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# Substance misuse problems during pregnancy with special emphasis on buprenorphine

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Academic Dissertation

To be presented by permission of the Medical Faculty of the University of Helsinki for public discussion in the Seth Wichmann Auditorium of the Department of Obstetrics and Gynecology; Helsinki University Hospital, Haartmaninkatu 2, Helsinki on 30th September, at noon.

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2

To my family

**CONTENTS**

## LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals.

I          Kahila H, Gissler M, Sarkola T, Autti-Rämö I, Halmesmäki E. Maternal welfare, morbidity and mortality 6–15 years after a pregnancy complicated by alcohol and substance abuse: A register-based case-control follow-up study of 524 women. Drug & Alcohol Dependence 2010; 111(3):215-21.

II         Sarkola T, Kahila H, Gissler M, Halmesmäki E. Risk factors for out-of-home custody child care among families with alcohol and substance abuse problems. Acta Paediatrica 2007; 96(11):1571-6.

III        Kahila H, Saisto T, Kivitie-Kallio S, Haukkamaa M, Halmesmäki E. A prospective study on buprenorphine use during pregnancy: effects on maternal and neonatal outcome. Acta Obstetricia et Gynecologica Scandinavica 2007; 86(2):185-90.

IV        Kahila H, Stefanovic V, Loukovaara M, Alfthan H, Hämäläinen E, Halmesmäki E. Prenatal buprenorphine exposure: Effects on biochemical markers of hypoxia and early neonatal outcome. Acta Obstetricia et Gynecologica Scandinavica 2008; 87(11):1213-9.

V          Hytinantti T*, Kahila H*, Renlund M, Järvenpää AL, Halmesmäki E, Kivitie-Kallio S. Neonatal outcome of 58 infants exposed to maternal buprenorphine in utero. Acta Paediatrica 2008; 97(8):1040-4.
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# ABBREVIATIONS

| | |
|---|---|
| AOR | adjusted odds ratio |
| ATC | Anatomic Therapeutic Chemical |
| BMI | body mass index |
| BMT | buprenorphine maintenance treatment |
| BPR | buprenorphine |
| CI | confidence interval |
| CPS | child protection services |
| cTnT | cardiac troponin T |
| CV | coefficient of variation |
| Da | Dalton, atomic mass unit (1/12 of carbon isotope 12C atom mass) |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders, Fourth edition |
| EPO | erythropoietin |
| GABA | gamma-amino butyric acid |
| HBsAg | hepatitis B surface antigen |
| HCVAb | hepatitis C virus antibody |
| HCV RNA | hepatitis C virus ribonucleic acid |
| HIVAb | human immunodeficiency virus antibody |
| ICD-9 | International Statistical Classification of Diseases and Related Health Problems, 9th Revision |
| ICD-10 | International Statistical Classification of Diseases and Related Health Problems, 10th Revision |
| MMT | methadone maintenance treatment |
| NAS | neonatal abstinence syndrome |
| NBUP | norbuprenorphine |
| NCU | neonatal care unit |
| NICU | neonatal intensive care unit |
| OGF | opioid growth factor |
| OMT | opioid maintenance treatment |
| OR | odds ratio |
| r | Pearson's or Spearman's correlation coefficient |
| SD | standard deviation |
| SGA | small for gestational age |
| SIDS | sudden infant death syndrome |
| SII | Social Insurance Institution of Finland (KELA) |
| STAKES | National research and development centre for welfare and health |
| S100 | S100 [beta] - protein |
| THL | National Institute for Health and Welfare |
| WHO | World Health Organization |

## ABSTRACT

Maternal substance misuse during pregnancy threatens the wellbeing of the next generation. Prenatal exposure to these substances has been associated with adverse events such as foetal and childhood growth impairment, foetal distress, neurobehavioural deficits, prematurity and child maltreatment.

In Finland, the number of problem users of amphetamines and opioids was estimated to be 14,500–19,100 in 2005, and of these, 3000–5000 (20–25%) were opioid users. 20–30% of problem users were women, mainly of child-bearing age. In Finland, buprenorphine – a widely used substitution medication in opioid maintenance treatment – has become the most misused opioid.

Although methadone maintenance treatment has been the "gold standard" of care in pregnant opioid-dependent women, both methadone and buprenorphine have been widely used in the treatment of opioid-dependent individuals. We wanted to study whether buprenorphine is a possible medication alternative for pregnant women as well. Also, the long-term effects of antenatal substance abuse on child and maternal welfare interested us.

Between 1992 and 2001, 524 women were followed up at special antenatal clinics set up for women with alcohol and/or substance misuse problems at Helsinki University Central Hospital, the Midwifery Hospital and Jorvi Hospital. To study long-term health and welfare after substance abuse problems identified during pregnancy we combined data on these women with data from several national registers such as the Cause-of-Death Register, the Hospital Discharge Register, the Drug Prescription Register and the SII registers, including information on rehabilitation periods, pensions and unemployment subsidies. The follow-up period was from the index pregnancy till the end of 2007 or death. For control purposes we had data on 1792 women obtained from the national Medical Birth Register.

Women with substance abuse problems had a significantly increased mortality rate (OR 38). The risk of death attributed to accidents and violence was especially high (OR 114). Their long-term morbidity was also significantly increased.

Recently, the need for out-of-home care as part of child protection services (CPS) has increased, mainly because of parental psychiatric and substance abuse problems. To study the need of out-of-home care in a high risk population whose maternal alcohol and/or substance misuse problem was identified during pregnancy, we combined antenatal data on 626 children born to the 524 women with substance abuse problems with data on the National Institute for

Health and Welfare (THL) Child Welfare Register concerning children and young persons placed outside the home as part of CPS. The follow-up period was from birth till end of 2003. During the study period, 50% (95% CI 46–54%) of the children were at some point and 38% (95% CI 34–42%) by the age of two years placed outside home by the CPS. During the whole follow-up period, 20% (95% CI 17–23%) of the children had been in custody for at least half of their lives.

We followed up 67 pregnancies among 66 buprenorphine-using women during 2002–2005 at Helsinki University Hospital. The outcome of these pregnancies was compared with data in the National Birth Statistics Year 2004 and within three subgroups: those who were able to quit buprenorphine use during pregnancy, those who continued supervised buprenorphine use and those who could not keep to the treatment.

The prematurity rate was no higher than in the national statistics, but the neonates were slightly lighter. Neonatal abstinence syndrome was diagnosed in 51 (76%) infants, and 38 (57%) needed morphine replacement therapy for it. Two (3%) sudden infant deaths (the national incidence being 0.019% in 2004) occurred.

We analyzed biochemical markers of hypoxia in cord serum samples after birth of 27 neonates born to buprenorphine-using women, 27 neonates exposed prenatally to maternal illicit drug abuse other than opioids, and 38 neonates born to healthy parturients. The biochemical markers analyzed were erythropoietin, cardiac troponin T and S100 in addition to standard clinical parameters (cord blood pH, Apgar scores, admission to a NICU). No significant differences were found between the three groups in cord serum levels of these biochemical markers.

We examined all 58 singleton infants who tested positive for buprenorphine at urinary drug screening after birth at Helsinki University Central Hospital between 2001 and 2005 for aspects of neonatal abstinence syndrome. Neonatal abstinence syndrome was diagnosed in 46 (79%) neonates. In total, 38 (66%) infants needed morphine medication for $20\pm10$ (SD) days (range 7–48 days). Morphine treatment was initiated at a mean age of $2.4\pm1.1$ days (1–6 days). Maternal smoking aggravated and use of benzodiazepines attenuated NAS. The maternal buprenorphine dose on the day of delivery correlated with the length of the infants' hospital stay (Spearman's correlation coefficient ($r$)=0.48, $p$=0.002) as well as with the morphine dose at the beginning of neonatal morphine treatment ($r$=0.49, $p$=0.049). The highest concentration of the infants' urinary norbuprenorphine in the first three days of life correlated significantly with the length of hospital stay ($r$=0.57, $p$<0.005) and duration of morphine treatment ($r$=0.46, $p$<0.008).

In conclusion, buprenorphine is an option for opioid maintenance treatment during pregnancy. A substance abuse problem revealed during pregnancy warrants a long-term comprehensive care for the mother-child dyad to cope with long-term welfare problems.

# INTRODUCTION

Substance misuse is hazardous during pregnancy and can have long-lasting effects on the next generation. It represents the most prevalent totally preventable cause of foetal, neonatal and childhood adverse outcomes in the developed world. The sequelae of intrauterine substance exposure include impaired foetal growth, foetal distress, stillbirth, premature rupture of membranes, birth defects and prematurity (*Sprauve et al. 1997*, *Jones 2011*, *Burns et al. 2006*, *Almario et al. 2009*, *Cleary et al. 2011*, *King-Hele et al. 2009*, *Pinto et al. 2010*, *Ney et al. 1990*, *Kennare et al. 2005*). Prenatally exposed children are also at increased risk of sudden infant death syndrome (SIDS), neurological deficits, behavioural changes, developmental delays, learning disabilities and child abuse (*MacMahon 1997*, *Hoyme et al. 2005*, *Burns et al. 2010*).

Women with substance misuse during pregnancy often remain unidentified by healthcare practitioners (*Chasnoff et al. 2001*, *Ostrea et al. 2001*, *Herzig et al. 2006*). They have a fear of being reported to the child welfare authorities and have negative attitudes as regards the efficacy of care, and as a result seek antenatal care late in pregnancy, if at all (*Datel 1990*, *Schempf et al. 2009*). In an American national cohort study 4.7% and 10% of pregnant women reported using an illicit drug or alcohol, respectively, within the previous 30 days in 2003–2004 (*Havens et al. 2009*), and recent pregnancy did not significantly decrease illicit drug use (*Vesga-Lopez et al. 2008*). In a Swedish study about 30% of women continued to consume alcohol in the same pattern during pregnancy as before pregnancy (*Göransson et al. 2003*). In Finland, it is estimated that 6% of children are born to mothers with alcohol and/or drug use disorder (*Pajulo et al. 2001*).

Alcohol and/or substance abuse during pregnancy is also an indicator of risky living environments and social habits (*Wright et al. 2007*). Previous studies on perinatal substance abuse intervention in obstetric clinics have shown it to reduce adverse neonatal outcomes (*El-Mohandes et al. 2003*, *Goler et al. 2008*, *Sweeney et al. 2000*), but the long-term outcomes of these women and their families remain unknown (*Keenan et al. 1993*, *Bauer et al. 2002*).

Opioid addicts are known to have unfavourable prognoses in terms of medical, legal and psychosocial outcomes. In a UK study by Nutt et al., comparing legal and illegal substances in respect to their harmfulness to the individual as well as to society, opiate misuse, namely heroin misuse, was the most harmful to an individual, and second harmful after alcohol misuse to others (*Nutt et al. 2010*).

As regards opioids there is specific opioid substitution treatment which has been shown to retain patients in treatment and suppress heroin use better than drug-free treatment modalities (*Fudala et al. 2003*, *Krook et al. 2002*, *Kakko et al. 2003*, *Mattick et al. 2003*). In the USA, there are long traditions of methadone maintenance treatment (*Dole et al. 1965*, *Ward et al. 1999*), including treatment of pregnant women (*Zuspan et al. 1975*). In France, buprenorphine maintenance treatment has been widely used since 1996 (*Auriacombe et al. 2004*), for pregnant women as well (*Gourarier et al. 2001*). The numbers of buprenorphine-treated pregnant patients are still small in the published literature (*Fischer et al. 2006*, *Johnson et al. 2001*, *Schindler et al. 2003*, *Simmat-Durand et al. 2009*, *Kakko et al. 2008*, *Jones et al. 2010*), and buprenorphine has not been officially accepted for treatment of pregnant women by the European Medicines Agency (*EMEA 2009*). The main problem with opioid substitution treatment during pregnancy is the frequent emergence of neonatal abstinence syndrome (NAS) (*Finnegan 1984*, *Seligman et al. 2010*, *Wouldes et al. 2010*, *Marquet et al. 1997*, *Kayemba-Kays et al. 2003*).

In Finland, buprenorphine maintenance treatment was first legalized in 1997 (*The Ministry of Social Affairs and Health 2008*). Demand for this kind of treatment has surpassed availability ever since, especially in the Greater Helsinki area (*Alho et al. 2007b*, *Alho et al. 2007a*). In order to enhance access to these programmes the Ministry of Social Affairs and Health gave special funding to healthcare providers in 2002–2003 to develop new services for individuals with opioid addiction. At Helsinki University Hospital the first child shown to have buprenorphine in his urine was born in 2001, which prompted the creation of a new service for pregnant women with opioid dependence in the Helsinki area.

As substance misuse during pregnancy seems to be a multifaceted problem, we wanted to study maternal long-term outcome and need of child protection services in our healthcare and social welfare systems. We also wanted to study prospectively the effects of buprenorphine use on pregnancy, on certain perinatal hypoxia markers and on neonates in real life situations to enhance the clinical care of this population.

**REVIEW OF THE LITERATURE**

*Epidemiology*

Prevalence of problem use of opiates in Finland

In Finland, the number of problem users of amphetamines and opioids was estimated to be 14,500–19,100 in 2005. Of these, 20–25% were opioid users, accounting for 0.13–0.18% of the total population. The proportion of female problem drug users was about 20–30% and most of them were of fertile age. These estimations are based on three different administrative statistics: amphetamine- or opioid-use-related diagnoses recorded in hospitals, penal information on drug offences involving the use or possession of these drugs or arrest for driving under the influence of them, and hepatitis C cases included in the infectious diseases register in connection with injecting drug abuse. The trends in use are shown in Table 1. Geographically, some 50–60% of all problem users were from Southern Finland and over half of them from the Greater Helsinki area (*Partanen et al. 2007*).

