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**Heroin detoxification during pregnancy:
A systematic review and retrospective study of
management of heroin addiction in pregnancy**

**Dr Katherine Verne Gilfillan MBChB FCPsych(SA)
GLFKAT001**

Thesis presented for the degree of Master of Medicine in
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Supervisor: Professor Dan J. Stein*

Co-supervisor: Dr Bavanisha Vythilingum*

*Department of Psychiatry and Mental Health, University of Cape Town

DECLARATION

I, Katherine Verne Gilfillan, hereby declare that the work on which this dissertation is based is my original work and that neither the whole work nor any part of the work has been, is being, or is to be submitted for another degree to any other university. This work has not been published prior to registration for the Masters of Medicine in Psychiatry degree.

Signed: _____

Cape Town, 15 August 2012

University of Cape Town

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PART A: PROTOCOL

Heroin Detoxification during Pregnancy

**A retrospective study and a systematic review
of management of heroin addiction in
pregnancy**

Katherine Gilfillan FCPsych (SA), Bavanisha Vythilingum,
FCPsych(SA) MMed(Psych)

Department of Psychiatry, Faculty of Health Sciences

University of Cape Town

Background

There is a widely-held view that opiate withdrawal should be avoided during pregnancy, although if it is undertaken, this should be done with caution between 14 and 32 weeks gestation. This view is largely the result of two influential case reports published in the 1970s. Rementena and Nunang described a case study of a stillbirth at term following acute methadone withdrawal,¹ and Zuspan *et al* described a case report of increased amniotic fluid epinephrine levels during methadone withdrawal, which resolved once the methadone dose was increased.²

These initial concerns have since been challenged. However, large-scale evidence-based data is still lacking in this field. Luty *et al* conducted a retrospective study in 2003, which reviewed 101 case reports of methadone withdrawal conducted at various stages of pregnancy. They concluded that detoxification treatment was not associated with any risk of miscarriage in the second trimester or premature delivery in the third trimester. While there was an increased risk of miscarriage in the first trimester, these results were not statistically significant.³

There are several options available in the treatment of heroin dependence during pregnancy. These include methadone or buprenorphine maintenance throughout the pregnancy, medication-assisted withdrawal using methadone or other opiates, and withdrawal using non-opiate symptomatic medications such as clonidine, other benzodiazepines and analgesics.⁴ Naltrexone has recently been suggested as another option for maintenance medication during

pregnancy after being successfully used in non-pregnant heroin users to discourage further illicit heroin use.⁵

Methadone hydrochloride is a synthetic opiate with pharmacological properties similar to morphine. It is a full mu opiate agonist with a prolonged duration of action (24 – 48 hrs). Because of its oral availability, long duration of action and cross-tolerance with other opiates, it is a useful agent in the maintenance treatment of heroin addicts. In 1965 Dole and Nyswander published a report advocating the use of methadone in opiate withdrawal. Since then it has been the primary maintenance agent used for heroin addicts, including pregnant women.⁶

Buprenorphine has recently been used as an alternative agent to methadone. It also reduces withdrawal symptoms and heroin cravings, but has lower sedative and euphoric effects. These differences are due to the fact that it is only a partial mu receptor agonist, and is also a kappa receptor antagonist. However, it is currently still classified as a Category C drug, which is contraindicated in pregnancy and lactation. Virginia and William conducted a study in 2004 in which they successfully treated twenty heroin-dependent pregnant women with buprenorphine. No adverse effects were reported, and they therefore suggested that the Category C classification be reviewed.⁷

Methadone maintenance is currently still viewed as the gold standard of management of pregnant heroin users. This is primarily based on the fact that mothers engaged in maintenance programmes are less likely to use illicit drugs or to engage in other maternal risk behaviours. There is also improved compliance with obstetric care programmes. These factors have consequently

been shown to secondarily improve neonatal outcomes, measured by overall heavier birth weights.⁸

However, maintenance management with methadone poses its own risks.

Methadone dependence at birth has been associated with fetal death, growth restriction, pre-term birth, meconium aspiration and neonatal abstinence syndrome.³ This syndrome has been shown to be worse in patients treated with high doses of methadone (>20 micrograms/ day) than in untreated heroin addicts. Therefore, it is recommended that patients be placed on a low dose regime (<20micrograms/ day) at least one month prior to delivery.⁶

Methadone withdrawal is the standard management of pregnant heroin addicts in state hospitals in South Africa. This is largely due to financial constraints, as methadone maintenance management is more costly than withdrawal. This concept has, however, been challenged by Daley *et al* who suggest that the health care costs should not be viewed in isolation. They argue that maintenance treatment reduces maternal criminal behaviour by reducing illicit drug use, which has secondary cost implications to society. The authors conducted a study in Massachusetts, USA, which showed that the cost of crime far outweighed that of substance abuse treatment. Inpatient methadone maintenance showed the greatest cost-benefit ratio, which supports the view of methadone maintenance being the gold-standard treatment.⁹

South Africa is currently experiencing a widespread surge in heroin use. It is therefore useful to explore the outcome of pregnant women who undergo

opiate withdrawal in state hospitals, and to enquire whether they should be managed differently.

Aims and Objectives

1. To conduct a retrospective review of all pregnant heroin-addicted patients who have been detoxified at Groote Schuur Hospital (GSH) in the last five years, and to explore the outcomes of these pregnancies.

Method

Study Population

All pregnant patients who were detoxified at GSH between 2005 and 2009.

GSH is a tertiary state hospital located in Cape Town. All these patients are managed in the acute psychiatric ward (C23).

Identification of cases

C23 keeps a register of all patients who have received methadone.

Identification of the patients treated during this period is carried out by information obtained from the methadone register.

Not all patients who are detoxified receive methadone. Therefore, an examination of all the discharge summaries of patients over this period will be conducted in order to ensure that all patients are identified.

Information will be extracted from the files. The following, in particular, will be looked at:

- Maternal age
- Stage of pregnancy, i.e. gestational age
- Quantity of heroin used by mother
- Other illicit substance use
- Course of detoxification at C23, and what drugs were used
- Obstetric outcomes, including intra-uterine deaths (stillbirths and miscarriages), preterm delivery, birth weight, APGAR scores.

Statistical Methods

Information obtained will be captured, processed and summarised by means of a computer data analysis program (SPSS version 17.0). Descriptive statistics will be used to characterise the sample.

Systematic review

The electronic database Medline will be searched using a combination of the following search terms: pregnancy, heroin, opiate, methadone, buprenorphine, treatment. Additional publications will be identified from the reference lists of retrieved articles. All relevant articles in English reporting original data related to the treatment of heroin addiction in pregnancy will be included.

Ethics

Only information that is relevant to the study will be extracted from the patient files, i.e. no additional data will be recorded. The data that is extracted will be recorded on numbered forms. Only the primary researcher will hold the codes which correlate the data on the forms with the individual cases. All the data will be de-identified. Patients will be referred to solely by means of letters of the alphabet when individual cases are described.

As this is a retrospective study, patient consent is not provided.

The study will be submitted to the ethics committee for approval.

References

1. Rementeria JL, Nunag NN. Narcotic withdrawal in pregnancy: Stillbirth incidence with a case report. *Am J Obstet Gynecol.* 1973; 116: 1152-1156.
2. Zuspan FP, Gumpel JA, Mejia-Zelaya A. Fetal stress from Methadone withdrawal. *Am J Obstet Gynecol.* 1975; 122: 43-46.
3. Luty J, Nikolaou V, Bearn J. Is opiate detoxification unsafe in pregnancy? *J Subs Abuse Treat.* 2003; 24: 363-367.
4. Jones HE, O'Grady KE, Malfi D, Tuten M. Methadone maintenance vs methadone taper during pregnancy: Maternal and neonatal outcomes. *Am J Addict.* 2008; 17: 372-386.

5. Hulse G, O'Neil G. Using naltrexone implants in the management of the pregnant heroin user. *Aust N Z J Obstet Gynecol.* 2002; 42: 569-573.
6. Allen MH. Detoxification considerations in the medical management of substance abuse in pregnancy. *Bull N Y Acad Med.* 1991; 67: 270-276.
7. Comer VG, Annitto WJ. Buprenorphine: A safe method for detoxifying pregnant heroin addicts and their unborn. *Am J Addict.* 2004; 13: 317-318.
8. Kaltenbach K, Berghella V, Finnegan L. Opioid dependence during pregnancy: Effects and management. *Obstetrics Gynecol. Clin North Am.* 1998; 25: 139-151.
9. Daley M, Argeriou M, McCarty D, Callahan JJ Jr, Shepard DS, Williams CN. The cost of crime and the benefits of substance treatment for pregnant women. *J Subst Abuse Treat.* 2000; 19: 445-458.

