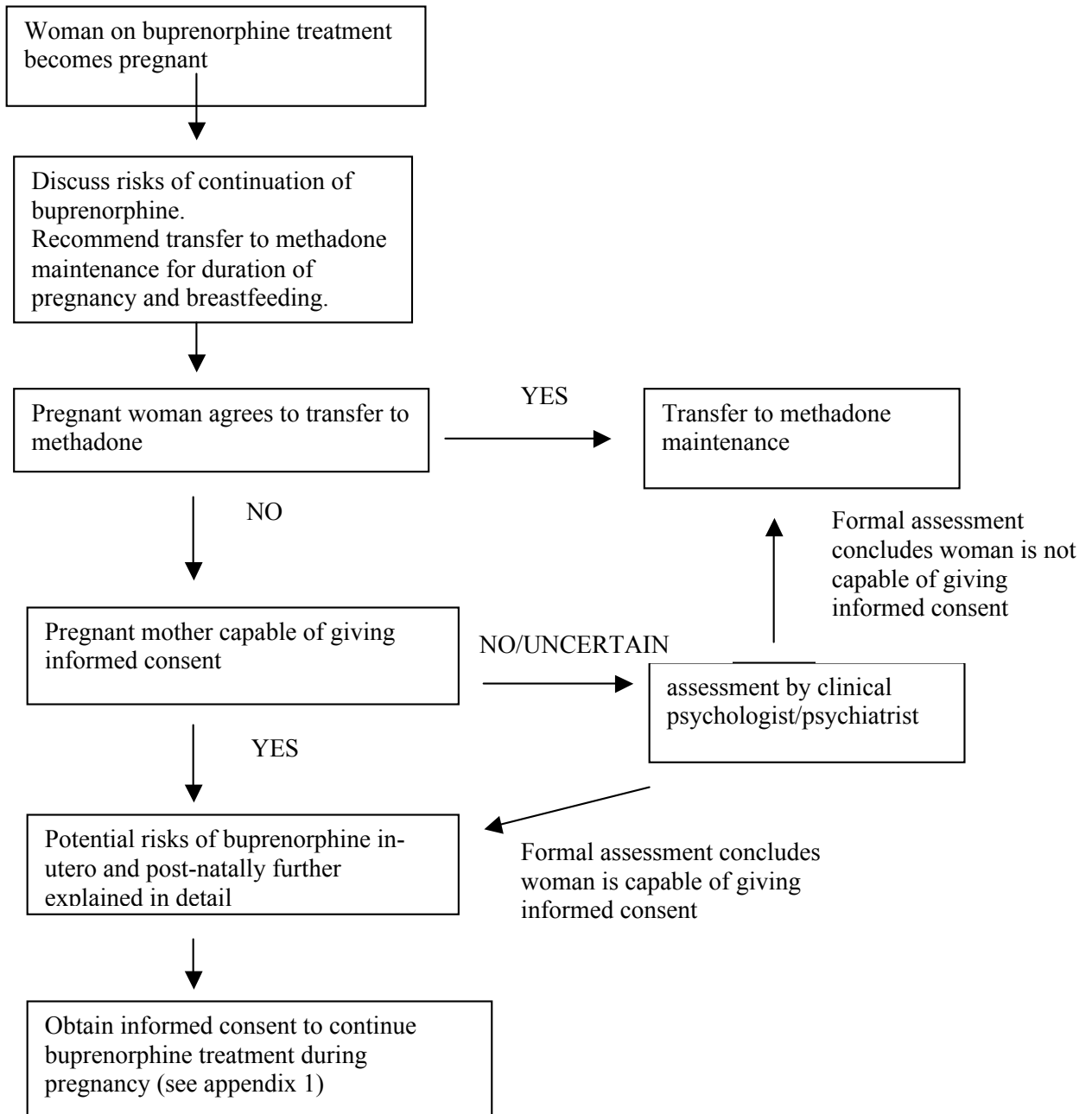
It should be recognised that it may take a period of time for a pregnant woman to fully consider the risks of ongoing treatment with buprenorphine and the option of transfer to methadone treatment. In this situation, pregnant woman should be given adequate time to consider their particular situation and provided with adequate support opportunity to ask questions and discuss the matter during this time.

