
**Review of the literature on pregnancy and psychosocially assisted
pharmacotherapy of opioid dependence
(including withdrawal management, agonist and antagonist maintenance
therapy and adjuvant pharmacotherapy)**

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Summary

Evidence-based treatment options in the field of opioid dependence and pregnancy are limited since trials are difficult to conduct in this area. Many of these women are poly-drug users, and so standardisation and interpretation of the study results is complex. As long as women continue to abuse opioids and other drugs, we will be faced with challenges in the management of pregnant addicts. Getting these women into multidisciplinary treatment as early as possible, where they can be maintained on medication and monitored regularly, is beneficial to both mother and child, in both the short and long term, and should be standard practice. Abstinence during pregnancy is difficult to maintain, but it presents the ideal goal. Opioid maintenance therapy (methadone and buprenorphine) is the recommended treatment approach during pregnancy and there appear to be few developmental or other effects on these children in the long term. However, there are few data concerning the neurological effects of opioid exposure *in utero* and it is unknown whether prolonged exposure may have a deleterious effect on developing nerve cells. In addition to standardized approaches towards pregnancy, equivalent attention needs to be given to the treatment of the neonatal abstinence syndrome (NAS), which occurs frequently also after opioid medication. Further research in this area would be welcomed, although this obviously presents serious methodological problems.

CONTENTS

<i>Introduction</i>	4
<i>Substance use/dependence, medication use and pregnancy</i>	4
<i>Psychiatric comorbidity in pregnancy</i>	5
<i>Management of psychiatric comorbidity in pregnancy</i>	6
<i>Multiple substance abuse during pregnancy</i>	8
<i>Opioid dependence during pregnancy</i>	12
<i>Treatment of opioid dependence during pregnancy</i>	14
<i>Special topics</i>	18
<i>Neonatal abstinence syndrome (NAS)</i>	19
<i>Treatment of NAS</i>	21
<i>Recommendations</i>	23
<i>Literature</i>	27

Introduction

Medline research on ‘opioid dependence and pregnancy’ yielded 617 citations, and 129 publications were listed during the recent 7-year period (between the years 2000 and 2006). With the exception of older ‘key publications’, the decision was made to concentrate on recent literature. One hundred and twenty four publications were listed under *methadone and pregnancy*, 44 were listed under *buprenorphine and pregnancy*, 112 under *heroin and pregnancy*, 293 under *morphine and pregnancy*, 4 under *opiate/opioid-detoxification and pregnancy* and finally 259 under *psychosocial care and pregnancy*.

Substance use/dependence, medication use and pregnancy

In the general population, 50% of all pregnancies are unplanned and a substantial number of women of childbearing age are on prescribed psychotropic drugs – many women are taking these medications at conception and continue to do so after this time (Taylor et al., 1999; Einarson et al., 2005). Refuerzo et al. found that more than 96% of all pregnant women report taking all kind of medications during pregnancy (Refuerzo et al., 2005). Fifty-six percent of pregnant women are on prescribed drugs and 4% are prescribed medications that have either positive evidence of human fetal risk or a risk of drug use outweighing a possible benefit (Riley et al., 2005). As pregnant women used rarely to be included in clinical trials, there is little information available regarding the use of the majority of medications during pregnancy. As a consequence, both patients and prescribing clinicians are challenged to find a balance regarding the risk/benefit ratio. If no information in regard to effects on the fetus is available, harm cannot be ruled out.

The problem of substance use/dependence during pregnancy is of focal interest for physicians, researchers and the public health sector, independent of the general consumption of legal (such as alcohol and nicotine) or illegal drugs (King, 1997). Both the extent of drug consumption during pregnancy and the effects of maternal drug consumption on the fetus and neonate are frequently underestimated (Feng et al., 1993; Fazey et al., 2002; Hasin et al., 2005; Rehm et al., 2005). Active substance-abusing pregnant women experience a number of somatic consequences: they are at a high risk of developing a state of malnutrition and often lack adequate obstetric care (Pregnancy and Drug Misuse, Council of Europe, 1997).

Substance abuse in pregnancy also leads to consequences for the pregnant women, the fetus and neonate in two additional ways: direct consequences due to substance use or abuse as well as indirect outcomes resulting from the influence of living environment. Substance dependence in women is often associated with difficult domestic circumstances such as violence, sexual abuse or substance abuse by a responsible family-member. Various reports are available on the impact of the experience of violence and abuse during childhood and a strong correlation has been found between childhood trauma and later drug dependence (Schnieders et al., 2006). Furthermore, based on the multifactorial cause of addiction, genetic loading becomes increasingly important (Lesso et al., 2004; Uhl, 2006). Therefore the need for a stabilizing environment for the developing child, including assistance through health authorities, becomes evident in order to prevent addiction in the second generation.

Poly-substance dependence and misuse of either licit or illicit substances lead to the manifestation of a neonatal abstinence syndrome (NAS) of varying intensity and characteristics in the neonate after delivery, requiring the initiation of standardized treatment. Standardized medical and psychosocial approaches from a multi- and inter-disciplinary team are therefore important in order to enable the stabilization of pregnant substance-dependent women.

Psychiatric comorbidity in pregnancy

In the majority of cases, we do not see the pregnant women presenting with only heroin dependence in the treatment facility. More often, we are confronted with patients with severe psychiatric and somatic illness and multiple substance dependence (Marsden et al., 2000; Willenbring, 2005; Galletly et al., 2006; Kurz, 2006; Winklbaaur et al., 2006; Whicker et al., 2006; Watkins et al., 2006; ICD-10; DSM-IV). Therefore, we would emphasize the importance of quality assured diagnosis (applying the ASI for diagnostic procedure) and the requirement for using a broad biopsychosocial approach to treatment that takes account of both psychiatric and somatic co-morbidities (Fischer et al., 1998; Kraigher et al., 2001).