**Table 1.** Proportion (‰) of amphetamine and opioid problem users in Finland in 1998–2005.

|                   | 1998      | 1999      | 2001     | 2002      | 2005     |
|-------------------|-----------|-----------|----------|-----------|----------|
| **Overall estimate** | 4.0–5.5 | 4.0–5.0 | 5.0–6.0 | 5.5–7.5 | 5.2–6.9 |
| **Amphetamine users** | 2.6–4.5 | 2.9–4.3 | 3.5–5.4 | 3.8–6.5 | 4.3–7.4 |
| **Opioid users** | 0.6–0.9 | 0.9–1.1 | 1.4–1.7 | 1.5–2.1 | 1.3–1.8 |
|                   |           |           |          |           |          |
| **Men** | 5.4–7.0 | 5.4–6.6 | 5.8–7.1 | 7.7–10.3 | 7.4–9.8 |
| **Women** | 2.0–5.8 | 1.4–2.4 | 2.0–3.1 | 2.9–5.7 | 2.0–3.1 |
|                   |           |           |          |           |          |
| **15–25-year-olds** | 6.7–11.2 | 7.3–10.2 | 8.1–10.4 | 9.3–13.0 | 6.3–9.5 |
| **26–35-year-olds** | 5.1–7.1 | 4.6–5.9 | 6.4–8.2 | 7.4–11.3 | 6.8–9.4 |
| **36–55-year-olds** | 1.4–2.5 | 1.9–4.6 | 2.2–3.6 | 2.5–5.0 | 3.0–5.4 |

Source: (*Partanen et al. 2007*, *Partanen et al. 2004*)

According to the 2009 data of the drug treatment information system of THL, which is based on anonymous data collection through the voluntary participation of treatment units in 2009, opioids were the primary problem substances of clients entering drug treatment, representing

55% of all substances, followed by stimulants (16%), alcohol (12%), cannabis (10%) and pharmaceuticals (7%) (Table 2). The proportion of persons seeking substitution treatment for opioid abuse has increased steadily since 2000, from 29% up to 50% by 2009. Opiates were most commonly used intravenously (81%). Buprenorphine was the primary problem substance for 33% of the clientele. The central role of BPR in intravenous use is marked among Finnish problem users (*Alho et al. 2007a*, *Tacke 2002*). In addition, polydrug use of various drugs, alcohol and pharmaceuticals is common in Finland (*Ruuth et al. 2009*). In an anonymous voluntary questionnaire for injecting drug users collected in Helsinki in 2005, only 28% used buprenorphine alone while the rest were classified as polydrug users (*Alho et al. 2007a*).

**Table 2.** Secondary and tertiary drugs used in a non-pregnant population, with the primary drug, in 2009 (%).

| Primary drug | Use of a second and a third drug in addition to the primary drug, % | | | | | |
|---|---|---|---|---|---|---|
| | No of users (%) | Opioids | Stimulants | Cannabis | Pharmac. | Alcohol |
| Opioids | 1818 (55) | 11 | 34 | 35 | 51 | 14 |
| - buprenorphine | 1100 (33) | 12 | 37 | 35 | 56 | 17 |
| Stimulants | 515 (16) | 35 | 8 | 42 | 30 | 28 |
| Cannabis | 336 (10) | 17 | 38 | 0 | 8 | 49 |
| Pharmaceuticals | 223 (7) | 28 | 19 | 30 | 8 | 49 |
| Alcohol | 411 (2) | 21 | 39 | 59 | 36 | 0 |

Source: Drug treatment information system, THL (*Ruuth et al. 2009*)

In Finland, it is estimated that 6% of children are born to women who have problematic substance abuse. This estimate is based on a sample of 391 women initially screened for depression and factors associated with it in primary maternity care centres in South-Western Finland (*Pajulo et al. 2001*). This estimate accounts for 3300–3600 neonates yearly (*Nikander 2009*). The number of prenatally opioid-exposed infants is not known.

*Substance abuse-related problems and their long-term consequences*

*Long-term health effects of substance abuse*

Alcohol has been causally related to more than 60 different medical conditions (Table 3). Approximately 4% of the global burden of disease and mortality is attributable to alcohol (*Rehm et al. 2009*, *Rehm et al. 2006*, *Room et al. 2005*).

**Table 3.** Diseases and health problems related to alcohol use (codes of ICD-10) (*Rehm et al. 2009*)

| | |
|---|---|
| Disorders arising during the perinatal period | P04 |
| Mouth and oropharyngeal cancers | C00–C14 |
| Oesophageal cancer | C15 |
| Colon and rectal cancers | C18–C21 |
| Liver cancer | C22 |
| Breast cancer | C50 |
| Other neoplasms | D00-D48 |
| Diabetes mellitus | E10–E14 |
| Alcohol-use disorders | F10 |
| Unipolar depressive disorders | F32–F33 |
| Epilepsy | G40, G41 |
| Hypertensive heart disease | I10–I14 |
| Ischaemic heart disease | I20-I25 |
| Haemorrhagic stroke | I60–I62 |
| Ischaemic stroke | I63 |
| Cirrhosis of the liver | K74 |
| Low birth-weight | P05–P07 |
| Road traffic accidents | many V codes |
| Falls | W00–W19 |
| Drowning | W65–W74 |
| Poisoning | X40–X49 |
| Other unintentional injuries | rest of V codes + some W, X, Y codes |
| Self-inflicted injuries | X60–X84, Y87.0 |
| Violence | X85–Y09, Y87.1 |
| Other intentional injuries | Y35 |

Both average volume of alcohol consumption and patterns of drinking have been shown to influence the alcohol-related burden of disease. Substance use problems are also overrepresented in emergency room patients (*Cherpitel et al. 2008*), e.g. binge-drinking is strongly linked to injuries and accidents (*Rehm et al. 2003*, *Taylor et al. 2010*). In gender-specific studies women have been shown to be more vulnerable to alcohol-related medical problems at lower levels of consumption than men, probably in connection with women's lower total body water and gender differences in alcohol metabolism (*Bradley et al. 1998*, *Brienza et al. 2002*). These studies have also shown an increased mortality rate in women with moderate-to-heavy alcohol consumption, particularly from breast cancer (*Schutze et al. 2011*, *Suzuki et al. 2008*) and cirrhosis (*Fuchs et al. 1995*).

Studies on Finnish women have shown an association between binge drinking and diabetes mellitus type 2, depressive symptoms and stroke (*Carlsson et al. 2003*, *Paljärvi et al. 2009*, *Sundell et al. 2008*). In Finland, the commonest causes of death among working-age women were alcohol-related causes according to the Cause-of-Death Register kept by Statistics Finland. In a Finnish epidemiological study 6.5% of total mortality was related to alcohol. One-third of the alcohol-related mortality was due to accidental and violent deaths, one-fifth directly to alcohol-attributable diseases (including liver cirrhosis), and 11% to diseases of the circulatory system (including cardiovascular diseases). Alcohol-related mortality was higher in lower educated women, and the educational gap widened towards the end of study period (2003) (*Herttua et al. 2007*).

As regards illicit drugs, it is more difficult to evaluate the associations *per se* because of their illegal nature (*Rehm et al. 2006*). Drug abuse has been linked to mental health problems such as depression, anxiety and antisocial personality, injury, accidents, overdose and suicide, and drug abuse by injecting can cause transmission of blood-borne viral infections such as hepatitis B and C, and HIV (*Nutt et al. 2010*, *Rehm et al. 2006*, *Mertens et al. 2005*, *Popova et al. 2007*, *Adrian et al. 2007*, *Adrian et al. 2003*, *Nutt et al. 2007*).

Women who regularly misuse opioids have been shown to be more vulnerable to adverse consequences of use than men, e.g. there is faster progression of dependence and an increased frequency of medical problems (*Hernandez-Avila et al. 2004*).

Psychiatric co-morbidities, especially depression, have been shown to be more common in women with substance use disorders than in men, and also to precede them more often (*Brienza et al. 2002*, *Kessler et al. 1997*, *Swendsen et al. 2010*, *Horrigan et al. 2000*). The majority of pregnant women with opioid dependence have concurrent mental or medical illness (*Kissin et al. 2001*).

In addition to pregnancy-related problems, alcohol, cocaine, marijuana and opiate use have been implicated in amenorrhoea, anovulation and spontaneous abortion (*Lex 1991*), although the data is scanty and controversial (*Lacroix et al. 2004*, *Maconochie et al. 2007*, *Strandberg-Larsen et al. 2008*, *Ness et al. 1999*, *Harlap et al. 1980*).

The non-medical use and use disorders of prescribed medications such as tranquilizers and pain-killers are common among people with substance use disorders (*Blanco et al. 2007*, *Rigg et al. 2010*).


*Need of child protection services (CPS)*

All personnel working in the health-care system in Finland are obliged to report to the CPS when confronted with a child who is suspected of being in significant need of social support. Family-oriented and individual child welfare comprises support intervention in community care, taking into care, substitute care and after-care. Support intervention in community care comprises ensuring supported accommodation, livelihood, school attendance and hobby activities of the child and any other support needed. It also includes support for the family and rehabilitation. As a measure of support intervention in community care, it is also possible to provide foster care.

According to the Finnish Child Welfare Act, the Social Welfare Board is obliged to take into care – i.e. to take responsibility for the care and upbringing of the child – a child who meets each of the following three criteria:

1) the child's health or development is seriously endangered by lack of care or other conditions at home, or the child seriously endangers his/her health or development through the abuse of intoxicants, or the child commits an illegal act other than a minor offence, or there is any other comparable behaviour

2) forms of support intervention in community care are not appropriate or possible or have proved to be inadequate

3) substitute care is considered to be in the best interests of the child.

Children placed outside the home refers to children placed outside their own home after a decision of the Social Welfare Board. The criteria for these custody decisions are variable, but each decision should be based on clear evidence of significant child maltreatment provided by multiple sources. The decisions must be reviewed at least once a year (Kuoppala et al. 2011). In Finland in 2009, a total of 6.5% of children were subject to child welfare intervention in community care and 1.3% were placed outside the home by child protection services (CPS), 60% of these as a result of custody decisions (*Kuoppala et al. 2011*).

Criteria and management in CPS procedures vary considerably in different countries (*MacMahon 1997*, *Ondersma et al. 2001*).

Child maltreatment places a considerable burden on both health and social services (*Sidebotham et al. 2006*). Child maltreatment has earlier been found to be associated with the mental health of a parent, poor parental social networks, inadequate housing, a low level of maternal education, unemployment, high number of previous children, earlier involvement of the CPS among family members, unplanned pregnancy, marital status and young maternal age (*MacMahon 1997*, *Sidebotham et al. 2006*, *Sidebotham et al. 2001*, *Kotch et al. 1999*, *Leventhal et al. 1997*, *Neuspiel et al. 1993*, *Wu et al. 2004*, *Bifulco et al. 2002*, *Stier et al. 1993*). An association between low birth weight and/or prematurity *vs.* child maltreatment has been controversial in earlier reports (*Sidebotham et al. 2006, Takayama et al. 1998, Sidebotham et al. 2003*). There is also an elevated risk of maltreatment among children with disabilities (*American Academy of Pediatrics 2001*, *Hibbard et al. 2007*).

Earlier work has revealed an association between parental alcohol and/or drug abuse and child maltreatment (*Sidebotham et al. 2001*, *Kotch et al. 1999*, *Walsh et al. 2003*, *Hurme et al. 2008*, *Wilson et al. 1996*). Studies linking parental substance abuse and child maltreatment suggest that substance abuse is present in half of the families in need of CPS as a result of child abuse and neglect, and that parental alcohol and/or drug abuse is the main reason for the greatly increased need of foster care over the past few decades (*Dore et al. 1995*, *McGlade et al. 2009*). Only a few investigations have addressed parental antenatal alcohol and/or substance abuse as a risk factor of postpartum child abuse (*Wilson et al. 1996*). These studies have mainly been focused on cocaine (*MacMahon 1997*, *Leventhal et al. 1997*, *Neuspiel et al. 1993*), and a few on maternal antenatal smoking (*Wu et al. 2004*, *Kalland et al. 2006*). An Australian study demonstrated a significant relationship between past severe sexual abuse as a child and opioid dependence in women (*Conroy et al. 2009*). This could partly explain the intergenerational transmission of substance abuse problems.

In Finland, significant parental alcohol and/or drug abuse problems have been found in 43% of families whose children end up in custody in the capital area of Finland. In families with children less than 12 years old the percentage was even higher, 63–72% (*Myllärniemi 2006*, *Heino et al. 2006*).

*Opioid pharmacology*

Naturally occurring alkaloids in the juice of the opium poppy seed capsule, such as morphine or codeine, as well as synthetic morphine-like compounds are called opiates. The term opioid is used for all compounds that work at the opioid receptors, including endogenous opioids, so called endorphins (*Waldhoer et al. 2004*). The endogenous opioids are produced in response to noxious stimuli. Opiates as well as endogenous opioids function as neurotransmitters in the central nervous system. The presynaptic action of opioids is to inhibit neurotransmitter release. The postsynaptic actions of opioids are usually inhibitory (*Chahl 1996*) (Figure1).

Opioid effects are mediated through opioid receptors located on neuronal cell membranes (figure 1). The opioid receptors, like many other membrane receptors, are coupled to guanine nucleotide binding proteins known as G-proteins. G-proteins consist of 3 subunits (a, b and g). When the receptor is occupied, subunit a is uncoupled and forms a complex which interacts with cellular systems to produce an effect (*Chahl 1996*).

**Figure 1.** Opioid receptor locations (Chahl 1996).

Opioids have been proposed to inhibit neurotransmitter release by inhibiting calcium entry, by enhancing outward movement of potassium ions, or by inhibiting adenylate cyclase (AC), the enzyme which converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). These actions are mediated through G-proteins to which opioid receptors are coupled.