PART B: LITERATURE REVIEW

Objectives of literature review

- To conduct a systematic review of the literature in order to assess current knowledge of the management of heroin addiction in pregnancy
- To identify key studies already performed in this field of research
- To determine whether there are any specific gaps in the knowledge, and whether there is a need for further research
- To identify limitations in previous studies and directions for future work.

Literature search strategy

The search was conducted using the electronic database PubMed. This is a well-established repository of peer-reviewed research articles pertaining to the life sciences.

The following key words were used in the search: *pregnancy, heroin, opiate, methadone, buprenorphine, treatment*. Additional publications were identified by hand-searching the reference lists of retrieved articles.

All relevant articles in English, reporting original data related to the treatment of heroin addiction in pregnancy were included. The search was not restricted to a particular time period. Only studies on humans were included. The

literature search was initially conducted in May 2011, and was revised in June 2012.

Using the terms described above, 12 English articles were located on a Pubmed search. Of these articles, 3 were relevant to the study. However, by using the article references, a total of 18 relevant articles were found and reviewed.

Summary of literature

Introduction

Diacetylmorphine was first synthesised in 1874 as a highly potent, acetylated form of morphine. However, it was only a few years later, in 1898, that Bayer pharmaceutical company first marketed this drug under the trademark name of Heroin. It was initially sold as a non-addictive morphine substitute and cough suppressant. However, heroin was soon found to be twice as powerful as morphine, due to the fact that it is highly fat-soluble and rapidly crosses the blood-brain barrier. As a result of this finding, the United States Congress banned its sale in 1924, and heroin is now classified as a schedule 1 drug, which makes its use illegal for non-medical purposes.

Despite these stricter controls, heroin remains the most widely used opiate. In 2009, there were an estimated 12–14 million heroin users worldwide. Europe and Asia remain the key opiate consumption markets, but opiate use in Africa

is, according to reports, increasing.¹ In South Africa, heroin appears to be used primarily by people between the ages of 21 to 24 years. According to a review by Parry et al in 2003, approximately 20–40% of people treated for heroin abuse in South Africa are female, which is a higher percentage than that for most other illicit substances.²

Opiate use is associated with menstrual irregularities, which, when added to the often erratic lifestyles of drug-abusing women, leads to a high rate of unplanned pregnancies. A significant proportion of the heroin-dependent population is comprised of women of childbearing age, and there are now a growing number of heroin-addicted pregnant women in South Africa. Many of these women only present to medical services at the time of delivery, but those that present earlier usually have complex problems that require a great deal of care.

Overview of management

The ideal goal during pregnancy is for the mother to remain abstinent from any drug use. When faced with a pregnant patient who is actively abusing heroin, one needs to offer treatment that will best minimise any further foetal and maternal harm. Most of the literature suggests that opiate-dependent individuals are usually unable to remain drug free, and therefore require some form of maintenance treatment. This has led to the widely-accepted view that methadone maintenance is the gold standard of treatment.³⁻⁵

An alternative to maintenance treatment is opiate withdrawal, using methadone. Methadone detoxification involves using tapering doses of methadone in order to create a smooth transition from heroin use to a drug-free state. Withdrawal from methadone is not generally recommended in the literature during pregnancy, except in specific situations. These include individual cases when a motivated patient expresses a wish to withdraw from all opiates, or when methadone maintenance is unavailable – as is the case in many South African public treatment facilities.

The way patients are managed in South Africa is inconsistent with recommendations in the literature, a fact that necessitates further investigation. Hence, a systematic review on heroin detoxification in pregnancy was conducted, and the relevant studies are listed in the following table:

	Title	Authors	Reference	Type Study	Summary
1	Maternal narcotic abuse and the newborn	Alroomi et al	Arch Dis Child 63(1): 81-83; 1988	Prospective case series	Opiate-exposed infants have higher rates of neonatal abstinence syndrome (NAS), preterm delivery, intrauterine growth restriction (IUGR) & neonatal mortality.
2	Infrequent neonatal opiate withdrawal following maternal methadone detoxification during pregnancy	Maas et al	J Perinatal Medicine, 18, 111-118; 1990	Prospective case series	Influence of maternal participation in a methadone detox programme was compared to street drug use on neonatal morbidity in 75 neonates. NAS occurred in 63% of neonates & was less frequent after detox.

3	Narcotic withdrawal in pregnancy: Stillbirth incidence with a case report	Rementeria et al	American J Obstet Gynaecol, 116, 1152-1156; 1973	Case report	Description of one patient who had a stillbirth following third-trimester methadone withdrawal. The authors therefore caution against methadone withdrawal in the third trimester.
4	Fetal stress from methadone withdrawal	Zuspan et al	American J Obstet Gynaecol, 122, 43-46; 1975	Case report	Description of one patient who developed increased amniotic fluid epinephrine levels while undergoing methadone withdrawal. The authors recommend avoiding detoxification.
5	Is opiate detoxification unsafe in pregnancy?	Luty et al	J Subs Abuse Treatment, 24, 363-369, 2003	Retrospective case series	101 pregnant opiate dependent women underwent detoxification at various pregnancy stages. Methadone detox was not associated with adverse effects in the second or third trimester.
6	Opioid detoxification in pregnancy	Dashe et al	Obstetrics & Gynaecology. 92(5), 854-858; 1998	Prospective case series	34 pregnant opiate dependent women offered methadone detoxification. 59% were successfully detoxified with no adverse pregnancy outcomes, or relapse to illicit substances.
7	Methadone maintenance program in a Swiss perinatal centre: Management and outcome of 89 pregnancies	Kashingwa et al	Acta Obstet Gynecol Scand. 84, 140-144; 2005	Prospective case series	84 pregnant opiate dependent offered maintenance. 11 attempted detoxification, but approx half returned to maintenance therapy. 64% continued illicit substances use while in the programme.

8	Methadone maintenance vs methadone taper during pregnancy: Maternal and neonatal outcomes	Jones et al	American Journal on Addictions, 17, 372-386; 2008	Prospective case series	175 opioid-dependent pregnant women given methadone maintenance, methadone withdrawal alone, or withdrawal followed by maintenance. Given the poor maternal outcomes with withdrawal alone, maintenance should be considered as the primary treatment approach.
9	Detoxification considerations in the medical management of substance abuse in pregnancy	Allen, MH	Bull NY Academic Medicine, 67, 270-276; 1991	Descriptive	Methadone maintenance has become the mode of therapy for most patients based on early case reports of methadone withdrawal during pregnancy.
10	Substance use in pregnancy	Wong et al	J Obstet Gynaecol Can.33(4):367-384; 2011	Guideline	Review of the literature of substance abuse in pregnancy. Methadone maintenance recommended due to reduced maternal relapse to illicit substances while pregnant.
11	Methadone maintenance in pregnancy: consequences to care and outcomes	Edelin et al	Obstetrics & Gynaecology. 71(3): 399-404; 1993	Retrospective case series	Pregnancy outcomes of 26 narcotic-addicted women enrolled in methadone maintenance programme compared to 37 polydrug users not in programme. No major difference in outcomes found between the two.

12	Treating pregnant women dependent on opioids is not the same as treating pregnancy and opioid dependence	Winklbaaur et al	Addiction, 103, 1429-1440; 2008	Guideline	Use of opioid medication for detox or maintenance should follow established national guidelines, but should be done in a coordinated and supportive environment.
13	Adverse neurodevelopmental outcome of infants exposed to opiate in-utero	Hunt et al	Early Human Development. 84: 29-35; 2008	Literature review & prospective case series	Review of the literature which examines neurodevelopmental outcome in infants with NAS. 33 opiate-exposed infants who were identified after development of NAS compared to controls. Opiate-exposed infants showed neurodevelopmental impairment and reduced growth.
14	The management of heroin misuse in pregnancy: time for a rethink?	Mactier, H	Arch Dis Child Fetal Neonatal Ed. 96: F457-F460; 2011	Descriptive	There is increasing evidence of adverse effects of methadone on developing cortical and visual function in children of treated heroin-addicted mothers. Studies are needed which take into account longer-term outcomes for the child.
15	The cost of crime and the benefits of substance abuse treatment for pregnant women	Daley et al	J Subst Abuse Treat. 19, 445-458; 2000	Prospective case series	Differences in criminal activity were measured in 439 pregnant women entering 5 different treatment programmes. The reduction in crime-related costs was greatest in residential substance abuse facilities. The cost of the treatment facility was more than covered by the cost-saving in crime reduction.