Psychiatric disorders are common among women of childbearing age, and affected women are frequently prescribed psychotropic drugs. However, despite the fact that most recent studies have documented the relative safety of these medications during pregnancy (although almost all results are based on a retrospective evaluation), a high level of anxiety regarding their

safety persists among patients and healthcare providers alike (Einarson et al., 2005). Teratogenic effects, postnatal behavioural disorders and perinatal syndromes are of particular concern to psychiatrists.

Burke et al. explored the risk of the development of depression in women and found a lifetime risk of 10–30%. Women of childbearing age are at an increased risk with a heightened prevalence of depression (Burke et al., 1991). Given the high risk for depression in women of reproductive age, treatment providers more often have to cope with opioid-dependent women of reproductive age, who additionally receive pharmacotherapy such as antidepressants. While pregnancy seems to afford a protective phase regarding the **first** manifestation of a psychiatric disease (O'Hara et al., 1984), others (eg Evans et al., 2001) report a higher risk of depressive disorders associated with pregnancy. The occurrence of a self-limited neonatal behavioural syndrome observed after *in utero* exposure to serotonin reuptake inhibitors (Moses-Kolko et al., 2005) further complicates the considerations in the care of reproductively active opioid-dependent women presenting with comorbid depression.

Neuropsychiatric comorbidity is higher in opioid-dependent patients compared to general population. Swartz et al. report that 60% of persons with schizophrenia use substances and 37% have a substance use disorder (Swartz et al., 2006). Merikangas et al. found 35% with the lifetime criteria for a mood disorder, 45% with anxiety disorder and 50% for either conduct or antisocial personality disorder (Merikangas et al., 1998). In another study of methadone maintenance patients, Callaly et al. found a comorbid psychiatric illness in 71% of the sample (Callaly et al., 2001).

Management of psychiatric comorbidity in pregnancy

All psychiatric pharmaceuticals cross the placenta barrier. Selective Serotonin Reuptake Inhibitors (SSRIs) are used for the treatment of a wide range of disorders such as major depression, anxiety and chronic pain. SSRIs are frequently prescribed and administered by physicians in pregnancy and postpartum (Lattimore et al., 2005). Although some early investigations into the effects of the SSRIs in pregnancy were misleading, the effects of SSRIs on the neonate are now known to include serotonergic overstimulation and withdrawal syndromes, as well as long-term effects on neurobehaviour and performance.

Fluoxetine and its active metabolite norfluoxetine are among the common SSRIs and have been investigated more than sertraline, paroxetine and fluvoxamine. Although early results showed that, during the first trimester of pregnancy, SSRIs did not seem to increase the risk of neonatal malformations, contradictory data are published now for paroxetine (Kulin et al., 1998; Ericson et al., 1999). Furthermore, some research has failed to show a higher risk for spontaneous abortions with fluoxetine (Chambers et al., 1996), while a literature review has revealed a possible link between fluoxetine and miscarriage (Baum and Misri, 1996). Pastuszak et al. explored a controversial outcome around the same issue (Pastuszak et al., 1993). Neonates exposed to fluoxetine in the third trimester of pregnancy are at a higher risk for developing neonatal complications like hypoglycaemia, hypothermia, respiratory distress, increased bilirubin, decreased Apgar Scores and increased incidence of prematurity. The observed symptoms may be caused by either a toxic serotonergic effect, abrupt drug withdrawal or a combination of both (Nordeng et al., 2005).

Chambers et al. performed a trial to explore the possible association between SSRIs in the third trimester of pregnancy and persistent pulmonary hypertension (PPHN) of newborns, a disorder that is associated with infant mortality and morbidity. They conclude that SSRI-linked PPHN may result from the lung acting as a reservoir for antidepressant drugs leading to an accumulation of antidepressant in the lungs (Suhara et al., 1998 and Lemberger et al., 1985). Increased levels of serotonin in the lungs of the newborn may result in the proliferation of smooth muscle cells typical of PPHN (Chambers et al., 2006).

Neonates exposed to any kind of SSRIs have an increased risk of convulsions and NAS. A total of 93 neonates (64 with paroxetine, 14 with fluoxetine, 9 with sertraline and 7 with citalopram) were found with a neonatal withdrawal syndrome relating to maternal treatment with SSRIs (Sanz et al., 2005).

If a mild form of depression occurs during pregnancy a non-pharmaceutical treatment like psychotherapy should be the first line approach. If major depression is diagnosed and risk of suicide is found in addition to psychotic symptoms, treatment with psychotropic drugs and inpatient care are indicated (Knoflach-Reichert et al., 2003).

At this time, no study has explored neonatal outcomes and the possible long term complications among depressed women not using medication, depressed women using SSRI

medication and unexposed healthy women (Lattimore et al., 2005). Lattimore et al. suggest that women with depression should not be withheld adequate pharmacological treatment in late pregnancy but the neonate should be monitored for possible complications after birth. In the light of the dual diagnosis of affective disorders and opioid dependence in a pregnant patient, the diagnosis must be well evaluated and appropriate treatment of both disorders initiated as an opioid-maintained patient with untreated depression may relapse and may then be difficult to stabilize. However, such treatment requires an informed risk-benefit assessment.

In addition, healthcare providers need to be vigilant for drug-drug interactions. Enzyme induction may either reduce or increase the opioid plasma level (eg fluvoxamine increases plasma levels of methadone) and appropriate dose adjustments are required in order not to destabilize either the mother-to-be or her fetus (Bertschy et al., 1994; Alderman et al., 1999; De Maria et al., 1999).

Multiple substance abuse during pregnancy

All of the published literature on the topic of opioid dependence and pregnancy refer to the consequences of either heroin or methadone and more recently to buprenorphine. Other substances co-abused by the target population, tend to be neglected in the analyses. The use of such substances represent potentially confounding factors that may be responsible for a variety of clinical features. For completeness, we have included these below.