Patient education about the potential risks of buprenorphine treatment during pregnancy and breastfeeding involves a discussion of the current evidence of risks to the women and baby, both in utero and postnatal. Evidence regarding the assessment of buprenorphine safety continues to be in a state of development. It is crucial that all pregnant women wishing to continue buprenorphine treatment understand the potential for associated adverse outcomes during pregnancy.

If a practitioner believes a woman is not capable or has impaired capacity to give informed consent for this issue, referral to a clinical psychologist or a psychiatrist should occur to assess this capacity before deciding on transfer strategy.

Consent to continue buprenorphine treatment should be sought after a comprehensive explanation of the risks of treatment. A sample consent form is attached as appendix 1 in these guidelines.

Figure 1 Discussion of risks of buprenorphine in pregnancy and informed consent



Transfer from buprenorphine to methadone

Due to the lack of adequate data on the safety of buprenorphine as a maintenance agent during pregnancy, pregnant women who are on buprenorphine maintenance are advised to transfer to methadone maintenance as soon as practicable after the diagnosis of pregnancy.

Transfer from buprenorphine to methadone is less complicated than transfer from methadone to buprenorphine. There is no risk of withdrawal precipitated by the first dose of methadone after buprenorphine. However, it may take several days for all buprenorphine to 'wash out' from a patient. Clinical titration of methadone doses is essential to stabilise patients as quickly as possible. Regular review, (optimally daily) is required during this period.

For those women who wish to transfer to methadone from buprenorphine, the following procedure is advised:

1. stabilisation of patient on a daily dose of buprenorphine dose prior to transfer
 - for patients on alternate day dosing, transfer back to daily dosing prior to transfer;
 - no increases / decreases in dose three days prior to transfer;
2. cessation of buprenorphine dosing;
3. assessment prior to dosing with methadone the next day;
4. commencement of methadone not less than 24 hours after the last dose of buprenorphine;
5. daily review for the next three days to monitor progress.
6. twice weekly review until stable (usually achieved within 1 to 2 weeks)

The following schedules are suggested:

Last buprenorphine dose	Initial methadone dose
≤ 4 mg	20 mg
> 4 , < 8 mg	30 mg
≥ 8 mg	40 mg

If there is any concern regarding the process of transfer from buprenorphine, or the overall stability of the patient, transfer should occur in a hospital inpatient setting.

Inpatient admission for transfer should occur in the following situations:

- patient with unstable opioid or other drug use;
- patient in unstable or unsupported home environment;
- transfer from doses greater than 16 mg buprenorphine;
- patients unable to attend for daily review during the transfer period;
- any additional obstetric risk;
- any additional medical or psychiatric risks

Management with buprenorphine during pregnancy

Some pregnant women, after being informed of the risks and benefits of buprenorphine maintenance, both to themselves and to their babies, will decide they wish to continue on buprenorphine rather than transfer to methadone maintenance.

This is a preferable outcome compared to the cessation of all opioid substitution during pregnancy.

Management of dependence

The management team for pregnant women should include:

- The team treating the pregnant women's substance use.
- The team managing the pregnant women's obstetric care.
- The team co-ordinating general health (e.g. primary care)

Management of opiate dependence with buprenorphine

Pregnant women who wish to continue buprenorphine treatment during their pregnancy may optimally be referred to a specialist addiction treatment service (e.g. specialist methadone services in Victoria) during their pregnancy. Practitioners managing pregnant women with buprenorphine during pregnancy should consult with an addiction medicine specialist and/or specialist obstetric alcohol and drug unit to discuss management during pregnancy.

(Contact number for Specialist Methadone Services and DACAS are listed in Appendix 5).

This should be done to facilitate appropriate co-ordination of medical care, case management and appropriate psychosocial services during pregnancy. In regions where this is practically difficult (e.g. rural areas, outer suburban regions), the doctor treating the patient for opiate dependence should consult with the medical consultant at the specialist addiction treatment service. Ongoing shared-care with a general practitioner buprenorphine prescriber may occur under these circumstances.

Notification of buprenorphine pregnancy

Notification should be made to the Victorian Buprenorphine Pregnancy Register on (Royal Women's Hospital; Women's Alcohol and Drug Service: 03 9344 3631) to facilitate monitoring of all pregnant women maintained on buprenorphine state-wide.