16	Improving treatment outcome in pregnant opiate-dependent women.	Chang et al	J Subst Abuse Treat. 9: 327-330; 1992	Prospective case series	Outcomes of 6 pregnant methadone maintained opiate-dependent women in an enhanced programme were compared to those of 6 women receiving conventional methadone maintenance. The enhanced programme participants had better pregnancy outcomes than those of the controls.
17	Management of pregnant drug-dependent women	Finnegan LP	Ann N Y Acad Sci. 311: 135-46; 1978	Prospective case series	The pregnancy outcomes of 367 opiate-dependent women were compared to 215 non-drug dependent women. The groups were further divided into those receiving an enhanced prenatal programme versus standard care. Infant mortality was reduced in the opiate-dependent group in the enhanced programme.
18	Methadone treatment during pregnancy	Wang, EC	JOGNN, 28, 615-621; 1999	Literature review	Methadone treatment improves pregnancy outcomes only if administered as part of a comprehensive care package.

Results

A total of 18 relevant articles were found, which were reported in 13 publications. The majority were prospective case series, but others included retrospective case series, case reports, literature reviews and descriptive studies, and there were two clinical guidelines.

Heroin is not considered to be grossly teratogenic, but it is highly lipophilic and readily crosses the placenta. Untreated heroin use has been reported to be associated with intrauterine growth restriction, premature delivery, increased neonatal mortality and neonatal abstinence syndrome (NAS).^{5,6} The latter syndrome is characterised by a variety of signs and symptoms in the neonate, which indicate dysfunction of the autonomic nervous system, gastrointestinal tract and respiratory system. There is, consequently, a need for any kind of intervention that will reduce or eliminate maternal heroin use, in order to improve pregnancy outcomes.

Maas *et al* published an intervention study in 1990 that compared the pregnancy outcomes of mothers joining a methadone detoxification programme to those of pregnant mothers who continued uncontrolled street drug use. They found that 17 women out of 58 were successfully detoxified during the antenatal period. The incidence of NAS was lower after maternal participation in the detoxification programme – 55% versus 88%. Newborns of mothers who had successfully detoxified experienced fewer withdrawal symptoms, and no adverse obstetric complications were reported in this group.⁷ This is the only intervention study that compares the pregnancy outcomes of methadone detoxification to continued heroin use. The significant

reduction in NAS demonstrated in this study highlights the importance of offering treatment to heroin-addicted pregnant women.

According to a clinical guideline by Wong *et al*, withdrawal is not advised in the first trimester because of the potential risk of inducing abortion.³ This view is largely the result of an influential case report published in 1975. Zuspan *et al* described a case report of increased amniotic fluid epinephrine levels during methadone withdrawal, which resolved once the methadone dose was increased.⁸

On the other hand, Winklbaur *et al* advise against detoxification after the 32nd week of pregnancy in their clinical guideline because of possible withdrawal-induced stress.⁵ This recommendation is similarly based on a single case study by Rementeria and Nuang, also published in the 1970s, of a stillbirth at term following acute methadone withdrawal.⁹ These authors suggest that lowering methadone levels can induce hyper-stimulation of the adrenal gland and other sympathetic nervous system components, which is manifested by increased amniotic fluid levels of epinephrine.

These initial concerns have since been challenged. Two studies, involving a total of 136 patients, showed positive pregnancy outcomes, with methadone withdrawal initiated at various stages of pregnancy. Dashe *et al* conducted a prospective study whereby 35 opioid-addicted pregnant patients were offered inpatient opiate detoxification with methadone.¹⁰ The mean gestational age of the patients was 24 weeks, and there was careful foetal monitoring throughout the process. Of these patients, 59% were successfully detoxified, and did not

relapse. There was no evidence of foetal distress during detoxification, no foetal death, and no delivery before 36 weeks.

Luty *et al* conducted a retrospective study in 2003, which reviewed 101 case reports of Methadone withdrawal conducted at various stages of pregnancy. The authors concluded that detoxification treatment was not associated with any risk of miscarriage in the second trimester or with premature delivery in the third trimester. While there was an increased risk of miscarriage in the first trimester as compared to the other two trimesters, these results were not statistically significant.¹¹

Apart from the risk of foetal harm during methadone detoxification, the major concern with not providing long-term methadone treatment is an increased risk of relapse with ongoing illicit drug use. Continued illicit substance use is characterised by cycles of intoxication and withdrawal, causing a wide variation in blood opiate levels. This ultimately increases the risk of foetal distress, growth restriction and premature delivery.⁵

Methadone maintenance treatment, however, does not guarantee abstinence. Kashiwanga *et al* explored the pregnancy outcomes among women in a major Swiss methadone maintenance programme. The 84 women enrolled in the programme were tested for additional illicit substance use, and 64% of the women were found to be co-users of cocaine and/or heroin. Using birth weight as a measure of pregnancy outcome, the authors suggested that illicit drug use reversed the benefits of methadone maintenance.¹²

The potential risk associated with methadone detoxification is not the primary reason that methadone maintenance has been the recommended standard of

care since the early 1990s.¹³ There is also a perception that mothers engaged in maintenance programmes are less likely to use illicit drugs, or to engage in other maternal drug-seeking behaviours, such as prostitution.¹⁴ A reduction in these risky behaviours will consequently reduce the woman's chance of acquiring sexually transmitted diseases, HIV and hepatitis infection.

Compliance with regular antenatal care is also assumed to improve in patients involved in methadone maintenance programmes. This combination of improved adherence to obstetric care and reduction in high-risk activities has been shown to secondarily improve neonatal outcomes, measured by overall heavier birth weights.¹³

Wong *et al* conducted a literature review of substance abuse in pregnancy with the aim of providing management recommendations. The authors concluded that methadone maintenance treatment is associated with longer adherence to treatment and decreased risk of relapse to opioid use. They therefore proposed that the preferred standard of care for pregnant opioid-dependant women is substitution therapy.³

This perception has, however, been challenged. Edelin *et al* conducted a retrospective analysis of pregnant women enrolled in a methadone maintenance programme. The authors compared the outcomes of the pregnancies with a similar group of pregnant poly-drug users who were not involved in the maintenance programme. They found no differences in the birth weights or in the infants' Apgar scores. These poor results were probably due to the fact that 88% of the women in the maintenance programme continued to use other illicit drugs during their pregnancy.¹⁵

Besides not always curtailing illicit drug use, management with Methadone poses its own risks. Methadone dependence at birth has been associated with foetal death, growth restriction, pre-term birth, meconium aspiration and neonatal abstinence syndrome (NAS).⁹ It has been estimated that 60–87% of neonates born to methadone maintained mothers require treatment for NAS.¹¹ Neonates suffering from NAS grow poorly in the neonatal period, and have reduced height compared to controls at 3 years of age.¹⁶

The longer-term implications of methadone maintenance treatment are also not clear. Hunt *et al* conducted a study on infants who had developed NAS, indicating that they had been exposed to opiates in utero. These infants had evidence of both cognitive and psychomotor deficit on psychometric testing, when compared to non-opiate-exposed controls.¹⁶ However, it is not clear from this study whether they had been exposed to methadone, heroin or a combination of opiates.

More than 30 years ago, reports were published about abnormal ocular findings in infants of methadone-maintained mothers. Recent literature has re-examined these effects, and found an increased risk of strabismus, nystagmus, refractive errors and delayed visual maturation. The majority of the infants reported in these studies had, however, been exposed to both opiates and benzodiazepines, so it is difficult to determine the exact aetiology.¹⁷ It is clear that the possibility of such long-term visual and cortical defects related to methadone exposure requires more attention and further research.