Nicotine

Worldwide figures show that 1.3 billion people smoke tobacco (Shafey et al., 2003). Despite warnings regarding the use of tobacco products during pregnancy, it is estimated that >20% of pregnant women in the general population smoke when pregnant (Narayanan et al., 2002). Twenty two percent of women in developing countries meet criteria of nicotine dependence (MacKay et al., 2003). Cornelius et al. report a wide range of between 28–62% of pregnant teenagers smoking tobacco (Cornelius et al., 1995). Estimates indicate that 90% of opioid-dependent women are heavy smokers (US Department of Health and Human Services, 1996; King, 1997). Smoking in pregnancy is particularly common among substance dependent pregnant women.

Tobacco smoke contains several compounds; nicotine and carbon monoxide are the most significant ones affecting health issues during pregnancy (Lambers et al., 1996). Nicotine reaches the fetus through the placenta and reaches fetal blood concentrations 15% higher than those of the mother. Nicotine is also transferred to the maternal milk, with the main metabolite's half-life persisting for 15–20 hours (Lambers et al., 1996).

Consequences of smoking in pregnancy include hypertrophic placenta, spontaneous abortion, deceleration of fetal growth, lower birth weight and premature rupture of the placenta. These complications correlate with elevated carbon monoxide levels, which can also lead to maternal and fetal hypoxia (Shah et al., 2000). Children of heavy smokers show signs of a neonatal withdrawal syndrome known as Fetal Tobacco Syndrome (FTS). Epidemiological studies have identified smoking in pregnancy as risk factor for Sudden Infant Death Syndrome (SIDS) (Mitchell, 1995; Kirchengast et al., 2003).

Symptoms such as low birth weight for gestational age have long been related to opioid use during pregnancy, however recent literature refers much more to the potential role of nicotine consumption (Choo et al., 2004).

Cannabis

The UNODC reports a prevalence of cannabis abuse between 0.8% and 11.3%, in a population aged 15–64 years in Europe, and shows figures for the US of 12.6%, Australia 13.3%, Asia between 0.004–6.4% and in Africa between 0.05–21.5% in the general population (World Drug Report, 2006). Marijuana misuse is very common in pregnant women (Hurd et al., 2005). However, the facts documenting the direct effects of prenatal cannabis exposure to fetal development are very limited. Hurd et al. report decreased mid-gestational fetal growth (Hurd et al., 2005). Ostrea et al. examined the incidence of SIDS associated with cannabis abuse in pregnancy and found no increased risk (Ostrea et al., 1997). The validity of these results is limited by the fact that only 11 cases of SIDS were investigated. Scragg et al. undertook a nation-wide case-controlled study in New Zealand with 393 cases and 1592 controls, which implicates cannabis exposure as a weak risk factor in SIDS (Scragg et al., 2001). Further research in this area is necessary, but in a real-world situation, solely cannabis-abusing pregnant women are difficult to recruit to prospective

studies. Meanwhile, the majority of opioid-dependent pregnant women are also using cannabis.

Alcohol

Alcohol has teratogenic potential that affects the development of the central nervous system of the fetus and newborn with potentially severe consequences. The rates of heavy drinking during pregnancy have remained relatively unchanged during last 3 decades. Early identification of fetal alcohol exposure and maternal abstinence can lead to improved infant outcomes (Handmaker et al., 2006). The consequence of alcohol dependency in pregnancy is a Fetal Alcohol Syndrome (FAS) and its prevention is counted as an important public health priority (Burd et al., 2006).

The World Health Organization (WHO) reports of 1 out of 5 male adolescents and 1 out of 12 female adolescents developing alcohol dependence (WHO, 1997). Regular consumption of alcohol was reported by 62.4% men older than 18 years and by 46% women older than 18 years of age in the United States of America (SAMHSA, 2005).

Cocaine

Following a major increase in cocaine use in the US over recent decades, the United Nations Office on Drugs and Crime (UNODC) has reported increasing figures for Europe, Asia and Australia – the prevalence ranges between 0.1% and 2.7% (World Drug Report, 2005).

Cocaine abuse represents an increasing and serious health problem, yet there is no proven medication for an effective pharmacological treatment. Cocaine abuse in pregnant women may lead to teratogenic effects in the fetus and may signify life-threatening complications like cardiac and cerebral ischemias, malignant hypertension, stroke and sudden death in the pregnant woman (Vascia et al., 2002; Brownlow et al., 2002; Egred et al., 2005).

Preclinical studies suggest that the reinforcing effect of cocaine that promotes its abuse is mediated by blockade of the presynaptic dopamine transporter (Carrera et al., 2004). At the moment support for cocaine-dependent women comprises education about the risks and the consequences of ongoing substance abuse for the mother and the fetus. Cognitive Behavioural Therapy and contingency management (CM) is the standard for the treatment of the cocaine-dependent pregnant woman, with the aim of cocaine abstinence (Breza et al., 2002).

Physiological changes in pregnancy have a direct effect on the metabolism of cocaine: cholinesterase slows cocaine's metabolism in the pregnant woman as well as in the fetus. Cocaine crosses the placenta rapidly by diffusion due to its lipophilic properties, which gives rise to increased plasma concentrations in the fetus (Farrar et al., 1989; Dempsey et al., 1998; Dempsey et al., 1999). Post-partum the neonate may develop an NAS. The symptoms of NAS resulting from prenatal cocaine abuse by the pregnant woman are: irritability, lethargy, increased appetite, yawning, sneezing, higher sleep requirement, foetal tachycardia and hypertension.

Amphetamines and Metamphetamines

Handmaker et al. report a larger cranial to body growth ratio in amphetamine-exposed neonates (Handmaker et al., 2006). In 2004, Chang et al. identified several possible consequences for neonates exposed to methamphetamine prenatally. Their results showed smaller subcortical volumes and associated neurocognitive deficiencies. These findings suggest a neurotoxic effect in the developing brain of the fetus related to metamphetamine abuse during pregnancy (Chang et al., 2004).