19
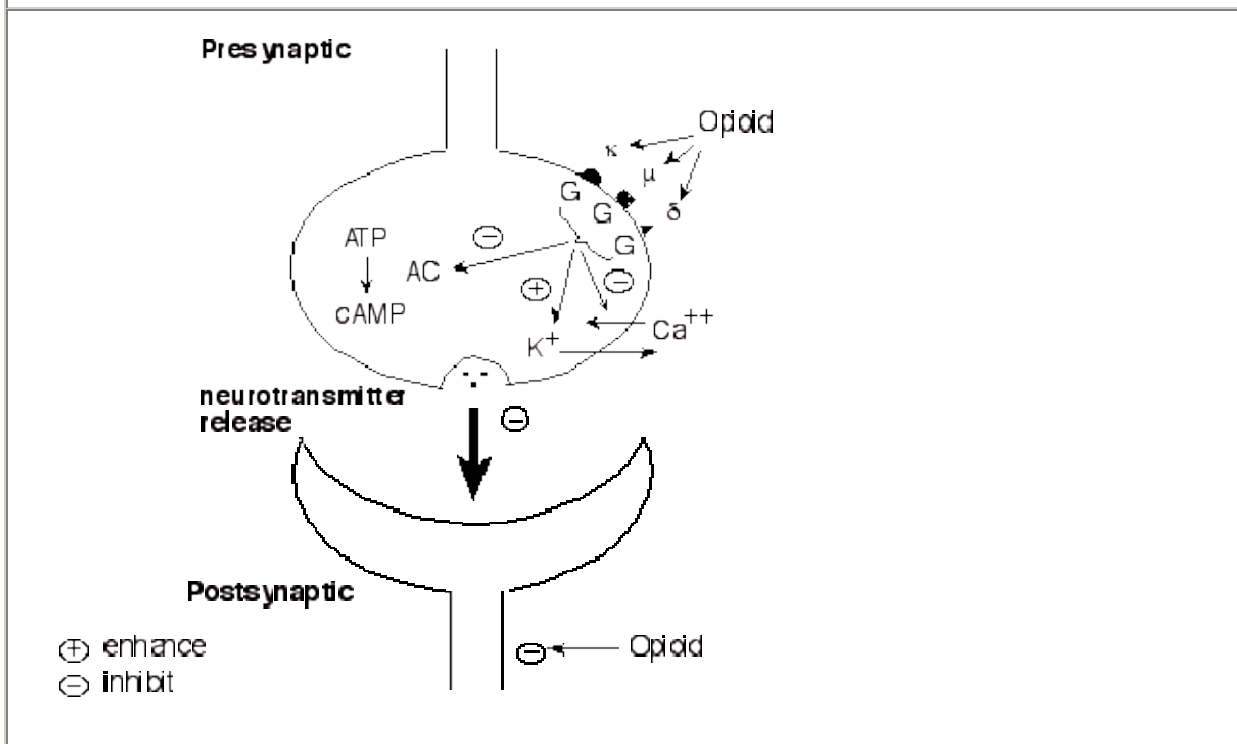
There are three classical opioid receptors (Table 4) in the central nervous system as well as throughout the peripheral tissues. Stimulation of the μ opioid receptors will result in supraspinal analgesia, euphoria, serenity, respiratory depression, decreased gastrointestinal motility, pruritus, prolactin release, physical dependence, anorexia, sedation and miosis. Stimulation of the κ receptors is related to spinal analgesia, sedation, dyspnoea, dependence, dysphoria and respiratory depression. Stimulation of δ opioid receptors may be responsible for psychomimetic and dysphoric effects, but they are not yet well studied (*Waldhoer et al. 2004*).

**Table 4.** Affinity of various opioid drugs at opioid receptors.

|  | Mu (μ) | Kappa (κ) | Delta (δ) |
|---|---|---|---|
| Morphine | Agonist +++ | Agonist ++ | + |
| Methadone | Agonist +++ |  |  |
| Buprenorphine | Partial agonist +++ | Antagonist ++ | ++ |

The number of + signs indicates potency.
Modified from (*Chahl 1996*).

Opioids activate presynaptic receptors on gamma-aminobutyric acid (GABA) neurons, which inhibit the release of GABA in the ventral tegmental area, increasing the release of dopamine. The excess dopamine in the nucleus accumbens is interpreted by the brain as intrinsically positive, rewarding (Figure 2). These pleasurable feelings reinforce behaviour so that it will be repeated (*Hyman et al. 2001*). Addictive drugs like opiates share with non-drug rewards (e.g. food) the property of stimulating dopamine transmission in the striatum, including the nucleus accumbens. The faster the rate of dopamine increase in the striatum, the more reinforcing the effect. Dopamine is critical for acute reward and initiation of addiction (*Terenius et al. 2010*).

Developed addiction is associated with decreased dopamine release and a reduction of dopamine receptors in the striatum. The reduction of receptors in the striatum is associated with reduced activity of the orbitofrontal cortex and the cingulate gyrus. This implies deregulation of the frontal regions by dopamine as regards the loss of control and compulsive

drug intake that characterize addiction (*Terenius et al. 2010*, *Kalivas et al. 2005*, *Volkow et al. 2007*).

**Figure 2.** Morphine binds to receptors on neurons in the ventral tegmental area and in the nucleus accumbens within the reward pathway (National Institute on Drug Abuse (NIDA)).



*Opioid misuse, withdrawal symptoms and dependence*

The acute pharmacological actions of opiate use include analgesia, autonomic inhibition and intoxication (i.e. a "high"). As use continues the person has to consume higher doses to achieve the same effect and finally only to feel healthy, because of the otherwise emerging withdrawal symptoms (*Hyman et al. 2001*). Tolerance is defined as the need for an increasing dose of opiate to achieve the same effect. An opiate addict can use 100- to 200- fold higher amounts than a non-addict. Such doses could be fatal to a non-experienced user, or after withdrawal (*Binswanger et al. 2007*).

Withdrawal symptoms (i.e. "cold turkey") follow the cessation of opioid use and they are a sign of physical dependence. The mechanism behind them is thought to be at least in part neuroadaptation. Sweating, lacrimation, yawning and restlessness occur 8–12 hours after cessation of opiate use, then after 18–24 hours ensue chills, hot flushes, muscle stiffness, large pupils, "goose pumps" and chest pain, and after 30–36 hours diarrhoea, vomiting, increasing restlessness, high blood pressure and high respiratory rate. The symptoms largely disappear within 7–10 days. Withdrawal is not life- threatening to healthy adults (*Mattick et al. 1996*, *Farrell 1994*).

Psychological dependence describes the emotional or motivational symptoms upon drug withdrawal, characterized by intense craving, loss of control over drug self-administration, compulsive drug-seeking and drug-taking despite adverse consequences. It is probably the strongest determinant of opiate addiction (*Nestler 1996*).

Diagnostic criteria of opioid abuse according to DSM IV (APA DSM-IV 2000a):

**A**. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

> (1) recurrent substance use resulting in failure to fulfil major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)
>
> (2) recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)
>
> (3) recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct)
>
> (4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)

**B**. The symptoms have never met the criteria for Substance Dependence for this class of substance.

Diagnostic criteria of opioid dependence according to DSM IV (APA DSM-IV 2000b):

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

(1) tolerance, as defined by either of the following:

> (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect
>
> (b) markedly diminished effect with continued use of the same amount of the substance

(2) withdrawal, as manifested by either of the following:

(a) the characteristic withdrawal syndrome for the substance (refer to criteria A and B of the criteria sets for withdrawal from the specific substances)

(b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms

(3) the substance is often taken in larger amounts or over a longer period than was intended

(4) a persistent desire or unsuccessful efforts to cut down or control substance use

(5) a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects

(6) important social, occupational, or recreational activities are given up or reduced because of substance use

(7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance


Opioid abuse and dependence are associated with adverse medical, legal and social effects. The most frequently seen health problems are those related to injection use: blood-borne infections such as chronic hepatitis B and C, HIV, septicaemia, endocarditis and cellulitis, and "puffy hands" syndrome. Insomnia and mental health problems are common, as well as nutritional deficiencies. Persons who abuse opioids are at an increased risk of hypoxic-ischaemic brain changes (*Andersen et al. 1999*, *Duersteler-MacFarland et al. 2000*). The ischaemia has been speculated to be a result of transient hypoxia related to respiratory depression, thromboembolism, vasculitis, or hypotension. Other neurological complications such as delirium, epilepsy, myelopathy, neural infections and polyneuropathy are also frequent in heroin users. Low blood pressure and cardiac problems are encountered. The mortality rate among opiate addicts is estimated to be approximately 13 times greater than for the general population (*Hulse et al. 1999*).

Opiate abuse is frequently related to marginalization and a chaotic criminal lifestyle, violence and prostitution (*Marsch 1998*). Its social implications are unemployment, lack of psychosocial support and inadequate housing, even homelessness.


*Opioid abuse during pregnancy*

An epidemiological study from the USA revealed a prevalence of opiate use during pregnancy ranging from 1.2% (maternal reports) to 2.3% (meconium analysis) (Lester et al.

2001). In the UK 2% of pregnant women have been found to be using opiates in early pregnancy (*Crome et al. 2007*). In Finland no such estimates are available.

Poor pregnancy outcome has been associated with ante-partum opiate abuse. Increased risks of obstetric complications such as intrauterine growth restriction, ante-partum bleeding, premature rupture of membranes, miscarriage, puerperal morbidity, foetal distress, meconium-stained amniotic fluid and foetal death have been addressed, as well as neonatal complications such as narcotic withdrawal, postnatal growth deficiency, small head circumference, neurobehavioural problems, increased neonatal mortality and prematurity (*Chasnoff et al. 1982*, *Hulse et al. 1998b*, *Hulse et al. 1998a*, *Hulse et al. 1997*, *Gillogley et al. 1990*). In addition, a chaotic life-style and polysubstance abuse including alcohol and tobacco, are common in this population, and are considered confounders in regard to adverse pregnancy outcome (*Bauer et al. 2002*, *Unger et al. 2010*).

In animal studies, water and food consumption among buprenorphine-exposed pregnant rats has been shown to decrease (*Robinson et al. 2001*). Opiates are known to promote anorexia and affect the nutritional status of the user (*Santolaria-Fernández et al. 1995*), which can have implications for the foetus.

Substance abuse may also be seen as a surrogate marker for a constellation of factors such as low socioeconomic status, low level of education, poor nutrition and low level of social support, and having inadequate prenatal care (*Kennare et al. 2005*, *Unger et al. 2010*, *Jansson et al. 1996*), all of which may contribute to poorer pregnancy outcome *per se* (*Luo et al. 2006*).


*Foetal consequences*

The physiochemical properties and possible placental metabolism of a drug are of interest when assessing drug transfer to the foetus. Lipophilic, unbound, neutral, small molecule-sized drugs (less than 500 Dalton) are known to cross the placenta easily. The main mechanism is passive diffusion (*Myren et al. 2007*, *Myllynen et al. 2005*). In animal studies opiates such as morphine and methadone have been shown to diffuse readily across the placenta. Heroin, based on its high degree of lipid solubility, diffuses across the placenta as well as the blood–brain barrier even more readily (*Gareri et al. 2006*).

Drugs of abuse modify signalling of neurotransmitter systems and intracellular messengers. These same neurotransmitters serve as molecules that regulate cell proliferation, survival, migration, circuit formation and establishment of topography (*Levitt 1998*). *In vitro*, morphine has been found to cause a four-fold increase in apoptosis of human foetal neurons and

microglia at an age of 16 to 22 gestational weeks. Because microglia play an important role in remodelling of the foetal brain, opiates could impair neuronal development directly and indirectly via microglia (*Hu et al. 2002*).

Endogenous opioids serve as natural inhibitory trophic factors, inhibiting mitosis and DNA synthesis in the developing brain. Selective μ-receptor activation has been demonstrated to inhibit proliferation, whereas selective δ-receptor agonists inhibit neuronal differentiation (Farid et al. 2008). In animal studies use of opioid agonists has delayed the maturation of the nervous system and use of opioid antagonists has accelerated this process. Opioid growth factor (OGF) and its receptor have a prominent role in the mediation of foetal cell proliferation. OGF has an inhibitory effect on cell proliferation. In humans and rats it is expressed during development in the cerebrum and cerebellum, and in somatic regions, for example heart, muscle and bone. Developmental delays observed after foetal exposure to opioid agonists, such as heroin or methadone, are postulated to result from their direct interaction with opioid growth factor receptor, retarding "normal" foetal development (*Farid et al. 2008*). Thus, small foetal and foetal head size could be linked to opiate use (*Jones et al. 2010*, *Brown et al. 1998*, *de Castro et al. 2011*, *Doberczak et al. 1987*, *Kaltenbach et al. 1987*).

Opioids of abuse have not been suspected of having a high potential as regards causing major congenital anomalies, but existing data is scarce. In a recent population-based case-control study of 30 types of major structural birth defects, Broussard et al. reported that first trimester exposure to therapeutic opioids was associated with a greater risk of conoventricular septal defects (OR 2.7; 95% CI 1.1–6.3), atrioventricular septal defects (OR 2.0; 95% CI, 1.2–3.6), hypoplastic left heart syndrome (OR 2.4;95%CI, 1.4–4.1), spina bifida (OR 2.0; 95% CI, 1.3–3.2), and gastroschisis (OR 1.8; 95% CI, 1.1–2.9)(*Broussard et al. 2011*).

Maternal opiate use is known to have nervous system depressive effects on the foetus, which are manifested clinically by decreased foetal body and breathing movements and heart rate variability (*Navaneethakrishnan et al. 2006*, *Wouldes et al. 2004*, *Farrell et al. 1996*).


*Perinatal hypoxia*
Opioids induce respiratory depression and hypoxia (*Lintzeris 2009*, *Mégarbane B et al. 2006*), warranting oxygen supplementation even when used under controlled occasions like pain relief in early labour (*Volmanen et al. 2008*). In a small study of ten cases and six controls, morphine also caused significant vasoconstriction in the placenta, shown by corresponding increases in Doppler indices of umbilical artery measurements, ending with decreased foetal

breathing movements and heart rate variability (*Kopecky et al. 2000*). In a case report, prolonged morphine infusion resulted in vasoconstriction of the placenta and foetal brain vasculature at 27 weeks of gestation in a patient requiring continuous morphine infusion (*Collins et al. 2005*). In another case report, absence of end-diastolic flow in the umbilical artery was observed in a foetus (29 weeks of gestation) whose mother was withdrawing from heroin. The end-diastolic flow returned to normal when withdrawal symptoms were controlled with methadone (*Wong et al. 1997*).