Methadone withdrawal is the standard management of pregnant heroin addicts in state hospitals in South Africa. This is largely owing to financial constraints, as lengthy methadone maintenance management is perceived to be more costly than withdrawal. This concept has, however, been challenged by Daley *et al* who suggest that the health care costs should not be viewed in isolation. They argue that maintenance treatment reduces maternal criminal behaviour by reducing illicit drug use, which has secondary cost implications for society. The authors conducted a study in Massachusetts, USA, which showed that the cost of crime far outweighed that of substance abuse treatment. In-patient methadone maintenance showed the greatest cost-benefit ratio, which supports the view of methadone maintenance being the gold-standard treatment.¹⁸

Two studies were conducted that examined methadone maintenance as part of a comprehensive care programme. Chang *et al* conducted a small study comparing the outcomes of pregnant methadone-maintained opiate-dependent subjects in an enhanced treatment programme, with women receiving conventional methadone maintenance. Enhanced treatment consisted of weekly prenatal care, relapse prevention groups, urine toxicology screening with positive contingency awards for abstinence, and therapeutic childcare during treatment visits. The women involved in the enhanced treatment programme demonstrated less overall illicit drug use and delivered heavier infants.¹⁹ This finding was confirmed by Finnegan, who found that methadone maintenance in addition to intensive antenatal care is compatible with an uneventful pregnancy and birth of a healthy infant.²⁰ We may also need to shift our focus from the medical management of cravings and

fluctuating maternal opiate levels, to the provision of a more comprehensive care package.

Having reviewed the various studies found in the literature, what is apparent is that the data on the safety and efficacy of methadone detoxification is limited. There are, however, good data on a need to develop comprehensive treatment programmes that go beyond the dispensing of methadone and/or other medication.²¹ Pregnancy is known to be a useful period for encouraging behavioural changes. However, methadone alone, whether given as detoxification or maintenance, does not correct all the underlying psychosocial problems or address behaviour changes. The best outcomes are most likely to be reached by using a holistic care plan incorporating medical, psychiatric and social work attention.

Identification of gaps or needs for further research

Overall, the literature on the management of heroin addiction during pregnancy is extremely limited. The studies identified in this review were conducted on small sample sizes, were not randomised, and only a few had control groups. Therefore, there is a general need for more robust evidence-based research in this field.

The literature on the efficacy and safety of methadone detoxification is particularly scanty. Large-scale studies conducted at various stages of pregnancy are required to determine whether the adverse effects reported in

early case reports are indeed valid. This may help to determine whether there is an optimum time for detoxification to occur during the pregnancy.

Some recent studies have raised concerns about the long-term effects of methadone maintenance on the infant. Given the fact that maintenance treatment is the current international gold standard in pregnancy, this is an area of research that requires urgent attention.

No studies were found which were conducted specifically on pregnant women in South Africa. Research within our unique, genetically diverse population group is needed, specifically with regards to our policy of methadone detoxification in public hospitals.

References

1. United Nations office on drugs and crime. World Drug Report, 2011; 45-55.
2. Parry CDH et al. Heroin treatment demand in South Africa: trends from two large metropolitan sites (January 1997 – December 2003). *Drug and Alcohol Review*. 2005; 24: 419-423.
3. Wong S et al. Substance use in pregnancy. *J Obstet Gynaecol Can*. 2011; 33(4): 367-384.
4. Fischer G et al. Pregnancy and substance abuse. *Archives of Women's*

- Mental Health*, 1999; 2: 57-65.
5. Winklbaur B et al. Treating pregnant women dependent on opioids is not the same as treating pregnancy and opioid dependence: a knowledge synthesis for better treatment for women and neonates. *Addiction*. 2008; 103: 1429-1440.
 6. Alroomi LG et al. Maternal narcotic abuse and the newborn. *Archives of disease in childhood*. 1988; 63(1): 81-83.
 7. Maas U et al. Infrequent neonatal opiate withdrawal following maternal methadone detoxification during pregnancy. *J Perinatal Medicine*. 1990; 18: 111-118.
 8. Zuspan FP, Gumpel JA, Mejia-Zelaya A. Fetal stress from Methadone withdrawal. *Am J Obstet Gynecol*. 1975; 122: 43-46.
 9. Rementeria JL, Nunang NN. Narcotic withdrawal in pregnancy: Stillbirth incidence with a case report. *Am J Obstet Gynecol*. 1973; 116: 1152-1156.
 10. Dashe JS et al. Opioid detoxification in pregnancy. *Obstetrics & Gynaecology*. 1998; 92(5): 854-858.
 11. Luty J, Nikolaou V, Bearn J. Is opiate detoxification unsafe in pregnancy? *J Subs Abuse Treat*. 2003; 24: 363-367.
 12. Kashingwa M et al. Methadone maintenance program in a Swiss perinatal centre: (I): Management and outcome of 89 pregnancies. *Acta Obstet Gynecol Scand*. 2005; 84: 140-144.

13. Jones H et al. Methadone maintenance vs methadone taper during pregnancy: Maternal and neonatal outcomes. *Am J Addict.* 2008; 17: 372-386.
14. Allen MH. Detoxification considerations in the medical management of substance abuse in pregnancy. *Bull N Y Acad Med.* 1991; 67: 270-276.
15. Edelin KC et al. Methadone maintenance in pregnancy: consequences to care and outcome. *Obstetrics & Gynaecology.* 1993; 71(3): 399-404.
16. Hunt RW et al. Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. *Early Human Development.* 2008; 84: 29-35.
17. Mactier H. The management of heroin misuse in pregnancy: time for a rethink? *Arch Dis Child Fetal Neonatal Ed.* 2011; 96: F457-F460.
18. Daley M et al. The cost of crime and the benefits of substance treatment for pregnant women. *J Subst Abuse Treat.* 2000; 19: 445-458.
19. Chang G et al. Improving treatment outcome in pregnant opiate-dependent women. *J Subst Abuse Treat.* 1992; 9: 327-330.
20. Finnegan LP. Management of pregnant drug-dependent women. *Ann N Y Acad Sci.* 1978; 311: 135-46.
21. Wang EC. Methadone Treatment During Pregnancy. *JOGNN.* 1999; 28: 615-622.

PART C: PUBLICATION READY MANUSCRIPT

Corresponding author:

Dr Katherine Gilfillan

katherine.gilfillan@gmail.com

Tel: 0027 21 440 3111

Fax: 0027 21 440 3199

Department of Psychiatry and
Mental Health

University of Cape Town,
Anzio Road, Observatory,
7925, Cape Town, South
Africa

Heroin detoxification during pregnancy:

A systematic review and retrospective study of management of heroin addiction in pregnancy

Authors: Katherine V. Gilfillan*
Dan J. Stein*
Bavanisha Vythilingum*

*Department of Psychiatry and Mental Health, University of Cape Town,
South Africa

Keywords: pregnancy outcomes, heroin dependence, methadone

Abstract

Background: There is a general consensus that methadone maintenance is the gold standard in the management of pregnant heroin users. However, in South African state hospitals, methadone withdrawal is the routine procedure offered to these patients, as methadone maintenance programmes are unavailable in the public sector.

Objectives: (1) To conduct a systematic review of the literature on heroin detoxification in pregnancy and (2) to retrospectively collect data of all pregnant heroin users who were detoxified with methadone at Groote Schuur Hospital (GSH) between 2006 and 2010.

Method: A PubMed literature search was undertaken to identify key publications on the management of heroin addiction in pregnancy. Patients for the study were identified from the GSH methadone registry, and data were collected from the clinical files.

Results: A total of 18 relevant publications were identified and reviewed. Two case reports published in the 1970s described an increased risk of stillbirths and fetal distress after methadone detoxification, but two more recent case series involving larger numbers of patients showed positive outcomes.

Methadone maintenance together with a social support programme was advocated by two clinical guidelines. Our study found that of 6 patients who received methadone withdrawal over a 5-year period at GSH, all of the neonates had good APGAR scores, did not require resuscitation, and were discharged home within 3 days of delivery.

Conclusion: There is limited evidence on the management of heroin addiction during pregnancy, and the only two guidelines identified suggest that methadone maintenance is preferable to methadone withdrawal. The favourable pregnancy outcomes of this small sample of patients managed with methadone withdrawal suggests that methadone withdrawal, which is used in resource-constrained contexts may be safe, and deserves further study.