Frequency of review

As significant gaps exist in the knowledge of using buprenorphine as a maintenance treatment during pregnancy, clinical review by the treating doctor and multi-disciplinary team should occur on a frequent and regular basis. It is recommended that pregnant women should be reviewed on a weekly to fortnightly basis to 30 weeks gestation and weekly until delivery.

Management of heroin use

As a general principle, buprenorphine doses should be clinically titrated upwards until patients cease heroin use. Usual maintenance doses associated with significant reduction in heroin use are 12-24 mg buprenorphine as a daily dose. Pregnant women should be encouraged to be stabilised on appropriate doses of buprenorphine. The available data for buprenorphine dose levels and incidence of neonatal withdrawal suggest no significant correlation.

There is no data on buprenorphine to suggest this will be different. In particular, low buprenorphine doses should not be encouraged as an end in itself. The maximum recommended daily dose for pregnant women should be no more than 32 mg daily.

Dose adjustments

Following from the general principles of opiate substitution maintenance during pregnancy, dose increments may be required throughout the pregnancy, especially during the third trimester.

Monitoring

Buprenorphine is not detected on routine urine toxicology screens. Gas mass spectrometry or specific antibody tests can detect buprenorphine in urine, however these are not available as a Medicare rebated service. Instant urine tests for buprenorphine are commercially available. Clinical review and discussion with the patient's dispensing pharmacist is the mainstay of monitoring a patients' progress on buprenorphine.

Dose reductions or detoxification during pregnancy.

Dose reductions are advised against during pregnancy. Withdrawal symptoms should be avoided as much as possible as they may cause considerable distress to the foetus. If the doctor managing the patient decides with the patient to do so, the 2nd trimester is considered to be the least harmful period for an adverse obstetric event.

Withdrawal off buprenorphine maintenance is strongly advised against during pregnancy due to the risk of relapse to dependent illicit opioid use. Abstinence, whilst being a longer-term goal, is often unrealistic during pregnancy and immediately after birth.

Frequency of dosing

Due to the lack of data concerning the use of buprenorphine, dosing with buprenorphine on a frequency less than daily (e.g. alternate day dosing) is not recommended. A proportion of patients on buprenorphine will experience opiate withdrawal when dosing with buprenorphine occurs less frequently than daily. It is recommended that all pregnant women on buprenorphine be placed on a daily dosing schedule during pregnancy.

Use of other substances

Other substances including nicotine, cannabis, benzodiazepines, alcohol, amphetamines and cocaine pose potential risks to pregnant women and their babies. Use of these substances should be discouraged. In particular, the use of multiple sedative drugs increases the risk of fatal and non-fatal overdose. The safety of the use of sedatives, whilst on buprenorphine treatment, is unknown. Overdoses on combinations of buprenorphine and benzodiazepines have been reported (Reynaud M, Petit G et al. 1998). The use of benzodiazepines by pregnant women is generally recommended against.

Psychostimulants (e.g. cocaine) have an association with teratogenicity during pregnancy. Pregnant women should be particularly cautioned against the use of stimulants during pregnancy.

The management of pregnant women using multiple substances during pregnancy, especially multiple sedatives (e.g. alcohol, benzodiazepines) and/or stimulants (e.g. amphetamines, cocaine) is complex and may be best done by a specialist multi-disciplinary team with experience in the management of drug and alcohol and obstetric issues. General Practitioners treating women using multiple substances should discuss management with a specialist addiction medicine clinic and consider referral.

Dispensing Issues

Pregnant women should be strongly encouraged not to miss doses of buprenorphine. Inability to pay for dosing fees should not be a reason to refuse treatment to pregnant women. Complex cases should be referred to specialist addiction treatment services (e.g. specialist methadone services).

Poor progress on buprenorphine

Pregnant women who are progressing poorly on buprenorphine should be monitored intensively in an effort to attain the best possible treatment. Examples of poor progress include:

- missing multiple doses of buprenorphine;
- poor attendance for review by the prescribing doctor;
- evidence of diversion of buprenorphine;
- ongoing significant heroin or other drug use despite high dose buprenorphine maintenance;
- poor attendance for obstetric review.