Opioid withdrawal symptoms are produced by noradrenergic hyperactivity, which also affects placental blood flow by altering blood pressure and pulse rate, thus indirectly affecting foetal growth and wellbeing. In animal studies, in the withdrawal phase foetal movements have been shown to increase, the demand for oxygen grows, blood pressure rises, pulse rate, pH and $pO_2$ fall and the foetus may pass meconium to the amniotic fluid (*Umans et al. 1985*). Foetal distress in narcotic withdrawal is known to increase foetal activity and oxygen demand in humans, as well (*Finnegan 1991a*). There are a few case reports on foetal demise (*Rementeria et al. 1973*) and foetal distress (*Zuspan et al. 1975*) while withdrawing from opiates, from the 1970's. These raised the question of the safety of detoxification (*Finnegan 1991a*, *Kaltenbach et al. 1998*, *Luty et al. 2003*, *Dashe et al. 1998*) and emphasized the importance of opioid substitution treatment during pregnancy.

Perinatal hypoxia is a major contributor to neonatal mortality, morbidity and adverse neurological outcome (*Ruth et al. 1988*, *Thorngren-Jerneck et al. 2001*, *Ingemarsson et al. 1997*).

Several biochemical markers such as erythropoietin (EPO), cardiac troponin T (cTnT) and S100 have been proposed as additional parameters to determine timing and severity of perinatal hypoxia (*Davis et al. 2003*, *Kakuya et al. 2002*, *Clark et al. 2001*, *Nagdyman et al. 2001*, *Michetti et al. 2002*, *Michetti et al. 2003*, *Richey et al. 1995*), and elevated levels of these markers are often seen in newborns with perinatal asphyxia either *in utero* or intra-partum (*Mäkikallio et al. 2002 30*, *Thorngren-Jerneck et al. 2004*).

Tissue hypoxia stimulates production of erythropoietin. EPO is a glycoprotein that regulates red cell production in the bone marrow (*Marti 2004*). It is produced mainly in the kidneys in the adult. During foetal life EPO is produced in hepatocytes, and in late-gestation also in foetal kidneys under normoxic conditions (*Davis et al. 2003*). In a foetal animal model, under hypoxic conditions EPO levels rose within four hours from normal (< 50 U/L) to hundreds of units per litre (*Widness et al. 1986*). Therefore, EPO can be used as an indicator of subacute asphyxia in humans as well (*Richey et al. 1995*). Under foetal hypoxia elevated

concentrations of EPO are seen in cord blood regardless of the underlying cause (*Jazayeri et al. 2000*, *Teramo et al. 2004*, *Jazayeri et al. 1996*, *Jazayeri et al. 1998*, *Doi et al. 1999*). Elevated cord blood EPO levels have also been shown in infants exposed to maternal alcohol (*Halmesmäki et al. 1990*) and tobacco use (*Jazayeri et al. 1998*). EPO has shown neuroprotective properties in various animal models, inhibiting apoptosis in neurones and inducing angiogenesis (*Marti 2004*).

Cardiac troponin T (cTnT) is a protein component of the tropomyosin complex regulating cardiac muscle contractility and it is usually found only in the myocardium. It is released rapidly after myocardial injury in direct proportion to the extent of injury (*Shelton et al. 1999*). Myocardial injury is seen in severely hypoxic foetuses (*Barberi et al. 1999*). These infants have been found to have significantly elevated cord blood cTnT levels (*Clark et al. 2001*), suggesting that it is a useful marker of myocardial damage secondary to severe perinatal hypoxia in neonates (*Mäkikallio et al. 2002*). In normal pregnancies, cord cTnT concentrations are not clinically significantly increased (>0.10 ng/mL)(*Mäkikallio et al. 2000*). Cardiac TnT levels in cord blood are also unaffected by gestation, birth weight or sex (*Clark et al. 2001*), but have been shown to be increased in term foetuses with intrauterine growth restriction in a prospective observational study (*Kocylowski et al. 2009*).

The family of S100 molecules are calcium-binding proteins which regulate a diverse group of cellular functions including cell–cell communication, cell growth, cell structure, energy metabolism, contraction and intracellular signal transduction. S100B is predominantly expressed by cells of the central nervous system, mainly astroglial cells (*Zimmer et al. 1995*). In an animal study, foetal hypoxaemia with associated acidaemia led to persistent elevation in plasma S100B concentrations that strongly correlated with foetal blood flow redistribution in order to spare vital organs (*Giussani et al. 2005*), and a significant correlation of damage degree with S100B in serum two hours after the insult was shown in another animal study (*Fujii et al. 2004*). In term infants, circulating concentrations of S100 indicated cell damage in the central nervous system two hours after hypoxic-ischaemic birth injury, and these concentrations were shown to correlate with the degree of damage (*Nagdyman et al. 2001*, *Michetti et al. 2003*, *Thorngren-Jerneck et al. 2004*, *Kocylowski et al. 2009*).


*Neonatal consequences*

As opiates cross the placenta they can cause physical dependency in the foetus. Cessation of supply of the substance to the infant at birth may result in neonatal abstinence syndrome (NAS). NAS develops in 55–94% of the opiate exposed neonates (*Cleary et al. 2011*,

*Kaltenbach et al. 1998*, *Lam et al. 1992*, *Kraft et al. 2011*, *Lejeune et al. 2006*). It is characterised by various forms of central nervous system and gastrointestinal dysfunction and metabolic, vasomotor, and respiratory disturbances such as high-pitched crying, hyperactive reflexes, tremors, high blood pressure, convulsions, frantic suckling of fists, poor feeding, regurgitation, diarrhoea, dehydration, yawning, sneezing, nasal stuffiness, sweating, skin mottling, fever, rapid respiration and skin excoriation (*Finnegan 1984*, *Bada et al. 2002a*, *AAP 1998*). Its clinical appearance mimics hypoxic-ischaemic encephalopathy. NAS is transient although it can lead to a prolonged hospital stay (*Kakko et al. 2008*, *Kraft et al. 2011*). The severity of NAS may be clinically documented by using validated scoring systems such as the Neonatal Abstinence Scoring System (Finnegan score). According to the Finnegan score (Appendix 1), which is used at our hospital, the neonatal abstinence score is made up of three components: central nervous system disturbances, metabolic–vasomotor–respiratory disturbances, and gastrointestinal disturbances. The newborn is assessed every four hours by medical staff, and if the scores are eight or more NAS is diagnosed. If the scores are eight or more three successive times pharmacotherapy is initiated. After stabilisation the pharmacotherapy dose is gradually decreased until the infant is weaned (*Finnegan 1984*).

Opiates have been shown to be the most effective treatment in controlling acute problems related to NAS caused by opiate exposure *in utero* (*Langenfeld et al. 2005*, *Coyle et al. 2002*, *Ebner et al. 2007*, *Jackson et al. 2004*). At our hospital, morphine hydrochloride has been the drug of choice.

There have been concerns about the long-term effects of opiate exposure on children's future development. In the few neurobehavioral studies that have been carried out it has been difficult to separate the impact of intrauterine exposure from the impact of the growth environment (*Messinger et al. 2004*). In an Israeli study, no cognitive impairment was detected in prenatally heroin-exposed children adopted at birth, when compared with children with environmental deprivation. Nevertheless, high rates of inattention, hyperactivity and behavioural problems were detected in the exposed (*Ornoy et al. 2001*).

In earlier studies, intrauterine exposure to opiate use has been shown to be associated with an increased risk of sudden infant death syndrome (SIDS)(*Kandall et al. 1993*, *Kahlert et al. 2007*), although there are many confounding factors such as tobacco smoking, intrauterine growth restriction and prematurity (*Hunt et al. 2006*). However, a specific effect of opiate use on breathing centre maturation has been speculated (*Suguihara et al. 1991*). Interestingly, SIDS infants have also been found to have structural changes due to intermittent hypoxia such

as brain stem apoptosis (*Kinney et al. 2009*) and neurotransmitter alterations in the brain stem, consistent with abnormalities in autonomic regulation (*Hunt et al. 2006*).

*Opioid substitution treatment*

Opioids are the only illicit drugs for which there is established pharmacological substitution treatment to this day (*Rayburn et al. 2004*). The rationale behind this kind of treatment is to improve health status as well as psychological and social functioning of the dependent person (*Ward et al. 1999, Farrell et al. 1994*). Usually, substitution treatment programmes are enriched with psychosocial treatment, which has been shown to increase the number of abstinent participants at follow-up (*McLellan et al. 1993, Fiellin et al. 2006*). In Finland in 2009, according to units participating in the drug treatment information system, medical out-patient or in-patient treatment designed for opiate addicts was received by 41% of the clients (*n*=4109) who had sought substitution treatment primarily for opiate addiction. Buprenorphine (53%) was more common in medical opiate addiction treatment than methadone (44%) (*Väänänen et al. 2010*).

*Methadone*

Methadone has been used since the 1960's in opioid replacement therapy (*Dole et al. 1966*). Methadone maintenance treatment (MMT) involves daily administration of this oral opioid agonist (*Ward et al. 1999, Farrell et al. 1994*). Randomized controlled trials have shown that MMT decreases illicit opiate use, criminal activity, and mortality rates in heroin-addicted adults (*Gruber et al. 2008*). Psychosocial wellbeing of patients on maintenance treatment has been enhanced (*McLellan et al. 1993, Fiellin et al. 2006*). MMT has been shown to increase treatment retention and reduce heroin use compared with methadone-assisted detoxification (*Gruber et al. 2008, Sees et al. 2000*). In addition, MMT reduces infectious disease transmission and improves health as regards the transmission of HIV, and hepatitis B and C (*Sees et al. 2000*).

In MMT the dose is adequate if it prevents withdrawal, reduces or eliminates drug craving, and blocks the euphoric effect of narcotics (*Strain et al. 1999*). The pure agonist nature of methadone has raised concerns about overdose-related problems (*Cairns et al. 1996*). Other serious medical risks have also been related to methadone use, such as the risk of QT interval prolongation and ventricular tachycardia, known as torsade de pointes (*Fonseca et al. 2009, Krantz et al. 2003*).

*Methadone during pregnancy*

Methadone use has also been widely accepted in the care of pregnant opioid-dependent women since the 1970's and has been seen as the "gold standard" of opioid replacement therapy during pregnancy. Methadone maintenance treatment has stabilised lifestyles, lessened risk-taking behaviour and reduced the incidence of preterm birth and intrauterine growth restriction (*Brown et al. 1998*, *Rayburn et al. 2004*, *Finnegan 1991b*, *Kandall et al. 1999*, *Burns et al. 2007*). It has been shown to improve antenatal care as a result of earlier and increased attendance at antenatal visits (*Finnegan 1991b*, *Burns et al. 2007*). Daily oral methadone dosing, combined with the long terminal half-life (18–24 h), avoids maternal withdrawal symptoms and results in continuous exposure of the neonate. Crude outcome measures such as gestational age at birth, birth weight and birth length have been within normal ranges, although lower than in the unexposed (*Kaltenbach et al. 1987*, *Kandall et al. 1999*, *Fischer et al. 1999*, *McCarthy et al. 2008*).

Maternal methadone administration has significant effects on foetal behavioural functions that are independent of maternal effects. At peak methadone concentrations, heart rate has been found to be slower, less variable, and to display fewer accelerations (*Archie et al. 1989*). Foetuses displayed less motor activity, fewer respiratory movements and the integration between heart rate and motor activity was also attenuated (*Wouldes et al. 2004*, *Jansson et al. 2005*). Split dosing at 12-hour intervals diminished these changes in foetal neurobehaviour (*Jansson et al. 2009*).

Mean methadone serum trough levels have been shown to be lower during the third trimester (*Pond et al. 1985*), and pre-pregnancy methadone doses have caused withdrawal symptoms among pregnant women during the third trimester. Dose increase has been recommended to avoid this (*Drozdick et al. 2002*). Different mechanisms considered to be behind this phenomenon have been physiologically increased maternal plasma volume and larger tissue reservoir for storage of methadone, as well as enhanced maternal and foetal hepatic metabolism and/or biotransformation of the drug by the placenta (*Pond et al. 1985*).

Neonatal abstinence syndrome has occurred frequently (*McCarthy et al. 2005*, *Bell et al. 2008*), with 60–90% of the neonates developing the condition. NAS requires prolonged hospital care, and it can be severe in nature. Pharmacological treatment is needed in 45–68% of cases (*Jones et al. 2010*, *Ebner et al. 2007*, *Jones et al. 2005*).

The relationship between methadone dose and incidence and severity of NAS has been controversial. There are studies showing a linear relationship between dose and incidence, such as a British study of 444 neonates. In this study 45.5% of neonates developed NAS

requiring pharmacological treatment. Only prescribed maternal methadone dose independently influenced the likelihood of an infant receiving treatment for NAS, and the likelihood was not modified by illicit drug abuse (*Dryden et al. 2009*). In an American study of 70 women, methadone dose on the last week of pregnancy was associated with duration of neonatal hospitalization, neonatal abstinence score, and treatment for withdrawal, and heroin supplementation did not alter the dose–response relationship. The median methadone dose was relatively low, 20 mg (range 0–150 mg), and divided into half in the morning and half in the evening (*Dashe et al. 2002*). In a recent US study, every increase of 5.5 mg of methadone in the mother was associated statistically with 1 additional day of NAS treatment for the infant (*Lim et al. 2009*).

Some other studies have revealed no relationship, such as an American study of 100 mother/neonate dyads when a cut-off level of > 80 mg/day methadone was used (*Berghella et al. 2003*) or a study of 32 infants with 72% showing signs of withdrawal, and the incidence of withdrawal not significantly different with a cut-off methadone dose of 50 mg/d (*Brown et al. 1998*). In recent US studies, maintenance doses of 100 mg/d and more were not associated with an increased rate or with the severity of NAS (*Seligman et al. 2010*, *Pizarro et al. 2011*).