University of Cape Town

Introduction

Diacetylmorphine was first synthesised by C R Alder Wright in 1874 as a highly potent, acetylated form of morphine. By 1898, Bayer pharmaceutical company marketed this drug under the trademark name of Heroin. It was initially sold as a non-addictive morphine substitute and cough suppressant. However, heroin was soon found to be twice as powerful as morphine, due to the fact that it is highly fat-soluble and rapidly crosses the blood-brain barrier. Despite subsequent strict controls imposed on the use of heroin, it remains the most widely used opiate.¹

In 2009, there were an estimated 12–14 million heroin users worldwide.¹ Europe and Asia remain the key opiate consumption markets, but opiate use in Africa is, according to reports, increasing.¹ The 2010 SACENDU statistics reveal that 5–20% of patients in specialist treatment centres in South Africa use heroin as their primary drug of choice. Heroin is primarily used by people between 22–30 years old in South Africa², and approximately 20–40% of people treated for heroin abuse are female, which is a higher percentage than that for most other illicit substances.³

Opiate use is associated with menstrual irregularities, which, when added to the often erratic lifestyles of drug-abusing women, leads to a high rate of unplanned pregnancies. Heroin-dependent pregnant women represent an extremely vulnerable group of patients, who present with various medical, obstetric and psychiatric problems. There has been considerable debate about how to best manage these patients, as the needs of both the foetus and mother require careful attention.

The ideal goal during pregnancy is for the mother to remain abstinent from any drug use. When faced with a pregnant patient who is actively abusing heroin, one needs to offer treatment that will best minimise any further foetal and maternal harm. Given the highly-addictive nature of opiates, it is difficult for many of these individuals to remain drug free, and therefore some form of maintenance treatment is usually offered.

An alternative to maintenance treatment is opiate withdrawal, using methadone. Methadone detoxification involves using tapering doses of methadone in order to create a smooth transition from heroin use to a drug-free state. Withdrawal from methadone is not generally recommended in the literature during pregnancy,⁴⁻⁷ except in specific situations. These include individual cases when a motivated patient expresses a wish to withdraw from all opiates, or when methadone maintenance is unavailable – a situation that is prevalent across all South African public treatment facilities.

Due to the fact that pregnant women are rarely included in psychotropic clinical trials, there is often relatively little information available about the use of medication during pregnancy. Therefore, the evidence-based management of pregnant patients who are dependent on opioids is particularly challenging. While guidance is scarce, the prevailing opinion is that methadone maintenance is the gold standard of treatment in pregnancy.⁴⁻⁷ This option is not available in South African state facilities, where only methadone withdrawal is offered. It would therefore be useful to review the data in the literature about the efficacy of methadone withdrawal in pregnancy.

The specific aims of this paper are: (1) to conduct a systematic review of the literature on heroin detoxification in pregnancy and (2) to report on pregnancy outcomes of heroin users who were detoxified with methadone at GSH, a teaching hospital in Cape Town, in the last five years.

Method

SYSTEMATIC REVIEW

The electronic database PubMed was searched using a combination of the following search terms: pregnancy, heroin, opiate, methadone, buprenorphine, and treatment. Additional publications were identified from the reference lists of retrieved articles. All relevant articles in English, reporting original data related to the treatment of heroin addiction in pregnancy, were included.

Using the terms described above, 12 English articles were located on a Pubmed search. Of these articles, 3 were relevant to the study. However, by using the article references, a total of 18 relevant articles were found and reviewed.

CLINICAL STUDY

Location

Groote Schuur Hospital is a tertiary state hospital that is situated in Observatory, Cape Town. The patients were managed in the labour ward or in C23 – the emergency psychiatric ward.

Subjects

The study population included all pregnant heroin-addicted patients who underwent methadone detoxification at GSH between 2006 and 2010. The labour ward and C23 keep a register of all patients who have received methadone.

Data collection

Pregnant patients treated during this period were identified by means of information obtained from the methadone register. Both methadone registers were carefully scrutinised to ensure that all pregnant patients treated at GSH were identified. The patients' hospital numbers are recorded on the register, so it was possible to access their files with the assistance of hospital clerks. The outcomes of these pregnancies were then determined by looking at specific maternal and foetal parameters.

Ethical considerations

The study was approved by the University of Cape Town Human Research Ethics Committee, and permission was granted to access information from the clinical files. Only information relevant to the study was extracted from the

patient files, and all the data was de-identified. As this is a retrospective study, patient consent was not sought.

Results

SYSTEMATIC REVIEW

A total of 18 relevant articles were found which were reported in 13 publications. The majority were prospective case series, but others included retrospective case series, case reports, literature reviews and descriptive studies, and there were two clinical guidelines.

[TABLE 1]

Heroin is not considered to be grossly teratogenic, but it is highly lipophilic and readily crosses the placenta. Untreated heroin use is associated with intrauterine growth restriction, premature delivery, increased neonatal mortality and neonatal abstinence syndrome (NAS).^{7,8} The latter syndrome is characterised by a variety of signs and symptoms in the neonate which indicate dysfunction of the autonomic nervous system, gastrointestinal tract and respiratory system. There is, consequently, a need for any kind of intervention that will reduce or eliminate maternal heroin use, in order to improve pregnancy outcomes.

Maas *et al* published an intervention study in 1990 that compared the pregnancy outcomes of mothers joining a methadone detoxification

programme to those of pregnant mothers who continued uncontrolled street-drug use. He found that 17 women out of 58 were successfully detoxified during the antenatal period. The incidence of neonatal abstinence syndrome was lower after maternal participation in the detoxification programme – 55% versus 88%. Newborns of mothers who had successfully detoxified experienced fewer withdrawal symptoms, and no adverse obstetric complications were reported in this group.⁹

According to most widely-accepted recommendations, withdrawal is not advised before 14 weeks' gestation because of the potential risk of inducing abortion, and should not be performed after the 32nd week of pregnancy because of possible withdrawal-induced stress.^{5,6} This view is largely the result of two influential case reports published in the 1970s. Rementeria and Nunag described a case study of a stillbirth at term following acute Methadone withdrawal,¹⁰ and Zuspan *et al* described a case report of increased amniotic fluid epinephrine levels during Methadone withdrawal, which resolved once the Methadone dose was increased.¹¹

These initial concerns have since been challenged. Luty *et al* conducted a retrospective study in 2003, which reviewed 101 case reports of Methadone withdrawal conducted at various stages of pregnancy. They concluded that detoxification treatment was not associated with any risk of miscarriage in the second trimester or with premature delivery in the third trimester.¹² Similarly, Dashe *et al* conducted a prospective study whereby 35 opioid addicted pregnant patients were offered inpatient opiate detoxification with methadone. 59% of these patients were successfully detoxified, did not relapse, and had no adverse pregnancy outcomes.¹³

Apart from the risk of foetal harm during methadone detoxification, the major concern with not providing long-term methadone treatment is an increased risk of relapse to illicit drug use. There is a perception that mothers engaged in maintenance programmes are less likely to use illicit drugs, or to engage in other maternal drug-seeking behaviours, such as prostitution.

Wong *et al* conducted a literature review of substance abuse in pregnancy in order to provide recommendations on management. The authors concluded that methadone maintenance treatment is associated with longer adherence to treatment and decreased risk of relapse to opioid use. They therefore proposed that the preferred standard of care for pregnant opioid-dependant women is substitution therapy.⁴

However, some studies have shown that methadone maintenance treatment does not guarantee abstinence. Kashiwanga *et al* explored the pregnancy outcomes among women in a major Swiss methadone maintenance programme, and 64% of the women were found to be co-users of cocaine and/or heroin.¹⁴

Besides not always curtailing illicit drug use, management with Methadone poses its own risks. Methadone dependence at birth has been associated with foetal death, growth restriction, pre-term birth, meconium aspiration and neonatal abstinence syndrome (NAS).¹⁰ It has been estimated that 60–87% of neonates born to methadone maintained mothers require treatment for NAS.⁷ Neonates suffering from NAS grow poorly in the neonatal period, and have reduced height compared to controls at 3 years of age.¹⁵

The longer-term implications of methadone maintenance treatment are also not clear. Hunt *et al* conducted a study on infants who had developed NAS, and found that they had evidence of both cognitive and psychomotor deficit on psychometric testing, when compared to non-opiate-exposed controls.¹⁵

Recent literature has also found an increased incidence of ocular abnormalities in infants of methadone-maintained mothers.¹⁶ The possibility of long-term visual and cortical defects is alarming, and requires further research.