If ongoing heroin use continues, the following strategies should be considered and implemented where indicated:

- buprenorphine dose increases to optimal maintenance doses (e.g. 12-24 mg daily doses);
- optimal involvement of psychosocial treatment and other social support services (e.g. accommodation, legal services);
- liaison with the treating obstetric drug and alcohol service;
- referral for inpatient stay in an obstetric hospital for stabilisation;
- referral to specialist addiction treatment service.

If continued ongoing poor progress continues, transfer to methadone may be appropriate. Ongoing heroin use significantly decreases the effectiveness of opiate substitution treatment in relation to birth and pregnancy outcomes (e.g. neonatal death, low birth weight).

Patients that have progressed poorly on buprenorphine may respond to methadone. Consideration should be given to the transfer occurring in a supervised (e.g. inpatient) setting. Consultation should occur with a specialist addiction medicine/obstetric unit regarding transfer to methadone.

The balance of risks of a pregnant woman who is progressing poorly in opiate substitution treatment requires consideration of the risks of drug use, including heroin in addition to opiate substitution with the risks of cessation of treatment and likely relapse to dependent heroin use.

Direct transfer from methadone to buprenorphine

Due to the risk of precipitated withdrawal and associated harm to the pregnancy, this procedure is contraindicated for pregnant women.

Induction onto buprenorphine after diagnosis of pregnancy

It is not recommended that general practitioners commence buprenorphine treatment after a diagnosis of pregnancy. Methadone maintenance is the treatment of choice during pregnancy. However, some pregnant women may be adamant of commencing buprenorphine rather than methadone after being informed of potential risks and issues of safety of both treatments. There are significant risks involved including opiate withdrawal precipitated by buprenorphine soon after a dose of heroin.

These cases should be referred to both an addiction medicine specialist and an obstetric specialist with alcohol and drug management expertise. General practitioners are strongly advised not to induct pregnant women onto buprenorphine without advice from the above specialist fields.

Turing Point Alcohol and Drug Centre can be contacted on 03 8413 8413.

The Royal Women's Alcohol and Drug Service can be contacted on 03 9344 3631.

Management of obstetric care

Pregnant women who wish to continue buprenorphine during their pregnancies should be referred to a specialist obstetric and paediatric hospital with experience in the management of drug dependence. In regions where this is practically difficult (e.g. rural areas), the obstetric unit treating the patient are strongly advised to consult with the Royal Woman's Hospital Women's Alcohol and Drug Service (or other obstetric hospitals with similar addiction and obstetric expertise).

Management of ante-natal care

Frequency of review

Patients should be reviewed as frequently as fortnightly until 30 weeks gestation then weekly until delivery. For unstable patients, review may be indicated more frequently.

Multidisciplinary team approach

Management should include a multidisciplinary team including the following disciplines as appropriate:

- medical including obstetric, paediatric, and addiction medicine;
- nursing including midwifery;
- allied health including social work, psychology, alcohol and drug clinician.

Clinical input may be required from a wider range of disciplines (e.g. medical including psychiatry; infectious diseases, dietetics). Optimally, case reviews/audits should occur with input from the disciplines listed above.

Monitoring of pregnancy

Third trimester monitoring is strongly recommend for all pregnant opiate dependent patients.

This may include the following:

- an ultrasound at 32 to 34 weeks gestation is suggested to look at foetal growth, and
- cardiotocograph (CTG) monitoring is suggested weekly from 35 weeks gestation to monitor foetal well-being (the CTG will be affected by maternal opiate and benzodiazepine use).

Timing of delivery

The decision on when to deliver the pregnancy will depend on a number of factors. Optimally, input from the mother and multidisciplinary team ought to be considered in deciding how long a pregnancy should continue and whether elective/semi-elective or urgent intervention for early delivery is indicated. In general principles the risks of continuing pregnancy should be balanced against the risks of early delivery.

The factors that will influence decision on the duration and outcome of pregnancy include:

- Maternal physical and obstetric condition/complications;
- Maternal psychiatric condition;
- Maternal condition from a social perspective;
- Attendance for antenatal care;
- Ongoing drug use, compliance with drug treatment;
- Foetal growth and well-being.

Delivery is usually at 38 to 40 week's gestation but may be at a lesser gestation if circumstances demand, or beyond the due date if deemed safe and appropriate by the obstetric team. The timing of delivery will depend on a number of factors including those listed above.