In clinical studies concerning NAS there is always the possibility of confounding factors such as additional use of methadone and other illicit substances, which has been shown to be common in pregnant women on MMT (*Almario et al. 2009*, *Brown et al. 1998*, *Kashiwagi et al. 2005*). A Swiss prospective study of 84 pregnant women on MMT showed that 64% were co-users of cocaine and/or heroin, with an average methadone dose of 40.9±32.7 (SD) mg/day at birth. Since a large percentage (90%) of methadone-treated women smoke while pregnant (*Haug et al. 2001*), and smoking has been shown to cause withdrawal syndrome in newborns (*Law et al. 2003*, *Pichini et al. 2006*), it has been addressed in relation to NAS. Tobacco smoking may influence aspects of NAS in a direct dose-dependent manner, as neonates born to heavily smoking methadone-maintained mothers (>20 cigarettes/day) have been found to have significantly higher NAS peak scores, and the scores took longer to peak than in neonates born to light smokers (<10 cigarettes/day)(*Choo et al. 2004*).

Premature infants may have less severe NAS compared with full term-infants (*Dysart et al. 2007*, *Doberczak et al. 1991*).

No major anomalies have been linked with the use of methadone (*Chiriboga 2003*, *Schempf 2007*). Methadone-exposed infants, like heroin exposed ones, have been found to have a smaller head circumference compared with unexposed controls (*Wouldes et al. 2010*, *Brown et al. 1998*).

31

During pregnancy the ideal is to stabilize the mother to low-dose methadone and wean her during the second trimester. According to the literature this has been almost impossible to achieve because of relapses, increased polysubstance use and threat of prematurity (*Finnegan 1991b*).

Despite previous recommendations to avoid detoxification during pregnancy there are studies showing successful withdrawal during pregnancy. In a retrospective study of 101 pregnant women in the UK, methadone detoxification treatment after the first trimester was not associated with any increased risk of miscarriage in the second trimester or premature delivery in the third trimester (*Luty et al. 2003*). An American study of 34 pregnant women showed a 59% success rate and no evidence of foetal distress, death or birth before 36 weeks after detoxifying at a mean gestational age of 24 weeks (*Dashe et al. 1998*).

Since MMT studies on pregnant women have been performed in centres offering both methadone and comprehensive services, including obstetric, health and psychiatric care, individual, group and family therapy, it is difficult to distinguish the benefits of methadone itself from measures of social and obstetric care (*Kaltenbach et al. 1987*, *Kandall et al. 1999*, *Fischer et al. 1999*, *McCarthy et al. 2008*, *Jones et al. 2005*, *Dryden et al. 2009*, *Kashiwagi et al. 2005*).

**Figure 3.** Buprenorphine chemical structure.
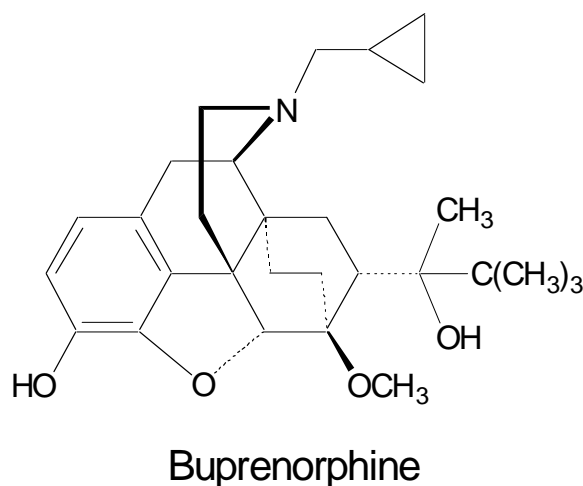


Buprenorphine

*Buprenorphine pharmacology*

Buprenorphine (BPR) is a semi-synthetic thebaine derivative. It is a partial opioid μ receptor agonist with high receptor affinity, but only partial efficacy. Its agonist properties produce

clinical effects: analgesia, sedation, euphoria and respiratory depression. BPR is highly lipophilic and protein-bound. Its molecular weight is 504 Da (*Kuhlman et al. 1996*) (Figure 3).

BPR is mainly metabolized by the liver. Specifically, the microsomal enzyme CYP3A4 (cytochrome P450 3A4) is responsible for this, as 75% of BPR is transformed to an active metabolite (norbuprenorphine) in the liver and excreted to faeces (*Cone et al. 1984*). Only 10–30% of BPR is excreted via the kidneys to the urine (*Kuhlman et al. 1996*).

The oral bioavailability of BPR is low. Its sublingual bioavailability is 35–50% making it an adequate way to treat opioid dependence (*Kuhlman et al. 1996*).

BPR has a dose-dependent ceiling effect on respiratory depression in high doses, although respiratory rate depression occurs at sublingual doses of 4 mg and higher, and oxygen saturation decreases at sublingual doses of 8 mg and higher from 98% to 95% in males (*Walsh et al. 1994*). This is considered a safety issue in view of the risk of overdose. However, BPR-related deaths due to asphyxia have been reported in association with misuse and/or co-administration of psychotropic substances e.g. benzodiazepines (*Bell et al. 2009*, *Megarbane et al. 2010*).

BPR has no significant effect on blood pressure, or respiratory or heart rate or length of the QT interval (*Baker et al. 2006*, *Anchersen et al. 2009*, *Jasinski et al. 1989*).


*Buprenorphine maintenance treatment*

In opioid-dependent individuals buprenorphine has been shown readily to cross-substitute and suppress symptoms of withdrawal from opiates, e.g. heroin and morphine (*Mattick et al. 2003*, *Ling et al. 2003*). BPR has gained attention as an effective pharmacotherapeutic agent for opioid abuse, because of a less severe and shorter abstinence syndrome compared with methadone, long duration of action enabling alternate day dosing, and an enhanced safety profile (*Marsch et al. 2005*, *Johnson et al. 2000*). In non-pregnant adults, few or no autonomic signs or symptoms of withdrawal are observed following abrupt withdrawal from BPR. BPR is statistically significantly superior to placebo medication in retention of opiate-dependent patients in addiction treatment (*Kakko et al. 2003*, *Johnson et al. 1995*). BPR at medium (8–15mg) and high doses (16 mg and over) can reduce heroin use effectively compared with placebo, although it is less effective than methadone at medium dose levels of between 60 mg and 120 mg per day. Psychosocial wellbeing has been enhanced with 1-year intensive psychosocial treatment combined with buprenorphine maintenance treatment (BMT) but not with the psychosocial treatment alone (*Kakko et al. 2003*).

*Buprenorphine pharmacology during pregnancy*

Buprenorphine crosses the placenta. The placenta acts as a depot for BPR and slowly renders it to the foetal circulation. *In vitro* it has been reported that <10% of the BPR used was transferred to the foetal circulation and BPR did not harm placental viability or function (*Nanovskaya et al. 2002*). The human placenta is also involved in metabolism of BPR. Aromatase is the enzyme responsible for the metabolism of certain xenobiotics like buprenorphine in the human placenta. It is also responsible for the conversion of androgens to estrogens (*Deshmukh et al. 2003*).

There are only a few case reports on BPR plasma concentrations in pregnant women. In these reports pregnancy status did not clinically significantly alter BPR plasma concentrations compared with non-pregnancy status. In a study of three opioid-dependent women maintained on 8–12 mg/day of buprenorphine for the last few months of pregnancy, trough buprenorphine plasma concentrations were measured before and after delivery. The trough plasma concentrations before delivery (mean 0.36 ng/mL, range 0.12–0.49 ng/mL) were similar to those after delivery (mean 0.37 ng/mL, range 0.12–0.79 ng/m L) (*Johnson et al. 2001*). This may be due to the fact that despite the physiological changes during pregnancy such as enlargement of the fluid compartment of the body and placental metabolism of BPR, the plasma concentration of BPR is not altered because it is highly lipophilic and protein-bound (*Kuhlman et al. 1996*).

In a French case report the buprenorphine concentration in a newborn's blood 20 hours after birth was approximately six times higher than her mother's trough blood level (i.e., 24 hours after administration), whereas norbuprenorphine concentrations were almost equal. It was speculated that this was due to immature liver function, as BPR is metabolized mainly by the liver (*Marquet et al. 1997*).


*Foetal effects*

No major birth defects have been recognised or suspected in humans with prenatal BPR exposure thus far (*Kakko et al. 2008*, *Lacroix et al. 2004*). In rats a significant increase in skeletal abnormalities has been observed after subcutaneous administration of BPR (*Johnson et al. 2003*). In addition, changes in synaptogenesis and myelinisation have been shown in animal studies (*Sanchez et al. 2008*).

In a recent report, BPR-exposed foetuses displayed higher levels of foetal heart rate variability, more accelerations in foetal heart rate and longer duration of motor activity compared with methadone-exposed foetuses (*Jansson et al. 2011*).

In animal studies, foetal demise, stillbirth and sex imbalance of the offspring in favour of females have been reported. In addition, problems of parturition have occurred. Sedation of the dam has been thought to be the reason for this. No reports on human parturition problems or sex imbalance among offspring have been published. In humans, a few spontaneous abortions have been reported thus far in the literature as well as a few stillbirths (*Kakko et al. 2008*, *Lacroix et al. 2004*, *Johnson et al. 2003*).

*Neonatal effects*

Neonatal abstinence syndrome has been frequently associated with use of BPR. The emergence of NAS has varied in different studies, being around 60% (*Kakko et al. 2008*, *Jones et al. 2010*, *Kayemba-Kays et al. 2003*, *Jones et al. 2005*, *Kacinko et al. 2008*). In the literature, BPR dosage and its impact on severity of NAS has not been investigated widely. In a Norwegian study, no correlation between BPR-dosage and NAS severity was found (*Bakstad et al. 2009*). In an American study of nine pregnancies, total BPR meconium concentrations and BPR/NBUP ratios were significantly related to NAS scores >4. As free BPR concentration and percentage of free BPR increased, head circumference decreased (*Kacinko et al. 2008*). On the other hand, it has been postulated that BPR has a unique withdrawal profile, with lower incidence and less severe NAS with higher BPR doses compared with lower BPR doses, which are associated with more severe NAS. The basis of this could be the high affinity of BPR to its receptors, allowing longer-lasting effects (*Lacroix et al. 2004*).

In a prospective French study on 259 women undergoing buprenorphine maintenance treatment (daily dose ~5 mg around the time of delivery) the only parameters found to be significantly associated with NAS were continuation of active drug addiction and non-compliance with the addiction treatment programme (*Simmat-Durand et al. 2009*).

Many chemicals can affect aspects of NAS in addition to top-up use of BPR, which is hard to detect. Maternal tobacco smoking has been shown to cause withdrawal symptoms in the neonate *per se* (*Law et al. 2003*), and to amplify the severity of BPR-related NAS (*Fischer et al. 2000*). Maternal use of benzodiazepines and illicit drugs has been shown to exacerbate NAS (*Simmat-Durand et al. 2009*, *Lacroix et al. 2004*). In addition, pregnant women and/or medical staff often want to reduce BPR doses for a fear of neonatal NAS (*Lejeune et al. 2006*). This may end with increasing abuse of other substances or top-up use of BPR (*Kakko et al. 2008*). Consequently, this may confound studies on the relationship between BPR dose and NAS.

*Buprenorphine maintenance treatment during pregnancy*

BMT and MMT have been initiated with similar maternal and foetal comfort and safety features during the second trimester of pregnancy (*Jones et al. 2005*). BMT may have advantages over MMT during pregnancy as it is not associated with an increased prematurity rate, and the incidence and severity of NAS have been lower (*Kakko et al. 2008*). BMT initiated prior to conception may have better outcomes in terms of incidence and severity of NAS than treatment initiated later (*Kakko et al. 2008*). It can be speculated that women who have been longer in OMT would show less additional use of opiates and other substances.

A large prospective observational French study of 259 pregnant women on BMT or MMT revealed no major differences between the two groups in terms of perinatal outcome and emergence of NAS. The prematurity rate was slightly higher in the methadone maintenance group (*Lejeune et al. 2006*).

In the present literature, there are only a few randomized controlled studies in which BMT and MMT have been compared during pregnancy (*Fischer et al. 2006*, *Jones et al. 2010*, *Jones et al. 2005*). An American study (*Jones et al. 2005*) of 15 women did not reveal any statistically significant difference between BMT and MMT in terms of NAS except for a 1.3-day shorter length of hospital stay in the BMT group. There was a tendency towards milder and rarer NAS in cases of BMT *vs.* MMT, however. In an Austrian study (*Fischer et al. 2006*) of 18 women there was somewhat greater treatment retention in the BPR group but significantly lowered use of additional opioids in the methadone group ($p$=0.047). There was also earlier onset of NAS in neonates born to the methadone group (mean 60 hours) *vs.* the BPR group (mean 72 hours after last medication). In a recent American randomized control study involving comparison of 131 neonates born to women who were in OMT to the end of pregnancy, it was found that the neonates exposed to BPR ($n$=58) required significantly less morphine for NAS, had a significantly shorter hospital stay, and had a significantly shorter duration of treatment for NAS compared with methadone-exposed neonates ($n$=73). However, retention was better in the MMT group than in the BMT group (82% *vs.* 67%) (*Jones et al. 2010*). Table 5 shows BPR and neonatal outcome in summary.

**Table 5.** Buprenorphine and neonatal outcome.

| Study | Year | Setting | N | NAS (%) | Medication for NAS (%) | Birth weight (g) | Apgar | Prematurity (%) | CS rate (%) | Head circum-ference |
|---|---|---|---|---|---|---|---|---|---|---|
| Kayemba-Kayes et al. | 2003 | Prospective follow-up | 13 | 85 | 77 | 3000 | normal | 8 | | |
| Schindler et al. | 2003 | Case report | 2 | 50 | 0 | 3115 | 9 | 0 | 50 | 34 |
| Lacroix et al. | 2004 | Prospective follow-up | 34 | 42 | 24 | 2796 | | 9.7 | | |
| Lejeune et al. | 2006 | Prospective follow-up | 159 | 78 | 52 | 2843 | 9.8 | 9 | 18 | $10 < 10^{th}\%$ |
| Kakko et al. | 2008 | Prospective follow-up | 47 | 40 | 15 | 3250 | 0<4 | 9 | 21 | 34 |
| Bakstad et al. | 2009 | Prospective follow-up | 12 | | 67 | 3130 | 8.4 | 8.3 | 33.3 | 34.3 |
| Jones et al. | 2005 | RCT | 9 | | 20 | 3530 | 8.1 | 0 | 11.1 | 34.9 |
| Fischer et al. | 2006 | RCT | 8 | | 50 | 2820 | 8.5 | 25 | 25 | |
| Jones et al. | 2010 | RCT | 58 | | 47 | 3094 | 8.1 | 7 | 29 | 34 |

## AIMS OF THE STUDY

The aims of this work were to study the effects of buprenorphine use on pregnancy and early neonatal outcome as well as long-term medical consequences as regards maternal health and need of child protection services after alcohol and/or substance misuse during pregnancy.