Benzodiazepines

Benzodiazepines are common drugs used for the treatment of anxiety, insomnia and epilepsy. Despite the fact that benzodiazepines have been on the market for more than 40 years, the safety of their use during pregnancy remains controversial because conflicting results regarding their teratogenicity have been reported (Dolovich et al., 1998; Eros et al., 2002). In addition to the postulated teratogenic component, benzodiazepines have postnatal consequences for the infant. In spite of the apparent equivalence in potentially harmful effects, benzodiazepines are still administered to avoid prescribed opioids during pregnancy and which have, in addition to the postulated teratogenic component, postnatal consequences for the infant (Kandall et al., 1977; Laegreid et al., 1990; Kohen, 2004; Einarson, 2005; Swortfiguer et al., 2005).

Dolovich et al. in a meta-analysis found studies that examined major malformations following benzodiazepine consumption in pregnancy: 11 of the studies reported oral cleft only and three cited other specific malformations (Dolovich et al., 1998). Although Dolovich et al's meta-analysis could not show a direct association between fetal exposure to benzodiazepines and

the risk of malformations or oral cleft alone in pooled data from cohort studies, the authors outline a significantly increased risk in data from case-control studies (Dolovich et al., 1998).

Eberhard-Gran et al. reported that benzodiazepines may cause adaptation problems in the newborn, concluding that the possible adverse effects of fetal exposure must be balanced against the adverse effects of an untreated maternal mood disorder (Eberhard-Gran et al., 2005).

Furthermore, in neonates of mothers with benzodiazepine use during pregnancy, NAS will occur with a prolonged course similar to that of benzodiazepine withdrawal in adults (Lag Reid et al., 1992; Coghlan et al., 1999). In addition to overly liberal prescription of benzodiazepines, including prescription to patients undergoing opioid maintenance therapy, there is a tendency within the substance-dependent group itself to gather this medication on the 'black market'. These patients often present on very high doses of benzodiazepines where, especially during pregnancy, a slow detoxification is required in order to avoid preterm labour or exacerbation of psychiatric symptoms (Swortfiguer et al., 2005; Eberhard-Gran et al., 2005).

Opioid dependence during pregnancy

The use of opioids continues to increase and it is estimated that a total of 8 million people worldwide are abusing them (van den Brink et al., 2003). In Europe, the prevalence of problematic illicit drug use, mainly opioid dependence, ranges from 0.3% in the Netherlands to 0.9% in Luxembourg and Portugal. The UNODC report an annual prevalence of opiate use of between 0.1% (Finland) and 2% (Russian Federation) in Europe. In Australia, a prevalence of 0.5% is reported. The United States of America show a prevalence of 0.6%. In Africa the prevalence ranges between 0.01–2.0%, and in Asia between 0.004–2.8% (World Drug Report, 2006). Among persons treated for drug problems in European countries, opioid dependence shows a high prevalence at 64.3% (World Drug Report, 2005).

Participation in opioid agonist treatment ranges from 22% (United Kingdom) to 86% (Spain). Fiellin et al. report 810,000 opioid-dependent individuals in the United States of America, but only 170,000 of those are in Methadone Maintenance Therapy (MMT) (Fiellin et al., 2001).

The European Monitoring Centre for Drugs and Drug Addiction reports a total of 422,655 in opiate agonist treatment and 36,807 in treatment with buprenorphine (EMCCDA, 2003).

Women of reproductive age represent approximately one third of patients in treatment facilities. Opioid dependence during pregnancy remains a significant public health problem. Data from the US National Survey on Drug Use and Health indicate that 27% of pregnant women reporting illicit drug use in the past 30 days reported use of heroin or the non-medical use of pain relievers (Substance Abuse and Mental Health Services Administration, 2005). This translates into more than 57,000 heroin- or pain reliever-exposed pregnancies each year. This prevalence rate is second only to marijuana and is nearly four times greater than cocaine, the third most prevalent substance reported.

Illicit opioid abusing women may often experience secondary amenorrhea, with an increased risk for unplanned pregnancies during the first ovulation (often occurring after opioid agonist treatment initiation). Such women also may not show structured family planning and very often present late because of their chaotic lifestyle (Finkelstein et al., 1997).

The continued abuse of illicit opioids during pregnancy leads to adverse consequences in the mother-to-be, fetus and neonate. However, in comparison to alcohol, cocaine or benzodiazepine abuse during pregnancy, opioids do not have teratogenic or cytotoxic effects (Chasnoff et al., 1984). The main risk factor is caused by the fluctuation of opioid concentration in the maternal blood, which may lead to withdrawal symptoms in the neonate as well as symptoms of overdose, in addition to difficult psychosocial environmental situations (Finnegan et al., 1992). Heroin use in pregnancy is also often associated with malnutrition in pregnant women and a poor outcome in neonates (Finnegan et al., 1992). Johnson et al. indicate the inadequacy of antenatal care programmes for women misusing illicit drugs, as they often remain in a violent environmental situation and receive poor medical and social care (Johnson et al., 2003). If pregnant women continue the illicit intravenous consumption of heroin, the risk of medical complications like infectious diseases, endocarditis, abscesses and sexually transmitted diseases (as a consequence of prostitution) is increased.

In addition, a high rate of assorted mating occurs. More than 50% have a co-addicted partner, and successful treatment is only possible if the partners are enrolled in adequate psychosocial and medical care as well (Fischer et al., 2000).

Despite major methodological flaws in published reports about the effects of heroin use during pregnancy (eg no control for nicotine dependence), a significant reduction in birth weight has been reported when compared to neonates of pure methadone-maintained mothers (Hulse et al., 1997).