Methadone withdrawal is the standard management of pregnant heroin addicts in state hospitals in South Africa. This is largely owing to financial constraints, as Methadone maintenance management is more costly than withdrawal. This concept has, however, been challenged by Daley *et al* who suggest that the health care costs should not be viewed in isolation. They argue that maintenance treatment reduces maternal criminal behaviour by reducing illicit drug use, which has secondary cost implications for society. The authors conducted a study in Massachusetts, USA, which indicated that the cost of crime far outweighed that of substance abuse treatment.¹⁷

It seems that we need to change our focus of attention from the medical management of cravings and fluctuating maternal opiate levels, to providing a more comprehensive care package. Two studies conducted by Chang *et al* and Finnegan found that methadone maintenance, in addition to intensive antenatal care, is compatible with an uneventful pregnancy and birth of a healthy infant.^{18,19}

Having reviewed the various studies found in the literature, what is apparent is that the data on the safety and efficacy of methadone detoxification are limited. There are, however, good data on a need to develop comprehensive treatment programmes that go beyond the dispensing of methadone and/or other medication.²⁰ Pregnancy is often described as a useful period for encouraging behavioural changes. However, methadone alone, whether given as detoxification or maintenance, does not correct all the underlying psychosocial problems or address behaviour changes. The best outcomes are most likely to be reached by using an integrated care plan incorporating pharmacological, psychotherapeutic and social interventions.

STUDY

Due to the fact that methadone is a highly addictive schedule II drug, its administration is recorded in a methadone register. This register shows that only six pregnant heroin-addicted patients received methadone detoxification at GSH between 2006 and 2010. The clinical details of these patients were tabulated.

[TABLE 2]

A total of six pregnant patients received methadone withdrawal at GSH between 2006 and 2010. The ages of the patients ranged from 17–37 years old. Four of the six patients were single, and half of them had high parity. Apart from patient D, all the patients booked late (defined as booking after 20

weeks gestation). All of the patients were HIV negative, and none had current syphilis infection.

Surprisingly, none of the patients abused alcohol, and only patient F used another illicit substance (methamphetamine). Five of the six patients received methadone detoxification either at GSH or at Stikland Hospital substance abuse facility prior to delivery. There was no record of any psychiatric follow-up for any of the patients after detoxification, apart from patient D who could afford a private rehabilitation facility.

Four of the patients delivered at term, and patient F delivered one week short of term. Half of the patients required caesarean sections. Interestingly, all of the neonates had APGAR scores ranging between 7–10, and none of them required resuscitation. None of the neonates showed signs of neonatal abstinence syndrome. All patients were discharged from the maternity ward within three days after delivery.

Discussion

The main findings of our literature review indicated that there is little data on the safety of methadone withdrawal, and information that is available is largely contradictory. The most striking feature of our case series is the relatively low number of patients who received methadone detoxification, despite the rising rates of heroin use and the burden of disease encountered in Cape Town.

Given that the 2010 SACENDU statistics reveal that heroin is the primary substance of abuse among 13% of substance abusers in the Western Cape,²

it may be speculated that heroin-addicted pregnant patients are inadequately screened for, or are offered detoxification with, only benzodiazepines and analgesics. There are two possible explanations for this. Firstly, these patients may face tremendous stigma, not only from their families and society, but also from health care providers and they may therefore be treated with little sympathy, being perceived as attempting to manipulate the system by requesting methadone treatment. Secondly, health care workers may be concerned about the risk of exposing the foetus to another potentially harmful substance.

Five of the six patients had received methadone detoxification prior to delivery, while patient B went into labour during her withdrawal. Of the five patients who completed their detoxification, only two resumed using heroin prior to their delivery. In this small sample, the relapse rate is low given the fact that only one patient received continued psychosocial support after discharge. This low rate of relapse indicates that methadone detoxification may be a successful way of managing these patients. One of the main criticisms of withdrawal treatment is the high rate of relapse to heroin use, which was shown not to be the case in this small population. Having said this, a relapse rate of 40% is not negligible, and ideally, further psychosocial measures should be implemented to assist in maintaining abstinence.

A major concern with methadone maintenance treatment is the high risk of the neonatal abstinence syndrome (NAS). This syndrome is characterised by central nervous system excitability in newborn infants, and in many cases requires pharmacological withdrawal treatment. All infants of the six patients described were born without showing any sign of opioid withdrawal, had good

APGAR scores and required no resuscitation. As mentioned earlier, the literature suggests that NAS requiring treatment occurs in at least two-thirds of infants born to mothers on methadone maintenance.⁸ The positive neonatal outcome in this group is therefore significant as it highlights a major advantage of methadone detoxification over maintenance.

Remerentia and Nunag cautioned against detoxification after 32 weeks' gestation due to concerns about precipitating early delivery.⁹ Four of the six patients (A, B, E and F) were detoxified after 32 weeks, and two of the four (A and B) went into labour during the detoxification process. This was problematic for patient B as it led to a premature delivery at 33 weeks. These findings support the view that detoxification is safest during the second trimester.

An interesting finding in these six patients was the low rate of co-morbid substance abuse, and the fact that none of them were infected with the human immunodeficiency virus or with syphilis. This group of patients is usually at high risk for poly-substance abuse, and sexually transmitted infections. The absence of these common additional problems may also partly explain the relatively good neonatal outcomes in the group.

What is disheartening is the apparent discrepancy in the resources available to heroin-addicted pregnant women in developed countries as compared to South Africa. The focus of most research has shifted from determining the merits of maintenance versus withdrawal to determining which medication is superior in maintenance management. South African state facilities continue to offer only methadone as substitution medication, and only for a limited

period while undergoing withdrawal. This highlights the need for a greater focus on pharmacological harm reduction strategies in low and middle income countries.

The limitations of the current data set include the small sample size, the retrospective ratings, and the lack of any follow up information. Despite this, however, these data suggest that favourable outcomes of pregnancies managed with methadone withdrawal are possible. Additional research is nevertheless required to confirm these preliminary findings.

References

1. United Nations office on drugs and crime. World Drug Report, 2011; 45-55.
2. South African community epidemiology network on drug use (SACENDU) Research Brief, Volume 13(2), 2010.
3. Parry CDH et al. Heroin treatment demand in South Africa: trends from two large metropolitan sites (January 1997 – December 2003). *Drug and Alcohol Review*. 2005; 24: 419-423.
4. Wong S et al. Substance use in pregnancy. *J Obstet Gynaecol Can*. 2011; 33(4): 367-384.
5. Fischer G et al. Pregnancy and substance abuse, *Archives of Women's Mental Health*, 1999; 2: 57-65.

6. Jones H et al. Methadone maintenance vs methadone taper during pregnancy: Maternal and neonatal outcomes. *Am J Addict.* 2008; 17: 372-386.
7. Winklbaur B et al. Treating pregnant women dependent on opioids is not the same as treating pregnancy and opioid dependence: a knowledge synthesis for better treatment for women and neonates. *Addiction.* 2008; 103: 1429-1440.
8. Alroomi LG et al. Maternal narcotic abuse and the newborn. *Archives of disease in childhood.* 1988; 63(1): 81-83.
9. Maas U et al. Infrequent neonatal opiate withdrawal following maternal methadone detoxification during pregnancy. *J Perinatal Medicine.* 1990; 18: 111-118.
10. Rementeria JL, Nunag NN. Narcotic withdrawal in pregnancy: Stillbirth incidence with a case report. *Am J Obstet Gynecol.* 1973; 116: 1152-1156.
11. Zuspan FP, Gumpel JA, Mejia-Zelaya A. Fetal stress from Methadone withdrawal. *Am J Obstet Gynecol.* 1975; 122: 43-46.
12. Luty J, Nikolaou V, Bearn J. Is opiate detoxification unsafe in pregnancy? *J Subs Abuse Treat.* 2003; 24: 363-367.
13. Dashe JS et al. Opioid detoxification in pregnancy. *Obstetrics & Gynaecology.* 1998; 92(5): 854-858.

14. Kashingwa M et al. Methadone maintenance program in a Swiss perinatal centre: (I): Management and outcome of 89 pregnancies. *Acta Obstet Gynecol Scand.* 2005; 84: 140-144.
15. Hunt RW et al. Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. *Early Human Development.* 2008; 84: 29-35.
16. Mactier H. The management of heroin misuse in pregnancy: time for a rethink? *Arch Dis Child Fetal Neonatal Ed.* 2011; 96: F457-F460.
17. Daley M et al. The cost of crime and the benefits of substance treatment for pregnant women. *J Subst Abuse Treat.* 2000; 19: 445-458.
18. Chang G et al. Improving treatment outcome in pregnant opiate-dependent women. *J Subst Abuse Treat.* 1992; 9: 327-330.
19. Finnegan LP. Management of pregnant drug-dependent women. *Ann N Y Acad Sci.* 1978; 311: 135-46.
20. Wang EC. Methadone Treatment During Pregnancy. *JOGNN.* 1999; 28: 615-622.