Care in labour

Induction

Induction of labour may occur depending on the obstetric circumstances with routine methods including prostaglandin jelly, artificial rupture of membranes, oxytocin.

Invasive techniques for monitoring during labour (including CTG monitoring with scalp electrodes, scalp pH monitoring) should be avoided due to the potential for vertical transmission of blood borne viruses (HBV, HCV, HIV).

Universal precautions should always be employed during labour according to the protocols of the institution.

Analgesia during labour and caesarean section

Buprenorphine is a partial opiate agonist at the μ (mu) opiate receptor with:

- low intrinsic activity (compared to full opioid agonists e.g. pethidine, morphine)
- high receptor affinity and
- slow rates of dissociation.

Management of analgesia using other opiates such as pethidine, morphine – is therefore not effective for women maintained on buprenorphine as full opioid agonists will be 'blocked' by buprenorphine. Alternative approaches to pain relief for women maintained on buprenorphine are thus required. These include:

During labour

- Non-pharmacological eg. showering, massage, mobilisation
- TENS machine for early labour
- Nitrous oxide inhalation
- Epidural anaesthesia for first and second stage pain relief
- Spinal anaesthesia for second stage pain relief
- Pudendal block for low instrumental delivery
- Local anaesthetic infiltration for episiotomy

Postpartum

- Paracetamol
- Non-steroidal anti-inflammatory medications (contraindicated for antenatal and intrapartum use)

Caesarean section

- Spinal anaesthesia
- Epidural anaesthesia with postpartum epidural infusion
- General anaesthetic
- Post-operative: Epidural infusion, Paracetamol, Non-steroidal anti-inflammatory medications

Occasionally, it may be necessary to transfer a woman on buprenorphine maintenance treatment to methadone treatment prior to a planned caesarean section. Discussion should involve an obstetrician and an addiction medicine specialist prior to this occurring.

Reasons for this procedure may include:

- expected difficulties in pain management post caesarean requiring full opioid agonist treatment
- instability on buprenorphine pre-caesarean

Use of buprenorphine post-partum

Buprenorphine maintenance should continue as long as clinically indicated post partum with regular clinical review to monitor the progress of all pregnant women. Rapid dose reduction should be avoided due to the risk of relapse. Consideration should be given to establishing breast feeding (see section below on breast-feeding) and coping with demanding parenting issues. Monitoring should continue to occur with the patients' obstetric and paediatric team.

Management of neonatal care

Neonates born to mothers who have been on opiate substitution programs with methadone or buprenorphine, or women who have been regularly taking other opiates (e.g. heroin) during their pregnancies, are at risk of developing a neonatal abstinence syndrome from opioids.

The use of opiate antagonists (e.g. naloxone) is strictly contra-indicated for neonates born to opioid dependent mothers due to risk of seizures in neonate.

Neonatal Withdrawal Syndrome

There is insufficient data to determine whether the neonatal withdrawal syndrome is more or less likely with buprenorphine compared to methadone. Preliminary data suggests the incidence of the neonatal withdrawal syndrome is similar to that seen with methadone. In keeping with current management strategies for neonates experiencing withdrawal, ideally the infant remains with the mother where possible.

All babies born to opioid dependent mothers should be observed by experienced staff for the development of withdrawal. A validated scale should be used to assess the presence and severity of the neonatal withdrawal syndrome (see Appendix 3 Finnegan scale).

Signs of withdrawal in the neonate include:

Common signs

- Irritability and sleep disturbances
- Sneezing
- Fist Sucking
- A shrill cry
- Watery stools
- General hyperactivity
- Ineffectual sucking
- Poor weight gain
- Dislike of bright lights
- Tremors
- Increased respiration rate

Less common signs

- Yawning
- Vomiting
- Increased mucus production
- Increased response to sound
- Convulsions (rare).

Withdrawal symptoms usually start within the first 12-48 hours of delivery but may take up to one week. Withdrawal from additional substances (e.g. benzodiazepines) concurrently used with buprenorphine may delay the onset of withdrawal symptoms.

Treatment of the neonatal abstinence syndrome due to buprenorphine exposure in utero is managed on the same basis as for methadone exposure. Non pharmacological approaches (e.g. reducing stimuli, cuddling, using pacifiers) combined with monitoring may be adequate to control the neonatal withdrawal syndrome. If pharmacotherapy treatment is indicated, oral morphine is recommended for the management of significant withdrawal from heroin, buprenorphine or methadone, using the Finnegan Scoring Protocol (see appendix 3).