Treatment of opioid dependence during pregnancy

Pharmacological treatment

Maintenance therapy

Opioids interact on three different receptors located in the central-nervous system as well as in peripheral organs: the mu (μ), kappa (κ) and delta (δ) opioid receptors. Morphine, diacetylmorphine (heroin), methadone and LAAM act as a full agonist on the μ -receptor, whereas buprenorphine acts as a partial mu-receptor agonist and a kappa-receptor antagonist. Naloxone and naltrexone act as a full antagonist to all of the three types of receptors and there is no indication for their use during pregnancy, based on animal data that refer to growth problems as well as to possible teratogenic effects (Christian, 1984).

The recommended treatment for opioid-dependent and so-called gold standard for pregnant women is methadone (SAMSHA, 1995, <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat5.section.22556>), although it has never been approved for use during pregnancy. Methadone in the context of comprehensive care is associated with more prenatal care, increased fetal growth and less neonatal morbidity and mortality than continued opioid abuse (Finnegan and Kaltenbach, 1992; Council of Europe, 2000; Johnson et al., 2003; Jones et al., 2005; Fischer et al., 2006). Investigations of oral methadone therapy as part of a multi-professional care system during pregnancy have highlighted many benefits over recent decades and the results are well documented: improvement of the medical condition in the pregnant woman, standardized pre-delivery care, prevention of premature birth and prevention of underweight babies (Fischer et al., 1998;

Fischer et al., 2000; Daley et al., 2001; Ashley et al., 2003; Jones et al., 2005). These studies also show that higher dosing yields to better results (Kaltenbach et al., 1998). Very often the once daily dose of methadone needs to be split into twice daily, taking into account the physiological changes in pregnancy relating to enzyme-induction during the last trimester (Pond et al., 1985; Drozdick et al., 2002).

Though clearly beneficial, the use of methadone remains imperfect. Infants born to mothers maintained on methadone may exhibit often some degree of NAS, a generalized disorder that includes dysfunction of the autonomic nervous system, gastrointestinal tract and respiratory system (Finnegan and Kaltenbach, 1992). It has been estimated that 60–87% of the neonates born to methadone-maintained mothers require treatment for NAS (Finnegan and Ehrlich, 1990; Lacroix et al., 2004; Jones et al., 2005; Lejeune et al., 2006; Fischer et al., 2006; Sarkar et al., 2006).

Buprenorphine, approved in many continents (1999 Europe, 2001 in Australia, 2002 in the United States of America) for the treatment of non-pregnant opioid-dependent adults, may reduce the incidence and/or severity of NAS. Buprenorphine demonstrates safety for mother and child, and shows effectiveness in the treatment of opioid-dependence during pregnancy, although limited controlled data are published so far (Kayemba-Kay's et al., 2003). To date, the scientific literature includes data on more than 450 babies prenatally exposed to buprenorphine. Results generally suggest that treatment with buprenorphine provides the same benefits to the mother as methadone but, more importantly, may attenuate NAS (Johnson et al., 2003; Kayemba-Kay's et al., 2003; Jones et al., 2005; Lejeune et al., 2006). The majority of information has been gained through French publications, where buprenorphine has been available for more than 10 years; as a result of the office-based prescription policy typical in France, many patients, including pregnant women, have been treated with buprenorphine. These naturalistic data indicate the safe use of buprenorphine in pregnancy and data are even available regarding buprenorphine use during conception (Jernite et al., 1999; Lejeune et al., 2001; Kayemba-Kay's et al., 2003; Lacroix et al., 2004; Lejeune et al., 2006). Limited data from prospective open-label controlled studies of neonates born to buprenorphine-treated mothers are available. Nevertheless, such data support the use of buprenorphine in pregnancy; their results suggest no NAS or a mild NAS, with only 17% of neonates requiring treatment (Fischer et al., 2000; Johnson, Jones, & Fischer, 2003; Johnson et al., 2001). A prospective report regarding buprenorphine use at the time of conception is

available: new-borns show low NAS scores and are in good health (Schindler et al., 2003). Buprenorphine is a possible alternative to methadone in maintenance therapy and is described as a safe drug for maintenance therapy of opioid-dependent women (Kayemba-Kay's et al., 2003).

Two randomized double-blind double-dummy controlled trials using similar methodology (ie Jones et al., protocol shared with Fischer et al.) were designed to obtain safety and efficacy data comparing methadone and buprenorphine in pregnant women (Jones et al., 2005; Fischer et al., 2006). Both of them indicate the safety of both substances for the mothers-to-be and the comparability in efficacy for retaining patients in treatment and in regard to concomitant consumption of illicit drugs, with some individual variability. A major influencing factor on outcomes appears to be the incidence of concomitant consumption, which can be reduced through contingency management approaches (Schottenfeld et al., 2005; Carroll et al., 2005; Kirby et al., 2006). Monetary vouchers were given to patients for opioid- and cocaine-negative urine tests in a study exploring the effectiveness of contingency management in patients with co-occurring cocaine and opioid-dependence by Schottenfeld et al. There may be an improvement in treatment outcome in combining buprenorphine or methadone with contingency management (Schottenfeld et al., 2005).

An ongoing multicenter NIDA-supported study, called MOTHER, is a double-blind, double-dummy, randomized, stratified, parallel group study comparing the efficacy of methadone vs buprenorphine. It should be noted that the protocols are dynamic and may be modified based on the collective experiences of the sites. Modifications made in the protocols are done to enhance comfort and retention.

Interpretation of data on both medications during pregnancy has often been complicated by a number of issues. The lack of blinded designs and random assignment has left results of many studies subject to potential bias. Concomitant drug use has been prevalent in many study samples, confounding results. Small sample sizes have limited the statistical power of such studies, making it difficult to draw clear conclusions. Attempts to combine results across studies have been difficult due to substantial differences in methodology. A minority of studies included the issue of nicotine dependence, which might be very influential on outcome parameters.