Table 1:

	Title	Authors	Reference	Type Study	Summary
1	Maternal narcotic abuse and the newborn	Alroomi et al	Archives of disease in childhood. 1988; 63(1): 81-83.	Prospective case series	Opiate-exposed infants have higher rates of NAS, preterm delivery, IUGR & neonatal mortality.
2	Infrequent neonatal opiate withdrawal following maternal methadone detoxification during pregnancy	Maas et al	J Perinatal Medicine, 18, 111-118; 1990	Prospective case series	Influence of maternal participation in a methadone detox programme was compared to street drug use on neonatal morbidity in 75 neonates. NAS occurred in 63% of neonates, and was less frequent after methadone detox.
3	Methadone treatment during pregnancy	Wang, EC	JOGNN, 28, 615-621; 1999	Literature review	Methadone treatment is only beneficial if administered as part of a comprehensive care package.
4	Narcotic withdrawal in pregnancy: Stillbirth incidence with a case report	Rementeria et al	American J Obstet Gynaecol, 116, 1152-1156; 1973	Case report	Description of one patient who had a stillbirth following third-trimester methadone withdrawal. The authors therefore caution against methadone withdrawal in the third trimester.
5	Fetal stress from methadone withdrawal	Zuspan et al	American J Obstet Gynaecol, 122, 43-46; 1975	Case report	Description of one patient who developed increased amniotic fluid epinephrine levels while undergoing methadone

					withdrawal. The authors recommend avoiding detoxification.
6	Is opiate detoxification unsafe in pregnancy?	Luty et al	J Subs Abuse Treatment. 24, 363-369, 2003	Retrospective case series	101 pregnant opiate dependent women underwent detoxification at various pregnancy stages. Methadone detox was not associated with adverse effects in the second or third trimester.
7	Opioid detoxification in pregnancy	Dashe et al	Obstetrics & Gynaecology. 92(5), 854-858; 1998	Prospective case series	34 pregnant opiate dependent offered methadone detoxification. 59% were successfully detoxified with no adverse pregnancy outcomes, or relapse to illicit substances.
8	Methadone maintenance programme in a Swiss perinatal centre: Management and outcome of 89 pregnancies	Kashingwa et al	Acta Obstet Gynecol Scand. 2005; 84: 140-144	Prospective case series	84 pregnant opiate dependent offered methadone maintenance. 11 attempted detoxification, but approximately 50% returned to maintenance therapy. 64% continued to use illicit substances while in the programme.

9	Methadone maintenance vs methadone taper during pregnancy: Maternal and neonatal outcomes	Jones et al	American Journal on Addictions, 17, 372-386; 2008	Prospective case series	175 opioid-dependent pregnant women given methadone maintenance, methadone withdrawal alone, or withdrawal followed by maintenance. Given the poor maternal outcomes with withdrawal alone, maintenance should be considered as the primary treatment approach.
10	Detoxification considerations in the medical management of substance abuse in pregnancy	Allen, MH	Bull NY Academic Medicine, 67, 270-276; 1991	Descriptive	Methadone maintenance has become the mode of therapy for most patients based on early case reports.
11	Substance use in pregnancy	Wong et al	J Obstet Gynaecol Can. 2011; 33(4):367-384.	Systematic review	Review of the literature of substance abuse in pregnancy. Methadone maintenance recommended due to reduced relapse to illicit substances.
12	Methadone maintenance in pregnancy: consequences to care and outcomes	Edelin et al	Obstetrics & Gynaecology. 1993; 71(3): 399-404	Retrospective case series	Pregnancy outcomes of 26 narcotic-addicted women enrolled in methadone maintenance programme compared to 37 polydrug users not in programme. No major difference in outcomes found between the two groups.
13	Treating pregnant women dependent on opioids is not the same as treating pregnancy and opioid dependence	Winklbaur et al	Addiction, 103, 1429-1440; 2008	Literature review	Use of opioid medication for detox or maintenance should follow established national guidelines, but should be done in a coordinated and supportive environment.

14	Adverse neurodevelopmental outcome of infants exposed to opiate in-utero	Hunt et al	Early Human Development. 2008; 84: 29-35.	Literature review & prospective case series	Review of the literature which examines neurodevelopmental outcome in infants with NAS. 33 opiate-exposed infants who were identified after development of NAS compared to controls. Opiate-exposed infants showed neurodevelopmental impairment and reduced growth.
15	The management of heroin misuse in pregnancy: time for a rethink?	Mactier H	Arch Dis Child Fetal Neonatal Ed. 2011; 96: F457-F460	Descriptive	There is increasing evidence of adverse effects upon developing cortical and visual function in children of treated heroin-addicted mothers. Studies are needed which take into account longer-term outcomes for the child.
16	The cost of crime and the benefits of substance abuse treatment for pregnant women	Daley et al	J Subst Abuse Treat. 2000; 19, 445-458.	Prospective case series	Differences in criminal activity were measured in 439 pregnant women entering 5 different treatment programmes. The reduction in crime-related costs was greatest in residential substance abuse facilities. The cost of the treatment facility was more than covered by the cost-saving in crime reduction.

17	Improving treatment outcome in pregnant opiate-dependent women.	Chang et al	J Subst Abuse Treat. 1992; 9: 327-330.	Prospective case series	Outcomes of 6 pregnant methadone maintained opiate-dependent women in an enhanced programme were compared to those of 6 women receiving conventional methadone maintenance. The enhanced programme participants had better pregnancy outcomes than those of the controls.
18	Management of pregnant drug-dependent women	Finnegan LP	Ann N Y Acad Sci. 1978; 311: 135-46.	Prospective case series	The pregnancy outcomes of 367 opiate-dependent women were compared to 215 non-drug dependent women. The groups were further divided into those receiving an enhanced prenatal programme versus standard care. Infant mortality was reduced in the opiate-dependent group in the enhanced programme.

Table 2:

	Patient A	Patient B	Patient C	Patient D	Patient E	Patient F
Age	24 yrs	37 yrs	21 yrs	34 yrs	17 yrs	28 yrs
Ethnicity	Coloured	Coloured	Coloured	White	Coloured	Coloured
Marital status	Divorced	Single	Single	Single	Single	Married
Gestational age	37+wks	33 wks	42+wks	39 wks	38+wks	36 wks
Obs History	G5P2M1 + 1SB	G1P0	G1P0	G5P1M2T1	G1P0	G4P3
Booking & antenatal visits	Booked at 29wks, then attended 8 antenatal clinic visits	Booked at 32wks, then admitted at following visit	Booked at 31wks, then attended 4 antenatal clinic visits	Booked at 11wks, then attended 5 antenatal clinic visits	Booked at 24wks, then attended 4 antenatal clinic visits	Booked at 33wks, then attended 1 antenatal clinic visit
Blood results	Rh+ RVD-VDRL-	Rh+ RVD-VDRL-	Rh+ RVD-VDRL-	Rh+ RVD-VDRL-	Rh+ RVD-VDRL-	Rh+ RVD-VDRL-
Alcohol use	no	no	no	no	no	no
Nicotine use	yes	yes	no	no	yes	yes
Other substance use	Heroin	Heroin, benzos	Heroin	Heroin	Heroin	Heroin, methamphetamine
Antenatal management of heroin use	Seen by Social Worker, and referred to SKH detox unit. Admitted 30/06/09-07/07/09	Admitted to GSH for detox on 05/06/08. Went into labour during detox admission	Admitted to GSH for detox from 09/03/10-11/03/10. Then referred to CTDC and put onto SKH waiting list	Treated by private GP with Buprenorphine until Feb 2010, then relapsed. Admitted to GSH for detox from 21/04/10-23/04/10. Then discharged to private rehab facility	Admitted to SKH for detox in May 2010. Relapsed, and admitted to GSH for detox from 15/07/10-21/07/10. Then transferred to SKH, and discharged on 27/07/10	Admitted to GSH for detox from 09/03/10-11/03/10. Put onto SKH waiting list
Date last used	27/10/2009	04/06/2008	22/05/2010	21/04/2010	28/07/2009	09/03/2010
Medical History	none	none	none	recurrent UTIs	none	none