The specific aims were to study:

- the long-term morbidity and mortality of women with alcohol and/or substance misuse while pregnant
- the need of child protection services after pregnancy exposed to alcohol and/or substances of abuse
- the effects of buprenorphine use on maternal and neonatal outcome
- the effects of prenatal buprenorphine exposure on perinatal biochemical hypoxia markers
- the effects of prenatal buprenorphine exposure on neonatal abstinence syndrome and well-being

## SUBJECTS, MATERIALS AND METHODS

*Ethics*

The studies were conducted with the approval of the Ethics Committees of the Department of Obstetrics and Gynaecology, and the Hospital for Children and Adolescents, Helsinki University Central Hospital.

In addition, for the register-based studies (Studies I, II) permission for data linkage was obtained from the Ministry of Social Welfare and Health and the register-keeping institutions: the National Institute for Health and Welfare (THL), Statistics Finland and the Social Insurance Institution of Finland (SII).

*Subjects*

*Studies I and II*

For the register-based studies we sought out all 526 women whose pregnancies were followed up at special antenatal clinics for women with alcohol and/or substance misuse problems, at Helsinki University Central Hospital, the Midwifery Hospital or Jorvi Hospital, and who gave birth between 1992 and 2001.

In Study I, for each case dyad, three mother-child control pairs were selected from the national Medical Birth Register. They were drawn and matched for maternal age, parity, and time (same day/same month) and place of birth of the index child. Exclusion criteria for the control dyads were any evidence of alcohol and/or substance misuse in any of the used national registers (Hospital Discharge Register, Institutional Care and Housing Services in Social Welfare register, Cause-of-Death Register, Social Insurance Institution of Finland register of medication reimbursement) at the beginning of follow-up. Two of the original 526 women (0.4%) could not be traced later in the databases and were excluded, leaving a total of 524 women. The number of control women was 1792.

Study II was a register-based cohort study of 626 children born to the women identified in Study I. The total number of children born from pregnancies followed up at the special antenatal clinics during the study period was 655, but 29 of these children were excluded. Exclusion criteria were death during follow-up (*n*=7), foetal death (*n*=3), adoption at birth (*n*=5) and missing data (*n*=14).

*Studies III–V*

The study subjects of cohort studies III, IV and V were partly overlapping (Table 6).

All 66 buprenorphine-using women and their 67 pregnancies prospectively followed up in a comprehensive service setting for pregnant women with substance misuse problems at a tertiary maternity centre at Helsinki University Central Hospital between 2002 and 2005 were included in Study III.

In nine of the 67 pregnancies, the women were already in a buprenorphine maintenance treatment programme before admission to our study, and in 24 pregnancies, the women had their buprenorphine-assisted treatment started at our clinic. In the other 34 pregnancies, the women had very chaotic lifestyles and could not commit themselves to out-patient treatment.

For further analyses, we separated the 67 pregnancies into three subgroups: group A, nine pregnancies, where the women were able to quit BPR use before delivery, the sufficiently committed group C of 21 pregnancies, where the women attended at least 50% of the scheduled appointments, and the poorly committed group B of 37 pregnancies, where the women skipped over 50% of their scheduled appointments.

In addition, we compared the pregnancy outcomes with national birth statistics in 2004 (the National Research and Development Centre for Welfare and Health, STAKES; since 2009 the National Institute for Health and Welfare, THL).

**Table 6.** Study subjects of Studies III-V.
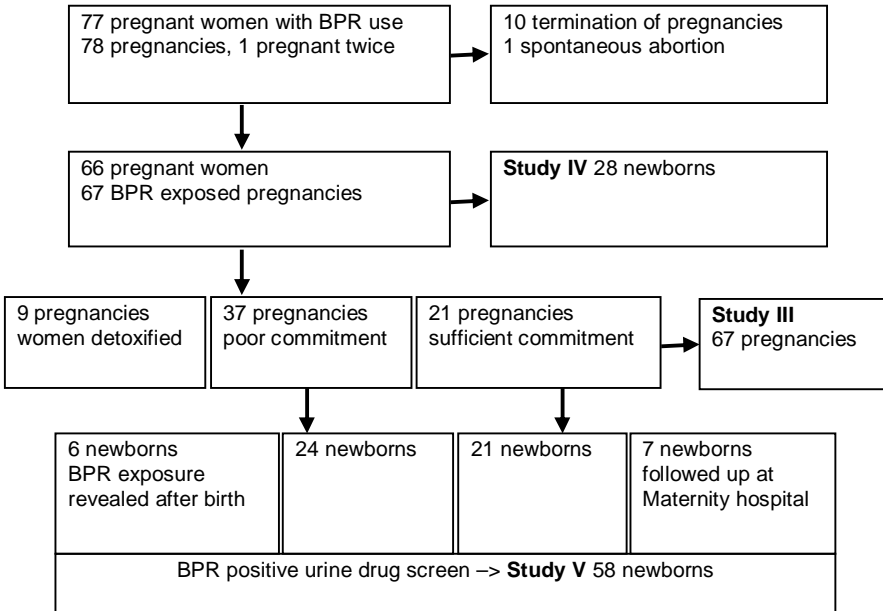
The subjects in Study IV consisted of 27 neonates born to 27 buprenorphine-using women. All 27 BPR-using women were followed up during pregnancy in the same service setting as the subjects in Study III, as were the 27 mothers of substance-exposed control neonates. These control neonates were exposed prenatally to maternal abuse of illicit drugs other than opioids. As non-exposed controls we had 38 neonates born to healthy parturients with no identified alcohol and/or substance misuse. All neonates were born between August 1, 2002 and April 4, 2007. All participants gave their informed consent. Exclusion criteria were preterm or multiple delivery, or pregnancy complication.

In Study V the subjects included all 58 singleton infants who tested positive for buprenorphine in urinary drug screening and in confirmatory analyses after birth at Helsinki University Central Hospital between the years 2001 and 2005. In 53 (91%) of the 58 pregnancies, the mothers were followed up in a comprehensive out-patient service setting for pregnant women with substance misuse problems and 45 of them were included in Study III. In five (9%) pregnancies, buprenorphine misuse was discovered only after labour. Four women gave birth twice during the study period. The women were divided into two subgroups: the sufficiently committed subgroup, in which the women attended at least 50% of the scheduled appointments ($n$=28), and the insufficiently committed subgroup, in which the women were poorly committed and skipped over 50% of their scheduled appointments ($n$=30).

*Methods*

*Studies I and II*

Studies I and II were register-based studies and the subjects were not contacted. The women were followed up from the index pregnancy during 1992–2001 until the 31st of December 2007, or death. Their children were followed up from birth in 1992–2001 until the end of 2003.

In addition to data concerning the antenatal, delivery and neonatal period obtained from the hospital charts, we recorded data from the appropriate registers concerning long-term maternal outcomes such as morbidity, mortality, use of medication, need for rehabilitation, employment and retirement (Study I) and for Study II we recorded data concerning need of out-of-home child protection services.

Data linkage among the registers was carried out by the register authorities, using personal identity numbers. The data (Studies I and II) was considered to be highly confidential by the

register authorities, and therefore it was possible to conduct the analyses only after the register authorities coded the results of data linkages into a useable but concealed form.

We used the following registers:

Data on pregnancy, delivery, and the mother's sociodemographic background were obtained from the Medical Birth Register kept by National Institute for Health and Welfare (THL).

Information on dates and all causes of death was received from the Cause-of-Death Register, kept by Statistics Finland. The causes of death are based on death certificates, and the ICD codes are checked by medical experts at a regional level and at Statistics Finland.

The Hospital Discharge Register of THL contained information on all in-patient periods of hospitalization (1992–2007) in private and public hospitals and on out-patient visits (1998–2007) within the public sector (name of hospital or other institution, dates of admission and discharge, diagnosis). Only primary diagnoses were carried out according to the International Statistical Classification of Diseases and Related Health Problems, 9th Revision (ICD-9, 1992–1995) and 10th Revision (ICD-10, 1996–2007), as appropriate.

The Social Insurance Institution of Finland (SII) had a Drug Prescription Register (1994–2007), which comprised date of distribution, names and amounts of drugs as regards 97% of all reimbursed drugs in Finland. Nearly all prescription-only drugs deemed necessary for treatment of an illness were partly reimbursable, and for higher reimbursement in connection with certain chronic diseases the patient could obtain a certificate from her physician.

Until 2005, prescription medication purchases were only reimbursed if the costs of one purchase exceeded the co-payment of 7.57 euros (in 1992) and 10 euros (in 2005). Since 2006 all reimbursed purchases have been registered.

Drugs were classified according to the Anatomic Therapeutic Chemical (ATC) classification system by the WHO Collaborating Centre for Drug Statistics Methodology, 2008.

SII was the major organizer of nationwide rehabilitation for the working-age population who were at high risk of becoming unable to work due to a disorder, disease or disability within the near future. The SII registers included information on all rehabilitation periods and diagnoses (1992–2007).

If rehabilitation was focused on forms of risky behaviour such as heavy alcohol or drug consumption, then it was organized by community-based social care and these resources may have differed between various municipalities. In-patient rehabilitation periods for drug or alcohol abuse were reported in the Register on Institutional Care and Housing Services in Social Welfare.

Information on employment or pension of a disabled person was obtained from the Finnish Centre for Pensions, the Insurance Supervisory Authority and SII.

A person could claim Unemployment Allowance (basic or earnings-related allowance) or Labour Market Subsidy according to her previous employment history. Earnings-related Unemployment Allowance was available to members of an unemployment fund only and required an employment history of at least ten months during the two years preceding the unemployment. Basic Unemployment Allowance and Labour Market Subsidy were claimed from SII. Those not eligible for Unemployment Allowances could claim Labour Market Subsidy.

In Finland, the granting of a disability pension required a medically confirmed illness, disease or injury that restricted or prevented working. The disability pension could be granted either indefinitely or it was for "rehabilitation subsidy". SII paid pensions to those persons who had no working history, or a short-term or low-paid working history (Kela.fi ediorial team 2011). For this study we were able to analyze only the pensions paid by SII.

The data concerning need of childhood out-of-home care were based on the National Institute for Health and Welfare (THL) Child Welfare Register concerning children and young persons placed outside the home as part of child protection services (CPS).


Statistics

All data were analysed by using SPSS software for Windows Version 13.0 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL). A $p$ value $< 0.05$ was considered statistically significant.

In Study I we used Student's $t$-test, the chi-square test and Fisher's exact test for comparisons between study groups, as appropriate. We calculated odds ratios (ORs) with 95% confidence intervals (95% CIs). Logistic regression was used to adjust for possible confounders (socioeconomic and marital status at the index birth) concerning in- and out-patient care and medication data, and the results expressed as adjusted odds ratios (AORs), with 95% CIs.

All analyses were performed using the women as denominators. Mortality rates were calculated per 1000 women. Only the primary diagnoses were analyzed and each diagnosis was calculated once per woman and separately for in-patient and out-patient care. Each medication purchase was calculated once per woman.

In Study II the risk of being taken into custody was calculated in relation to maternal and perinatal factors by using crude risk ratios (RRs) with 95% CIs. Statistical tests were

performed by using tests for relative proportions, Student's *t*-test and the chi-square test. The Kaplan–Meyer curve was applied in relation to the proportion of children taken into custody.

*Studies III–V*

Clinical care of the pregnant women known to be misusing buprenorphine and to be dependent on it consisted of follow-up in a multidisciplinary service setting including visits to an obstetrician, a midwife, a psychiatric nurse and a social worker at a tertiary maternity hospital. The women were referred to this kind of intensified care by a public health nurse or an addiction treatment clinic. Appendix 2 shows the follow-up scheme during pregnancy. A paediatrician met all the mothers in the third trimester.

The women were referred to combined psychiatric and addiction care if not involved earlier. Daily out-patient supervised BPR-assisted treatment at the maternity clinic was initiated for those women on street BPR who were motivated to undergo this kind of treatment while waiting for opioid maintenance treatment (*Krook et al. 2002*). These women received their medication (starting dose of 2–4 mg/day) sublingually on a daily basis under supervision. The dose was increased according to individual need up to 12 mg/day. Motivated patients were encouraged to decrease doses or even undergo BPR detoxification throughout their pregnancies. Maternal substance use was recorded in detail at every visit: substances used, dose and route of use, and there was maternal urinary drug screening (*Kacinko et al. 2009*, *Azadi et al. 2008*).

After birth the Finnegan scoring system (Appendix 1) was applied by medical staff every 4 hours to assess possible neonatal abstinence syndrome. If the score was ≥8, NAS was diagnosed and scoring was done every 2 hours. If the Finnegan scores were ≥8 on three successive occasions at 2-hour intervals, the neonates were given oral morphine hydrochloride mixture. Gradual weaning (10% daily) began when the Finnegan scores were under 8 for 72 h (*Finnegan 1984*).

The hospital charts were reviewed as regards maternal sociodemographic data, obstetric and substance abuse history, pregnancy complications, delivery and the length of hospital stay. As for neonatal data we recorded early neonatal wellbeing (cord blood pH, Apgar scores and admission to a neonatal intensive care unit (NICU), growth, neonatal urine toxicology, aspects of possible NAS and the length of hospital stay.

In order to evaluate the possible adverse effects of prenatal buprenorphine exposure on early neonatal wellbeing we analysed biochemical markers of hypoxia in cord serum:

erythropoietin (EPO), cardiac troponin t (TnT) and S100 in addition to standard clinical parameters (Study IV).

Laboratory analyses

We used commercially available established laboratory assays for all analyses.