Another candidate treatment approach is slow-release morphine, although data on this treatment option is derived from small-scale studies and the medication is registered for treatment in only a few countries (Geistlich et al., 1998; Fischer et al., 1999; Eder et al., 2005; Kraigher et al., 2005).

The treatment of opioid-dependence with levo-alpha-acetylmethadol (LAAM) was explored by Marsch et al., who compared LAAM, buprenorphine and methadone and found no difference in outcome (Marsch et al., 2005; Valdivia et al., 2000). In comparison with low-dose methadone, the administration of LAAM resulted in a longer duration of continuous abstinence (Johnson et al., 2000). In an experimental study, Nanovskaya et al. explored the effects of LAAM and its pharmacologically active metabolite, norLAAM, on placental tissue. The aim of the study was to assess the safety of LAAM as a possible alternative in maintenance therapy for pregnant opioid-dependent women. NorLAAM was detected in higher concentrations than LAAM, potentially leading to adverse effects on the placenta (Nanovskaya et al., 2003).

In some European countries (Switzerland, UK, Germany, Spain) injectable heroin (diamorphine) is available as additional treatment option for patients who fail in conventional treatment programmes or do not sufficiently benefit from methadone maintenance (Perneger et al., 1998; van den Brink et al., 2003). The importance of the context of providing injectable drugs in assessing clinical treatment outcomes has to be taken into consideration (Lingford-Hughes et al., 2004).

Opioid detoxification/abstinence

Abstinence throughout the course of pregnancy is the ideal clinical outcome. However, this is often unachievable and overemphasis on achieving abstinence can be unhelpful. The quest for abstinence may place the mother under a great deal of stress and studies have shown that most opioid-dependent women cannot remain drug free for the duration of the pregnancy (Dashe et al., 1998; Luty et al., 2003; Fischer et al., 2006). This means that many women relapse to opioid use and the resulting continued cycle of intoxication and withdrawal. This causes wide variations in blood opioid levels, which lead to fetal stress.

This is not to dismiss abstinence out of hand. In well-motivated individuals under close medical supervision and with appropriate treatment – ie slow reduction of a synthetic opioid,

not later than week 32 in pregnancy to avoid preterm delivery – abstinence can be achieved. However, the prospect of abstinence often discourages opioid-dependent mothers from seeking help and can lead to them not using treatment services. The course of action to be taken needs careful discussion between doctor and patient to confirm that the appropriate treatment is given on an individual basis.

Psychosocial intervention/counselling during prenatal care

Services should be provided in a supportive, culturally sensitive, and non-judgmental environment by all healthcare personnel, from the receptionist to the physician. Literacy- and reading-level information will affect patient education efforts and the ability to obtain informed consent so an assessment should be made of the woman's literacy and reading level. The woman may enter prenatal care in different stages of pregnancy and from a variety of settings, including hospital emergency rooms, community health centers, family planning clinics, abortion clinics or social service offices. It is essential to be able to offer assessment, triage, case coordination and referral services from any or all of these settings.

Case management services that coordinate the care of the pregnant, substance-using woman and her family are critical. Ideally, case conferences and referral to appropriate services should be managed by one healthcare professional who oversees the multidisciplinary team. An outreach worker who visits the woman in her home should be part of this team. The most difficult issue to resolve, given the financial and staffing constraints experienced by most healthcare and service providers, is the identification and designation of a case manager.

Counseling about and obtaining of written informed consent for medical procedures and treatment are important, as is the clear explanation of confidentiality, privacy and other patient rights. Equally important seems the involvement of the partner. The earlier in pregnancy that opioid-dependent pregnant women have access to psychosocial support, the higher the likelihood of establishing an appropriate living environment for the new family and of settling juridical and financial problems (Kaltenbach et al., 1998; Finnegan, 1991; Grella et al., 2006).

Special topics

Labour and delivery

During prenatal care, the delivery method must be agreed. The majority of published

information refers to vaginal delivery with epidural anesthesia (Silver et al., 1987; Cassidy et al., 2004). Pain management has to be provided as appropriate and so obstetricians/gynaecologists need to be informed that the opioid the patient is maintained on is not providing analgesia. Notification of social services might be appropriate if not involved so far. Fetal monitoring can be undertaken if indicated, however, the neonates appear comparable to non-opioid-treated mothers (with the exception that they are usually small for their gestational age) with comparable APGAR-scores. NAS tends to develop hours to days later (Jones et al., 2005; Fischer et al., 2006). Mothers should be encouraged to stay in hospital with their neonates for a minimum of 5–8 days in order not to miss the onset of NAS as well as offering the woman more confidence in handling her newborn.

Breastfeeding

A number of opioid-maintained women express a desire to breastfeed their infants. Breastfeeding is not contraindicated in a methadone/buprenorphine-maintained patient if she is known to be free of other drug use and is known to be HIV-seronegative (McCarthy et al., 2000; Philipp et al., 2003; Jansson et al., 2004). If an opioid-maintained mother wants to breastfeed her child, this should be encouraged: it can be helpful for mother-child bonding, and it might decrease NAS symptoms (Abdel-Latif et al., 2006). If the mother is abusing multiple drugs that would expose the infant to diverse agents in varying levels, then breastfeeding may still be contraindicated. Breastfeeding is not recommended if the mother is HIV-infected. Nursing and weaning under opioid maintenance therapy needs to be under special assistance of physicians, as rapid weaning would cause withdrawal in the neonate.

Neonatal abstinence syndrome (NAS)

A Medline search on 'pregnancy and NAS' was undertaken and yielded 84 citations and 44 publications between 1998 and 2006.