Admission date	27/10/2009	05/06/2008	24/05/2010	16/06/2010	11/08/2009	23/03/2010
Methadone administration during labour	28-30/10/09: 10ml, 31-1/11/09: 8ml, 2-3/11/09: 6ml	9-11/06/08: 8ml	none	none	none	none
Delivery	C/Section for placental abruption & fetal distress 4/11/09	Vacuum delivery after spontaneous labour 10/06/08	C/Section on 25/05/10 for fetal distress	C/Section for previous C/S	Prelabour ROM on 11/08/09, given Pitocin, NVD 13/08/10	NVD
APGAR score	8/10, 10/10	7/10, 9/10	9/10, 10/10	9/10, 10/10	8/10, 10/10	09/10, 09/10
Sex	female	male	male	female	male	female
Birth weight	2.26 kgs	2.11 kgs	3.96 kgs	2.60 kgs	3.54 kgs	3.24 kgs
Head Circumference	33cm	34cm	36cm	31cm	33cm	34cm
Resus required	none	none	none	none	none	none
Neonatal withdrawal	none	none	none	none	none	none
Discharge date	7/11/09. referred to C23, but discharged herself against doctor's advice	13/06/08 on diazepam only	28/05/10, no meds	19/06/10, no meds	14/08/09, no meds	24/04/10, no meds

PART D: SUPPORTING DOCUMENTS



UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6626 • Facsimile [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

15 February 2010

REC REF: 072/2010

Dr B Vythilingum
Psychiatry

Dear Dr Vythilingum

PROJECT TITLE: HEROIN DETOXIFICATION DURING PREGNANCY: A RETROSPECTIVE STUDY AND A SYSTEMATIC REVIEW OF MANAGEMENT OF HEROIN ADDICTION IN PREGNANCY.

Thank you for submitting your study to the Research Ethics Committee.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study including the following documentation.

Approval is granted for one year till the 20th February 2011.

Please submit an annual progress report if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

S Thomas

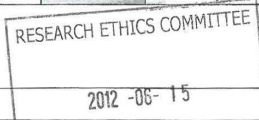
This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

FHS017: Annual Progress Report
Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)	
<input checked="" type="checkbox"/> Approved	Annual progress report
<input type="checkbox"/> Not approved	See attached comments
Expiry date	30 June 2013
Chairperson of the HREC signature	Date 16/6/2012

Principal Investigator to complete the following:



1. Protocol information

Date	14/06/2012	2012-08-15
HREC REF Number	072 / 2010	HEALTH SCIENCES FACULTY
Protocol title	Heroin Detoxification during pregnancy review of the management of heroin addiction in pregnancy.	UNIVERSITY OF CAPE TOWN
Protocol number (if applicable)		
Principal Investigator	Dr Katherine Gilfillan	
Department / Office Internal Mail Address	Office 3, Education Centre, Valkenburg Hospital 1 Observatory Street, Observatory.	
1.1 Does this protocol receive US Federal funding?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

2. Protocol status (tick ✓)

<input type="checkbox"/>	Research-related activities are ongoing
<input checked="" type="checkbox"/>	Data collection is complete, data analysis only

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval	6
Total number of records or specimens collected, reviewed or stored since last progress report	
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

4. Signature

Signature of PI		Date	8/6/12
Signature of Supervisor (if PI is a student)		Date	8/6/12



DEPARTMENT of HEALTH

Provincial Government of the Western Cape

GROOTE SCHUUR HOSPITAL

spatel@gwc.gov.za
Tel: 021-404-6286 Fax: 021-404-6125
Private Bag, Observatory, 7925
www.capegateway.gov.za

REFERENCE: Research: Katherine Gilfilan
ENQUIRIES: Dr B. Patel

Dr Katherine Gilfilan

E-mail address: katherine.gilfilan@gmail.com

Dear Dr Gilfilan

RESEARCH: A Retrospective Study and a Systematic Review of Management of Heroin Addiction In Pregnancy

Your recent letter to the hospital refers.

You are hereby granted permission to proceed with your research.

Please note the following:

- a) Your research may not interfere with normal patient care
- b) Hospital staff may not be asked to assist with the research.
- c) No hospital consumables and stationary may be used
- d) Please introduce yourself to the person in charge of an area before commencing.

I would like to wish you every success with the project.

Yours sincerely

Dr Bhavna Patel
SENIOR MANAGER: MEDICAL SERVICES

Date: 9th March 2011



Groote Schuur Hospital
Private Bag,
Observatory, 7935
Telephone : 021 404-9111

African Journal Of Psychiatry (Ajop)

Material submitted for publication in the AJOP is accepted on condition that it meets the requirement of the Editor-in-Chief. The publisher reserves the copyright of the material published. All authors must give consent to publication, and the AJOP does not hold itself responsible for statements made by contributors. The Journal's primary aim is the publication of review and original articles, case reports and letters to the editor aimed at specialist mental health care and other professionals working in the neurosciences as well as primary care practitioners. All material will be sent for peer review.

Manuscript preparation

Copies should be neatly typewritten, with double spacing and wide margins. The manuscript should be submitted electronically. Authors are required to state that their material is original and not previously published or currently submitted elsewhere.

All abbreviations should be spelt out when first used in the text and thereafter used consistently.

Scientific measurements should be expressed in SI units throughout, with two exceptions: blood pressure should be given in mmHg and haemoglobin values in g/dl.

Author's full name & surname, affiliation & correspondence address (including email address) to be set out in full on title page of article.

All articles (review, original research etc) are to have an abstract, giving a brief succinct overview of the article. The abstract should reflect the essence of the paper and be 200 to 250 words. For Original Research articles, the abstract should be structured as follows:- Objective, Method, Results and Conclusion.

Authors must give a minimum of three key words, and should use the MeSH (Medical subject headings list of index medicus) catalogue.

A clear statement on ethical issues in clinical and animal research must be provided; conflict of interests and patient confidentiality issues must be indicated.

For multi authored papers, the International Committee of Medical Journal Editors (ICMJE) states that, there are three necessary conditions one must meet in order to claim (co) authorship:

Substantial contributions to conception and design, or acquisition of data, or analysis and interpretations of data.

Drafting the article or revising it critically for important intellectual content.

Final approval of the version to be published.

Those, and only those who meet all three of the above stipulations, can be named authors, while those who meet only some of the requirements or otherwise facilitate the research by contributing to funding, data collection, editorial work, etc. should be named in the 'Acknowledged' section.

Accordingly, multi-authored papers need a declaration of relative contribution.

Illustrations

Figures consist of all material which cannot be set in type, such as photographs and line drawings. Photographs should be forwarded electronically.

Tables and legends for illustrations should be typed on separate sheets and should be clearly identified. Tables should carry Roman numerals, thus I, II, III, etc, and illustrations Arabic numerals, thus: 1, 2, 3, etc.

Where identification of a patient is possible from a photograph the author must submit a consent to publication signed by the patient, or by the parent or guardian in the case of a minor.

If any tables or illustrations submitted have been published elsewhere, written consent to republication should be obtained by the author from the copyright holder and the author(s).

References

References should be inserted at the end of the sentence, outside the full stop, as superior numbers, and should be listed at the end of the article in numerical order. Do not list them alphabetically.

It is the author's responsibility to verify references from the original sources.

References should be set out in the Vancouver style, and only approved abbreviations of journal titles should be used; consult the List of Journals Indexed in Index Medicus for these details. Names and initials of all authors should be given unless there are more than six, in which case the six names should be given followed by "et al". First and last page numbers should be given.

Journal references should appear as follows:

Peter S. Acute hamstring injuries. *Am J Sports Med* 1994; 12(7):395-400.

Book references should be set out as follows:

Williams G. *Textbook of Sports Medicine*. 2nd Edition: Butterworth, 1989: 101-104.

Vandermere P, Russel P. Biomechanics of the hip joint. In: Nordien PE, Jeffcoat A, eds, *Clinical Biomechanics*. Philadelphia: WB Saunders, 1990:472-479.

4. "Unpublished observations" and "personal communications" may be cited in the text, but not in the reference list. Manuscripts accepted but not yet published can be included as references followed by "(in press)".

All manuscripts and correspondence should be emailed to:

**Professor CP Szabo,
email: christopher.szabo@wits.ac.za**

University of Cape Town