Urine samples collected from the women during pregnancy and from the neonates on the day of birth (day 0) and on the two consecutive days were screened by means of Roche Diagnostics Abuscreen OnLine automated semiquantitative assays for drug abuse (Indianapolis, IN, USA): buprenorphine equivalents (analytical range 5–200 μg/L), amphetamine (5–500 μg/L), barbiturates (5–200 μg/L), benzodiazepines (5–100 μg/L) and cannabinoids (5–50 μg/L). The tests are accredited according to the Finnish Standards Association European Norm (SFS-EN) ISO/IEC 17025 and ISO 15189.

Confirmatory analyses were performed at the Department of Forensic Medicine, University of Helsinki for all screen-positive samples. For total buprenorphine analysis, a 1-mL urine sample was hydrolyzed with beta-glucuronidase prior to extraction. The analyses of BPR and norbuprenorphine were carried out by liquid chromatography triple-quadruple mass spectrometry using reversed phase C18 chromatography, gradient elution and electrospray ionization. The limit of quantification in urine was 1.0 μg/L, the analytical range was 1–200 μg/L and the expanded uncertainty of measurement was 30%.

In Study IV we collected cord artery serum samples at delivery, which were then frozen at -18° C and later analyzed in the same batch.

Cord serum erythropoietin (EPO) concentrations were quantified by using an immunochemiluminometric assay in an IMMULITE analyzer (DPC, Los Angeles, CA, USA). The detection limit of the assay is 0.2 U/L. The within-run and total coefficient of variation (CV) was <9% in the concentration range of 7–148 U/L.

Cord serum levels of cardiac troponin T (cTnT) and S100B were measured by electrochemiluminescence immunoassays (ECLIAs) using an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany). The monoclonal assay antibodies selectively detect the beta chain of the S100 protein, and therefore it measures both the homodimer S100BB and the heterodimer S100A1B. Our intra-assay CV for serum cTnT was <2.4% and total CV <6.3% (tested range: 0.11–2.90 μg/L). For serum S100, the intra-assay and interassay CVs were <3.1% (range: 0.036–4.71 μg/L) and <6.2% (0.22–2.59 μg/L), respectively. The assays were linear up to a concentration of 30 μg/L.

Statistics

All data were analysed by using SPSS software for Windows Version 13.0 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL). A $p$ value $< 0.05$ was considered statistically significant.

In Study III unpaired $t$-tests were used to compare continuous variables between subgroups (A *vs.* B, A *vs.* C and B *vs.* C). The chi-square test or Fisher's exact test (expected frequencies $< 5$) were used to compare dichotomous data between the subgroups.

In Study IV comparisons between the three study groups were first conducted using one-way analysis of variance (ANOVA), then Dunnett's $t$-test to compare group means of the EPO, TnT and S100 data. Spearman correlation coefficients were calculated to examine bivariate relationships between EPO, cTnT and S100 concentrations and umbilical artery pH, gestational age, birth weight and placental weight.

In Study V unpaired $t$-tests were used to compare the compliant and non-compliant groups, benzodiazepine-positive and -negative groups as well as groups smoking $\geq 10$ and $<10$ cigarettes/per day. Correlations between infant urinary buprenorphine/norbuprenorphine concentrations *vs.* length of hospital stay, duration of morphine treatment and morphine dose were calculated by using Pearson's two-tailed correlation test. Correlations between maternal buprenorphine dose on the day of delivery *vs.* length of the infants' hospital stay, infant urinary buprenorphine/norbuprenorphine concentrations and morphine dose were also calculated by using Pearson's two-tailed correlation test, as were correlations between Finnegan scores *vs.* length of the infants' hospital stay and duration of morphine treatment.

**RESULTS**

*Maternal welfare, morbidity and mortality 6–15 years after a pregnancy complicated by alcohol and substance abuse (Study I)*

During the study period (follow-up from the index pregnancy during 1992–2001 until the 31st of December 2007) 42 cases and 4 controls died (OR 38, 95% CI 14–108). Alcohol-related diseases were the cause of death in seven cases (OR 100, 95% CI 14–733), and 31 deaths among the cases and one among the controls were attributed to accidents or violence (OR 114, 95% CI 16–838).

Almost all cases (520 women, 99.2%) and controls (1753 women, 97.8%) had been hospitalized at least once. However, the mean length of hospital stay (10.3 *vs.* 4.4 days, respectively) was significantly longer among the cases ($p<0.001$). Selected primary diagnoses regarding in- and out-patient care are shown in Table 7. The cases had more out-patient visits than the controls (23 216 *vs.* 31 410, OR 2.7, 95% CI 2.7–2.8). The primary diagnoses in out-patient care were similar to those in in-patient care. In the category of diseases of the genitourinary system the cases more often had menstrual cycle aberrations (AOR 2.8, 95% CI 1.5–5.3) and urinary tract infections (AOR 2.1, 95% CI 1.4–3.1).

Almost all cases (521, 99.4%) and controls (1765, 98.5%) received basic reimbursement for at least one form of medication during the follow-up period. Reimbursement for antipsychotics (AOR 7.8, 95% CI 5.7–10.6), anxiolytics, hypnotics and sedatives (AOR 3.4, 95% CI 2.8–4.1), benzodiazepine derivatives (AOR 3.7, 95% CI 2.6–5.2), antidepressants (AOR 2.5, 95% CI 2.0–3.0), stimulants (AOR 10.4, 95% CI 2.8–39.1) and opioid analgesics (AOR 2.4, 95% CI 1.8–3.1) was more often allowed for cases.

Special reimbursement (any medication) was given to 141 (27.0%) cases and 334 (18.4%) controls (OR 1.4 95% CI 1.1–1.7).

**Table 7.** Selected primary diagnoses of in- and out-patient hospital care per 100 women (%) by ICD codes.

| Diagnosis | In-patient care | | | Out-patient care | | |
|---|---|---|---|---|---|---|
| | Cases (%) | Controls (%) | Adjusted OR (CI 95%) | Cases (%) | Controls (%) | Adjusted OR (CI 95%) |
| F00-F99 Mental and behavioural disorders, any | 46.0 | 3.6 | 8.8 (6.5-11.9) | 47.1 | 8.3 | 4.5 (3.5-5.6) |
| F10-F19 Mental and behavioural disorders due to psychoactive substance use | 30.5 | 0.9 | 33.9 (19.7-58.4) | 26.5 | 1.0 | 25.4 (14.9-43.3) |
| F10 Alcohol | 14.5 | 0.5 | 32.7 (16.4-65.4) | 12.4 | 0.6 | 22.4 (12.0-41.6) |
| F11 Opioids | 8.4 | 0.2 | 44.9 (13.5-148.8) | 8.0 | 0.1 | 58.2 (13.8-245.5) |
| F15 Amphetamine | 8.6 | 0.1 | 62.9 (14.7-269.8) | 5.5 | 0.2 | 28.5 (8.2-98.7) |
| F19 Multiple drugs | 5.7 | 0.2 | 39.9 (11.4-139.6) | 6.7 | 0.1 | 70.9 (16.4-307.0) |
| S02 Fractures of skull and facial bones | 1.7 | 0.2 | 9.3 (2.2-39.8) | 2.3 | 0.6 | 5.9 (2.4-14.6) |
| S82 Fracture of lower leg | 4.6 | 0.5 | 10.9 (4.8-24.9) | 4.8 | 0.6 | 8.3 (4.0-17.4) |
| T36-65 Poisoning by drugs, medicines and chemicals | 11.5 | 1.1 | 8.1 (4.7-14.0) | 18.1 | 1.6 | 10.4 (6.5-16.7) |
| B20-24 HIV infection | 1.3 | 0.1 | 15.6 (1.7-139.9) | 1.9 | 0.1 | 15.8 (3.1-79.9) |
| B18 Chronic viral hepatitis | 0.8 | 0.1 | 116.8 (15.4-887.6) | 11.1 | 0.2 | 77.1 (23.6-252.2) |
| A40-41 Septicaemia | 2.1 | 0.1 | 36.5 (7.4-180.6) | 2.1 | 0.2 | 12.4 (3.5-43.9) |
| O00-O03 Spontaneous abortions | 30.7 | 16.2 | 1.9 (1.5-2.5) | 14.1 | 12.6 | 1.6 (1.3-2.1) |
| O04 Induced abortions | 30.2 | 11.0 | 1.9 (1.5-2.5) | 25.2 | 10.8 | 1.6 (1.3.-2.1) |

Adjusted OR: adjusted by socioeconomic position and marital status.

The cases had 264 (50.4%) episodes and the controls 36 (2.0%) episodes of care in social welfare institutions (OR 17.0, 95% CI 11.9–24.3), most of these as a result of in-patient rehabilitation for alcohol or drug abuse (261 and 32, respectively, OR 19.0, 95% CI 13.0–27.6).

A minimum unemployment subsidy was granted to 329 (63.4%) patients and 397 (22.2%) controls (OR 2.1, 95% CI 1.8–2.5). Unemployment subsidies calculated on the basis of earlier

yearly earnings and paid by The Insurance Supervisory Authority were granted to 30 (5.8%) patients and 293 (16.4%) controls (OR 0.4, 95% CI 0.2–0.5).

Disability pensions were granted to 88 (16.8%) cases and 40 (2.2%) controls (OR 8.8, 95% CI 6.0–13.0). These pensions were granted for an indefinite period in 38 (7.3%) cases and 13 (0.7%) controls (OR 10.0, 95% CI 5.4–18.6). For a fixed-period, pensions were granted in 65 (12.4%) cases and 34 (1.9%) controls (OR 6.5, 95% CI 4.4–9.8).

Rehabilitation allowance was granted to 50 (9.5%) of the cases and 101 (5.6%) of the controls (OR 1.6, 95% CI 1.2–2.3). Vocational rehabilitation for persons with impaired working capacity was awarded to 17 (3.2%) of the cases and 20 (1.1%) of the controls (OR 2.9, 95% CI 1.5–5.5). Discretionary rehabilitation services were awarded to 39 (7.4%) cases and 87 (4.9%) controls (OR 1.5, 95% CI 1.0–2.2). Of the rehabilitation and disability pension diagnoses, 69% in the cases and 45% (one diagnosis missing) in the controls were related to mental and behavioural disorders.


*Risk factors for out-of-home custody child care among families with alcohol and substance abuse problems (Study II)*

During the 2- to 12-year (median 5.8) follow-up period 50% (95% CI 46–54%) of the children were in custody at some point (Figure 4). All children were followed up to the age of two years, and 236 (38%, 95% CI 34–42) of the children were at some point placed outside home by the CPS by two years of age. During the whole study period 128 (20%, 95% CI 17–23) children had been in custody for at least half of their lives. Table 8 shows the statistically significant connections between maternal characteristics and child's risk of placement in out-of-home care. Table 9 shows the statistically significant connections between perinatal factors and child's risk of placement in out-of-home care.

**Figure 4.** Proportion of children remaining in the home of their biological parents by child's age (in years) when first taken into custody (with 95% CI).
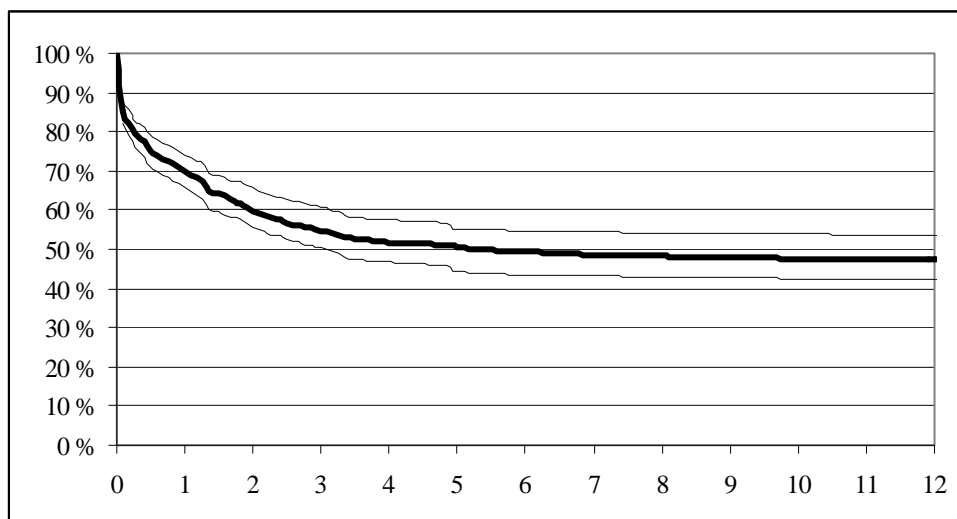


**Table 8.** Connection between maternal characteristics and child's risk of placement in out-of-home care.

| | Out-of-home care at less than 2 years | Out-of-home care more than half of life |
|---|---|---|
| | Risk ratio (95% CI) | Risk ratio (95% CI) |
| **Housing** | **p<0.001** | p=0.100 |
| Owner-occupied | 1.00 | 1.00 |
| Rental | **2.19 (1.03-4.56)** | 1.73 (0.67-4.47) |
| Institution | **3.42 (1.61-7.25)** | 2.23 (0.83-5.99) |
| Homeless | **2.71 (1.22-6.06)** | **3.00 (1.08-8.30)** |
| Unknown | 1.61 (0.70-3.67) | 1.65 (0.58-4.69) |
| **Education** | **p=0.030** | **p=0.018** |
| Graduated tertiary or secondary education | 1.00 | 1.00 |
| Vocational education | **1.65 (1.05-2.59)** | 1.91 (0.89-4.09) |
| Elementary school | **1.47 (1.01-2.13)** | **1.94 (1.04-3.62)** |
| Uncompleted elementary school | **2.27 (1.35-3.80)** | 2.47 (0.95-6.42) |
| Unknown | **1.64 (1.10-2.44)** | **2.46 (1.28-4.71)** |
| **Employment** | **p<0.001** | **p<0.001** |
| Working | 1.00 | 1.00 |
| Non-employed[1] | **2.06 (1.44-2.94)** | **3.38 (1.77-6.49)** |
| Unknown | **1.83 (1.10-3.04)** | **2.80 (1.19-6.61)** |