Treatment should be based on the severity of the withdrawal signs.

- Use the Finnegan Screening Instrument (Appendix 3). Treatment should be commenced when the score is 8 or more on three consecutive observations, or, if the total score of three consecutive occasions is greater than or equal to 24.
- Improvement should be monitored using scores on the screening tool.
- Treatment with morphine syrup could cause respiratory depression and should be used with caution.

MORPHINE THERAPY FOR NAS:

<u>Score</u>	<u>Dosage (oral)</u>
8-10	0.5 mg/kg/day every 4 hours
<i>if increases to for 2 scores:</i>	
11-13	0.7 mg/kg/day every 4 hours
<i>if further increases to for 2 scores:</i>	
14+	0.9 mg/kg/day every 4 hours

Once abstinence has been controlled (three consecutive scores less than 8) using this dosage regime, the following should be implemented: Please note that all doses for entire period of withdrawal management are calculated on birth weight and not current weight.

- Maintain control for 72 hours
- Initiate the detoxification process by decreasing the total daily dose by 10% every 72 hours.
- When dosage levels reach 0.2mg/kg/day - maintain this dose for 72 hours
- Change from 4 hourly to 6 hourly dosage regime (same dose) for 72 hours prior to ceasing all medication.

When oral morphine treatment is discontinued, neonatal abstinence syndrome scoring should continue for a further 72 hours.

Breast feeding and buprenorphine

There is a lack of clinical data on the safety of breastfeeding for women who continue on buprenorphine after giving birth.

Consideration should be given to the potential risks and benefits of breastfeeding for women maintained on buprenorphine in making a recommendation regarding breastfeeding for pregnant women.

Breast milk contains similar amounts of buprenorphine to maternal serum levels. However, due to significant first pass metabolism, buprenorphine has reduced oral bioavailability. Infants will be exposed to proportionally less of the total active amount available.

If women decide to wean their babies from breast milk, they should be advised to wean their babies slowly to avoid withdrawal in the infant.

Recommendations

If a management decision is made to continue breastfeeding while the mother is on buprenorphine, neonates and infants should be regularly reviewed to monitor their development.

Monitoring is most practically done by measuring weight gain. Other indices (e.g. progressive developmental assessment) can be used in addition. Monitoring would include:

- weight gain as an index of feeding and performance;
- routine medical assessment

Ideally a comprehensive developmental assessment of all babies exposed to buprenorphine through breast milk should occur at 2 years.

Prescribing requirements

The treating doctor must hold a permit to prescribe methadone or buprenorphine for pregnant women, prior to the commencement of opioid substitution treatment.

During periods of admission to an inpatient hospital the permit must be transferred to a hospital treating doctor; on discharge liaison needs to occur so the community prescriber can recommence treatment.

In emergency situations during weekends and after hours, there is a capacity for a hospital doctor to commence treatment with opiate substitution agents without contacting the Drugs and Poisons Unit. The prescriber should attempt to gain a collateral history of the patients' treatment including recent dates of dosing and doses dispensed. The Drugs and Poisons Unit of the Department of Human Services (tel: 1300 364 545) should be contacted and informed as soon as possible the next working day.

Appendix 1. Patient Consent Form for Buprenorphine Treatment During Pregnancy / Breastfeeding

I, am currently in treatment with buprenorphine for the management of my opiate dependence, and wish to continue treatment with buprenorphine during my pregnancy / period of breastfeeding, rather than:

- transfer to methadone, or
- withdraw from buprenorphine

In making this decision, I understand that:

- the safety of buprenorphine during pregnancy or breastfeeding remains uncertain at this stage,
- pregnancy and breastfeeding are currently listed as contraindications for the use of buprenorphine in Australia by the Therapeutic Goods Administration,
- I will need to attend regularly (and as directed) for antenatal care at Hospital,
- I will need to attend regularly for appointments with my treatment team at
- Notification of my pregnancy will be made to the confidential Victorian Buprenorphine Pregnancy Register for monitoring purposes.