An important aim and challenge in the treatment of pregnant opioid-dependent women is avoiding the development of NAS or minimising its severity and duration. The incidence of NAS in neonates of opioid-dependent women is between 70% and 95%. NAS is characterized by a variety of symptoms of variable intensity: sneezing, yawning, hyperactive Moro reflex, sleeping after feeding, tremor, increased muscle tone, myoclonic jerks, high pitched crying, excoriation, mottling, generalized seizure, convulsions, fever, sweating, nasal stuffiness,

tachypnea, retractions, nasal flaring, poor feeding, excessive sucking, vomiting, diarrhoea, failure to thrive, excessive irritability and, in very rare cases, convulsions (Finnegan and Kaltenbach, 1992).

NAS can onset from any time during the first 24 hours up to 10 days postnatally, dependent on the medication applied during pregnancy or substance abused. With heroin, the withdrawal syndrome in the neonate sets in during the first 24 hours. With methadone it does not develop until after 48 hours (Fischer et al., 2006). An even later onset of withdrawal symptoms can be observed if the neonate was exposed to buprenorphine, benzodiazepines or barbiturates *in utero*.

The dosage of opioid-medication (methadone, buprenorphine, slow-release morphine) does not generally appear to correlate with withdrawal or NAS in neonates (Kaltenbach and Finnegan, 1986; Brown et al., 1998; Berghella et al., 2003; Jones et al., 2005; Fischer et al., 2006; Lejeune et al., 2006). A limited number of recent scientific reports do refer to a positive correlation of maternal dose and severity of NAS, however, some of these are confounded by additional consumption (Doberczak et al., 1993; Malpas et al., 1995; Marquet et al., 2002; Dashe et al., 2002). Importantly, higher dosing seems to gain better results for the mother during the course of treatment (Kaltenbach et al., 1998).

Different standardized and validated scoring systems are available to assess the severity of NAS. The majority of publications refer to the Finnegan Score (Finnegan, 1979; Finnegan, 1985): this Score comprises 21 items and a maximum of 45 points. Treatment is initiated at a Finnegan Score greater than 10 points while a reduction in medication starts at a rating of 10 and less. The Finnegan Score should be assessed six times a day. However many scientists and physicians working with NAS and related scorings use an adaptation of the Finnegan score (different items, different scorings, different threshold for treatment initiation) (Sarkar et al., 2006). This fact complicates the comparability in scoring of NAS in different medical centers in relation to duration and intensity. This also limits the comparability of publications. Another scoring system, which has been used more widely for NAS is the Lipsitz score (Lipsitz, 1975). The heterogeneity of rating and treatment approaches is also confirmed by Sarkar et al (Sarkar et al., 2006).

Treatment of NAS

It is not easy to determine which substances are the most beneficial in the treatment of NAS, as there are currently no double-blind controlled studies available. Until 1998, the drug of choice was paregoric in the USA, a substance consisting of 44–46% alcohol with opium, benzoic acid, camphor and glycerin. Now, however, some clinicians prefer using phenobarbital, benzodiazepines or morphine (Kaltenbach and Finnegan, 1986; Chiang and Finnegan, 1995; Kandall, 1995; Rohrmeister et al., 2001; Lejeune et al., 2006). Phenobarbital and paregoric appear to be equally effective, but studies tend to favor paregoric because of the better sucking behavior during this therapy (Kron et al., 1976). The American Academy of Pediatrics recommends that, when choosing a pharmacological treatment, tincture of opium should be used for opiate withdrawal, and phenobarbital should be the drug of choice for sedative-hypnotic withdrawal (AAP Committee on Drugs, 1998). A combined use of phenobarbital and diluted tincture of opium (DTO) has been favored because of shorter duration of hospitalization and less severe withdrawal, but it should be mentioned that in this study neonates were tapered from phenobarbital on an outpatient basis for an average duration of 3.5 months, which may have been a confounding factor (Coyle et al., 2002).

The effectiveness and safety of opiate treatment in newborn infants has been explored recently in the Cochrane Reviews and opiates are concluded to be the preferred initial therapy for NAS, especially for infants of mothers using opioids during pregnancy (Osborn et al., 2005). A number of reports highlight the utility of morphine in this respect. Jackson et al. also show the superiority of morphine sulphate in the treatment of NAS, although 83% of mothers gave a positive urinalysis for concomitant drug consumption at the time of delivery (Jackson et al., 2004). Theis et al. show that diazepam is clearly inferior in the treatment of neonatal withdrawal syndrome (Theis et al., 1997). In a comparison study, Langenfeld et al. suggest morphine drops as an alternative for the treatment of NAS, compared to tincture of opium (Langenfeld et al., 2005). It should be emphasized, however, that in all these reports, no standardized information about urine toxicology during pregnancy in regard to concomitant consumption has been available. According to a short report by Pacifico et al., morphine hydrochloride is recommended as the best therapy in the treatment of NAS, but the study does not provide any details (Pacifico et al., 1989). Shaw and McIvor refer in their study to a successful treatment with oral morphine in neonates born to methadone-maintained mothers, where 37% received that medication for withdrawal with a median length of treatment of six days (Shaw and McIvor, 1994). Morphine hydrochloride is dosed at 0.05–0.1 mg/kg per dose

p.o. (Rohrmeister et al., 2001) (morphine syrup 0.05%; 1 ml = 0.5 mg; preparation: 1 ml oral solution (5 mg/ml) and syrup simplex 10 % ad 10 ml).

The fetus of a substance-abusing pregnant woman is often exposed to multiple drugs. In the treatment of neonates exposed to multiple drugs, phenobarbital seems to be the most effective treatment (Finnegan et al., 1984; Finnegan et al., 1990). Phenobarbital is dosed by bodyweight at 5–10 mg/kg/day. In case of uncertainty, plasma levels are analyzed with normal ranges from 50–170 µmol/l. Maintenance therapy at this level should continue as long as NAS symptoms (score > 10) persist. After a score of < 10 is reported for a period of 24 hours, phenobarbital treatment is immediately stopped. Due to its long half-life, slow reduction of the treatment is not required. Phenobarbital is prepared as a solution (0.1 ml = 1 mg; preparation: natrium phenylethylbarbituricum 0.22 g, preservatives 0.3 ml and aqua purificata ad 20 ml).

The application rate of Tinctura opii is 0.3–0.8 mg per kilogram per day p.o. The dosage is divided into 4–6 daily doses. Administration should be tapered by approximately 10% a day. (0.4mg morphine/1 ml oral solution; preparation: 1 ml Tinctura opii + 24 ml water = 25 ml 0.04% morphine oral solution) (Roos et al., 2000).

Recommendations

1. FIRST VISIT OF PREGNANT OPIOID-DEPENDENT PATIENT TO THE TREATMENT CENTER :

A standardized evaluation with the Addiction Severity Index (ASI) would guarantee reliable and standardized gained information (Gsellhofer et al., 1999).

1. Detailed health history, including alcohol and other drug use and psychosocial assessments
2. Comprehensive examination, focusing on the multiple problems of this population
3. Family psychosocial, medical, and alcohol and other drug use history
4. Health, psychosocial, and alcohol and other drug use history of the baby's father
5. Routine prenatal panel, *plus* other laboratory tests, including urine and/or blood toxicology screening, tuberculin test with an antigen panel, and baseline sonogram
6. Optional tests as needed, including screening for HIV and hepatitis
7. Attention to areas of special concern in substance-using women: eg violence, financial situation, housing
8. Attention to medical complications encountered in pregnancy
9. Referrals to gynaecology: an optimal approach would be to have an established multiprofessional programme with psychiatrists, OBGYN, neonatologists, infectiologists: Don't send the patient around but provide a model where the individual physicians are integrated.
10. Initiate opioid maintenance
11. Additional referrals as needed

Opioid substitution therapy. (1998). In: Pregnancy and drug misuse. Recommendations. Council of Europe Publishing, pp. 154–155, ISBN 92-871-3784-6.

Opioid substitution therapy.

Recommendations:

Substitution treatment, wherever available for opiate-dependent persons, should consider and respect the following rules in case of pregnancy:

1. Assessment

- 1.1. Standard diagnostic and assessment procedures provided generally in obstetrics should apply as well for substance-dependent pregnant women (including referral to specialists, testing for STDs, sonogram, etc).

- 1.2. Appropriate diagnostic and assessment procedures provided generally in the treatment of substance dependence should also apply in cases of pregnancy (including standardised assessment of substance use and its sequelae, present conditions and treatment history).

- 1.3. Special attention to the following should be considered:
 - Urine tests for substances abused.
 - Tests for HIV, hepatitis, tuberculosis.
 - Psychiatric comorbidity.
 - Psychosocial background.
 - Perspectives for the future.
 - Perspectives for rearing the child.

2. Indication

- 2.1. The use of substitute opioid medication for detoxification or maintenance purposes should follow established rules for its general applicability.

- 2.2. In cases of pregnancy, the advantages and possible disadvantages of substitution therapy should be considered carefully; as a rule, well-controlled substitute medication should be preferred over the continued use of street drugs. This also makes controlled monitoring of pregnancies feasible in cases which that are otherwise difficult to reach.

- 2.3. There is evidence that substitution treatment can be in the best interest of mother and child and wherever there is provision for substitution, pregnant drug users should not be excluded from it.

3. Treatment

- 3.1. Substitution therapy should be carried out according to established rules of good practice and specific national guidelines.

- 3.2. Drug dosage should be individually determined and not minimised in order to avoid additional use of non-prescribed drugs..
- 3.3. The choice of substance used in substitution therapy should consider the scientific evidence available (oral methadone being by far the best researched and documented modality) and the specific effects on the unborn child.
- 3.4. Close monitoring including urine screening for non-prescribed drugs, nutritional supplements, re-testing for hepatitis and HIV (in cases of initial seronegativity) is indispensable.
- 3.5. A continuation of substitution therapy after delivery is recommended in all cases where relapse is expected.
- 3.6. Treatment planning and management should include the participation of the partner of the pregnant woman; if the partner is opiate dependent as well, provision of substitution therapy should be considered (if possible the same type of substitution for both partners).
- 3.7. Standardised documentation and evaluation of all substitution therapies in cases of pregnancy are highly recommended.

Working with pregnant drug misusers/projects. (1998). In: Pregnancy and drug misuse. Recommendations. Council of Europe Publishing, pp. 157, ISBN 92-871-3784-6.

Working with pregnant drug misusers/projects. Recommendations:

We consider a drug free state as the ideal for individuals who are pregnant. Pregnant drug misusers need medical care and comprehensive support, as do the children born to such individuals.

There is a need for a basic level of care both pre- and postnatally. While recognising that different countries will deliver this care and support in different ways, parents should be given every assistance to provide such care to themselves and their children.

1. In order to ensure best care for pregnant drug users and their children, there is a need for a multidisciplinary approach, specifically including psychiatric care wherever there is an indication for comorbidity.
 1. medical care (general health care)
 2. The pregnancies of drug misusers are of high risk, therefore there is a need for close co-ordination of medical treatment (multi-professional).
 3. social care
 4. housing and financial support
 5. co-ordination of outreach activities
 6. health insurance
 7. psychological care: single, and group therapies
 8. welfare system
 9. educational care: parenting and basic child education
 10. nutritional care
2. Ideally a comprehensive range of treatment options for the pregnant drug users and their children should be available. While the ideal is a drug free state, where drug misuse continues harm reduction approaches should be accessible for pregnant women. This could include the following adequate prenatal care and postnatal care: outreach services, detoxification, therapeutic communities and substitution.
3. Basic care for the child should be prepared. This basic care would, for example, include the following list:
 1. The presence of normal provisions such as housing
 2. Sufficient daily care for child
 3. Medical care
 4. Emotional care
 5. Schooling
4. Partners of pregnant drug-dependent subjects should be included in the programme.
5. If the pregnant mother already has children, they should be included in the comprehensive care as well.

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