Name:

Signed: Date / /

Witness: Date / /

Appendix 2 Letter from obstetric service to general practitioners managing pregnant women on buprenorphine

Date / / 200

Dear Dr.....,

Thank you for referral of Ms.....for management of her pregnancy.

As you are aware, Ms.....is opiate dependant and currently being maintained on buprenorphine as an opiate substitution agent. Buprenorphine is listed as a category C medication in pregnancy by the Australian Drug Evaluation Committee. The Therapeutic Goods Administration of Australia has listed pregnancy and breastfeeding as contra-indications for the use of buprenorphine.

I have recommended that Ms.....transfers back to methadone for the duration of her pregnancy. However, she has decided, after being aware of the lack of adequate data on the safety of buprenorphine in pregnancy, to continue on buprenorphine rather than transfer to methadone.

I am happy to continue to management her obstetric care.

Yours sincerely,

.....

Appendix 3 Neonatal Abstinence Score - Finnegan Score

(Finnegan 1980)

NEONATAL ABSTINENCE SCORING SYSTEM

NAME:

Date and Time in Hours

System	Signs and Symptoms	Score																	
CENTRAL NERVOUS SYSTEM DISTURBANCES	Excessive High Pitched (OR Other) Cry	2																	
	Continuous High Pitched (OR Other) Cry	3																	
	Sleeps < 1 hour after Feeding	3																	
	Sleeps < 2 hours after Feeding	2																	
	Sleeps < 3 hours after Feeding	1																	
	Hyperactive Moro Reflex	2																	
	Markedly Hyperactive Moro Reflex	3																	
	Mild Tremors Disturbed	1																	
	Moderate-Severe Tremors Disturbed	2																	
	Mild Tremors Undisturbed	3																	
	Moderate-Severe Tremors Undisturbed	4																	
	Increased Muscle Tone	2																	
	Excoriation (Specify Area):	1																	
	Myoclonic Jerks	3																	
Generalised Convulsions	5																		
METABOLIC/VASOMOTOR/ RESPIRATORY DISTURBANCES	Sweating	1																	
	Fever (37.3 – 38.3C)	1																	
	Fever (38.4C and higher)	2																	
	Frequent Yawning (> 3 – 4 times)	1																	
	Mottling	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																	
TOTAL SCORE																			
INITIALS OF SCORER																			

Appendix 4: Issues for clinical discussion

Suggested list of issues to discuss with pregnant women on buprenorphine maintenance who are considering continuing the medication

- Effectiveness of methadone maintenance during pregnancy
- Potential risks and benefits of methadone maintenance during pregnancy
- General principles of methadone maintenance during pregnancy
- The risk of neonatal withdrawal, management of neo-natal withdrawal
- ADEC classification and registration of buprenorphine, pregnancy being listed as a contra-indication
- Potential risks and benefits of buprenorphine during pregnancy
- Lack of adequate research to establish the safety of buprenorphine during pregnancy
- General principles of management using buprenorphine during pregnancy
- Particular issues with the management of labour
- Breastfeeding and buprenorphine
- Any particular obstetric/medical/psycho-social issues for the patient

It is imperative the patient is given adequate information and the appropriate time to make an informed decision regarding transfer to methadone or buprenorphine maintenance.

If a pregnant women makes an informed decision to continue buprenorphine, a signed record of informed consent should be obtained.

Appendix 5 Contact phone numbers

Telephone services:

Direct Line: 1800 888 236

Drug and Alcohol Clinical Advisory Service (DACAS): 1800 812 804

Specialist Alcohol and Drug Services:

Turing Point Clinical Services: 03 8413 8444

DASWest (Drug and Alcohol Service, Western Hospital) 03 8345 6666

South City Clinic 03 9525 7399

Austin Hospital Specialist Methadone Service: 03 9496 5999

Western Region Alcohol and Drug Service (WRAD): 03 5560 3222

Obstetric / alcohol and drug services:

Royal Women's Hospital, Women's Alcohol and Drug Service: 03 9344 2277

Mercy Hospital for Women Transitions Clinic: 03 9270 2266

Monash Medical Centre (ADAPT): 03 9594 5628

Box Hill Hospital, Birralee Maternity Services 03 9895 3348

Sunshine Hospital (Mobile Outreach Support Service): 03 8345 1680

Peninsula Health Care Chemical Dependency Unit: 03 9784 7701

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