50

| | | |
|---|---|---|
| **Previous births** | p=0.102 | **p<0.001** |
| No | 1.00 | 1.00 |
| 1 | 1.16 (0.90-1.49) | **1.65 (1.11-2.43)** |
| 2 | **1.34 (1.02-1.77)** | **2.24 (1.49-3.36)** |
| 3 or more | 1.38 (0.99-1.92) | **2.56 (1.64-4.01)** |
| **Child taken into custody previously** | **p<0.001** | **p<0.001** |
| No | 1.00 | 1.00 |
| Yes | **1.80 (1.29-3.53)** | **2.20 (1.37-3.53)** |
| No information | 1.06 (0.53-1.35) | 0.84 (0.53-1.35) |
| **Mother taken into custody in her childhood** | **p<0.001** | **p=0.021** |
| No | 1.00 | 1.00 |
| Yes | **2.06 (1.54-2.77)** | **2.06 (1.19-3.54)** |
| Unknown | **1.51 (1.19-1.91)** | **1.86 (1.00-3.47)** |
| **Planning of present pregnancy** | **p=0.001** | **p=0.021** |
| No | 1.00 | 1.00 |
| Yes | **1.76 (1.25-2.48)** | **2.06 (1.19-3.54)** |
| Unknown | 1.44 (0.96-2.17) | 1.86 (1.00-3.47) |
| **Daily smoking during pregnancy** | **p<0.001** | **p<0.001** |
| No | 1.00 | 1.00 |
| Yes | **2.08 (1.33-3.26)** | **2.67 (1.29-5.50)** |
| Unknown | 1.15 (0.60-2.19) | 1.01 (0.34-3.01) |
| **Alcohol consumption before pregnancy** | p=0.146 | **p=0.022** |
| Daily | 1.21 (0.96-1.53) | **1.85 (1.29-2.64)** |
| Unknown | 0.94 (0.73-1.21) | 1.20 (0.81-1.78) |
| **Alcohol consumption during pregnancy** | p=0.176 | **p=0.002** |
| Daily | 1.10 (0.81-1.49) | **1.82 (1.21-2.74)** |
| Unknown | 0.85 (0.68-1.05) | 0.96 (0.68-1.36) |
| **Drug in urine sample during pregnancy** | **p=0.022** | **p<0.001** |
| No | **1.85 (1.29-2.64)** | 1.00 |
| Yes | 1.20 (0.81-1.78) | **2.15 (1.46-3.16)** |
| **Regular health care contact re. alcohol and/or substance abuse before pregnancy** | **p=0.045** | **p<0.001** |
| No | 1.00 | 1.00 |
| Yes | 1.10 (0.84-1.52) | **1.95 (1.40-2.73)** |
| **Mother's care re. alcohol and/or substance abuse after delivery** | **p<0.001** | **p<0.001** |
| No | 1.00 | 1.00 |

| | | |
|---|---|---|
| Out-patient care | **1.42 (1.14-1.77)** | **1.42 (1.05-1.52)** |
| In-patient care | **2.42 (1.87-3.11)** | **3.76 (1.91-7.40)** |
| **Partner with alcohol and/or substance abuse** | **p=0.002** | **p=0.001** |
| No | 1.00 | 1.00 |
| Yes | **1.91 (1.22-3.00)** | **1.97 (1.04-3.73)** |
| Unknown | 1.48 (0.93-2.36) | 1.25 (0.64-2.46) |

**Table 9.** Connection between perinatal factors and child's risk of placement in out-of-home care.

| | Out-of-home care at less than 2 years | Out-of-home care more than half of life |
|---|---|---|
| | Risk ratio (95% CI) | Risk ratio (95% CI) |
| **Neonatal abstinence symptoms** | **p=0.002** | **p<0.001** |
| No | 1.00 | 1.00 |
| Yes | **1.67 (1.29-2.16)** | **2.51 (1.74-3.62)** |
| Unknown | 0.87 (0.61-1.22) | 1.12 (0.69-1.79) |
| **Treatment for neonatal abstinence symptoms** | **p=0.007** | **p=0.010** |
| No | 1.00 | 1.00 |
| Yes | **2.03 (1.44-2.86)** | **2.52 (1.40-4.53)** |
| **Newborn's special care (surveillance unit of NICU)** | **p<0.001** | **p<0.001** |
| No | 1.00 | 1.00 |
| Yes | **1.59 (1.30-1.95)** | **2.29 (1.68-3.12)** |
| Unknown | 0.86 (0.59-1.26) | 0.83 (0.44-1.54) |
| **Newborn's delayed discharge (8 days or more)** | **p=0.009** | **p<0.001** |
| No | 1.00 | 1.00 |
| Yes | **1.59 (1.27-2.00)** | **2.16 (1.53-3.05)** |
| Unknown | 1.06 (0.76-1.46) | 1.54 (1.00-2.39) |
| **Newborn's delayed discharge (8 days or more)** | **p<0.001** | **p<0.001** |
| No | 1.00 | 1.00 |
| Yes | **2.15 (1.79-2.59)** | **2.87 (2.12-3.88)** |
| Unknown | 0.68 (0.43-1.08) | 0.72 (0.37-1.43) |

*Buprenorphine use during pregnancy; effects on maternal and neonatal outcome (Study III)*

Pregnancy

The clinical characteristics of the women and their pregnancies and neonates are shown in Table 10.

Of the women, 76% were able to decrease their daily buprenorphine dose during pregnancy. The buprenophine dose used by gestational age is shown in Figure 5. The misuse of buprenorphine by injecting could not be definitively ruled out in any of the women. A total of 65 (97%) women were smoking tobacco, 56 of these (84%) over 10 cigarettes daily. According to maternal urine samples, 13 foetuses (19%) were exposed to cannabis (8 in Group B, 3 in A, 2 in C), 6 (9%) to amphetamine (B=5, C=1), and 9 (13%) to opiates other than buprenorphine (B=4, C=4, A=1).

Fifty-one (76%) of the women were hepatitis C-positive. None was HIV-positive.

No foetal malformations were observed in ultrasound scans.

Comparisons between the previously defined subgroups are shown in Table 11. The women in Group A had no previous children.

Delivery

Data concerning delivery is shown in Table 10. The prematurity rate was comparable between the study groups. There were no differences between subgroups A, B and C as regards gestational age at delivery, mode of delivery, Apgar scores or umbilical artery pH (data not shown).

**Table 10.** Clinical characteristics of the subjects (n=67 pregnancies/deliveries/neonates). General figures from Finland in 2004 (source: National Research and Development Centre for Welfare and Health Register) are included, as available.

| | Subjects *n*=67 | Finland 2004 *n*=57 759 |
|---|---|---|
| | mean±SD (range) n (%) as appropriate | |
| Age (years) | 24.6±4.9 (18–40) | 30.0 |
| Cohabiting with the father of the child | 44 (66%) | 94% |
| Gestational age at delivery (weeks) | 39.2±1.6 (35–42) | 39.2 |
| Induction of labour | 30 (45%) | 16.7% |
| Vaginal delivery | 56 (84%) | 83% |
| Premature delivery (< 37 weeks of gestation) | 3 (4.5%) | 2942 (5.2%) |
| Mother's discharge from hospital (days after delivery) | 5.2±2.4 (2–15) | 3.4 |
| Mother discharged to another institution with or without the infant | 28 (42%) | |
| Weight (g) | 3180±503 (1460–4560) | 3512 |
| Length (cm) | 49.0±2.3 (43–54) | 50.1 |
| Head circumference (cm) | 34.2±1.3 (30-37) | 34.9 year 2005 |
| Apgar score at 1 min <6 | 2 (3%) | 5.4% |
| Umbilical artery pH <7.05 | 1 (1.5%) | 585 (1.0%) |
| Admission to neonatal care unit (NCU) | 61 (91%) | either NCU or NICU 10.6% |
| Admission to neonatal intensive care unit (NICU) | 1 (2%) | |
| Length of hospital stay (days) for infant | 18.8±14.7 (3-59) | 3.1 |
| Infant at home at the age of 7 days | 13 (19.4%) | 92.3% |
| Taken into care from maternity hospital | 7 (10%) | |

**Figure 5.** Buprenorphine doses (mg) used by gestational age, reported as mean.



**Mean buprenorphine dose**
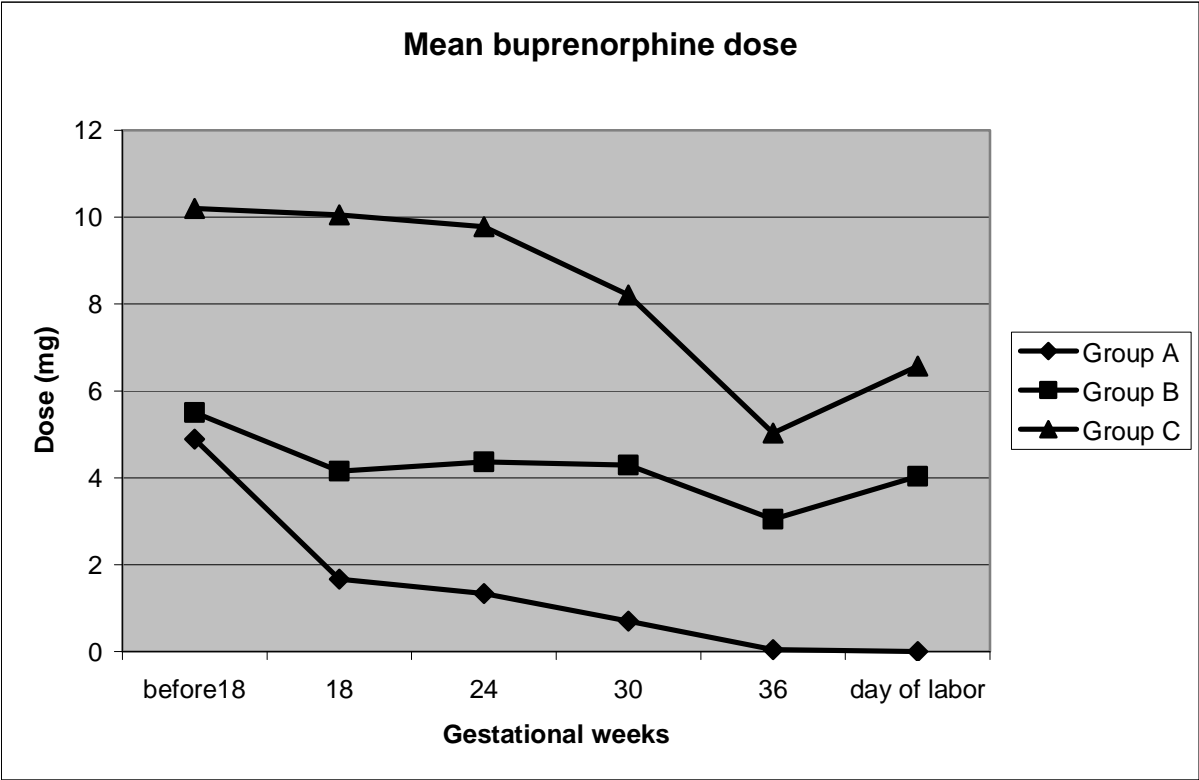
Neonates

Immediate outcome among the infants was uneventful as judged by Apgar scores and umbilical artery pH values (Table 10). The buprenorphine-exposed neonates were lighter than average in national statistics ($p$=0.001), more often needed extra surveillance after birth and stayed longer in hospital. In total, 18 (27%) infants had drug-free urine samples and no NAS. Of the urine samples, 45 (67%) were positive for BPR. NAS was diagnosed in 51 (76%) infants, and 38 (57%) needed morphine medication for it. Medication was started at 2.5 days of age (median, range 2–5 days). There were two cases of sudden infant death syndrome, one at the age of 2.5 months and the other at the age of 5 months.

**Table 11.** Clinical characteristics and misuse history of the three subgroups: those who managed to achieve abstinence (group A), those who did not commit themselves to the treatment (Group B), and those who committed themselves to treatment but did not achieve abstinence (Group C).

| | Group A Abstinence achieved $n$=9 (%) | $p$ between A and B | Group B Poor commitment $n$=37 (%) | $p$ between B and C | Group C Sufficient commitment $n$=21 (%) | $p$ between A and C |
|---|---|---|---|---|---|---|
| Age (mean, SD) | 21.8±3.31 | NS | 24.8±5.58 | 0.02 | 25.4±3.93 | NS |
| Age when any substance misuse started | 13.3 | NS | 13.4 | NS | 13.8 | NS |
| Duration (years) of use of buprenorphine | 2.8 | NS | 3.2 | NS | 3.6 | NS |
| Registered before 15 weeks of gestation | 9 (100%) | 0.0062 | 18 (49%) | NS | 16 (76%) | NS |
| Dose of buprenorphine on the day of giving birth (mg, mean) | 0 | | 4.0* | 0.03 | 6.6 | |
| Delivery before 37 weeks | 0 | | 2 | NS | 1 | |
| SGA** | 0 | | 5 | NS | 2 | |
| Infant's urine sample positive for buprenorphine*** | 0 | | 24 (67%)* | 0.0021 | 21 (100%) | |
| NAS | 2 (22%) | 0.0016 | 30 (81%) | 0.0413 | 21 (100%) | <0.001 |
| Morphine replacement therapy for NAS | 2 (22%) | 0.0491 | 18 (49%) | NS | 18 (86%) | 0.0017 |
| Infant's discharge from hospital (days, mean) | 11.6 | NS | 15.7 | 0.0012 | 28.1 | NS |
| SIDS**** | 0 | | 1 | | 1 | |

*data missing from one subject (born in another hospital)

**SGA according to Finnish foetal growth curves (Pihkala et al. 1989)

***benzodiazepine-positive: 1 in group A, 11 in group B and 1 in group C; two amphetamine-positives in group B

****the national incidence of SIDS in 2004 was 0.19/1,000 live births (Statistics Finland, www.tilastokeskus.fi)

*Prenatal buprenorphine exposure: effects on biochemical markers of hypoxia and early neonatal outcome (Study IV)*

All the newborns were born in good condition as defined by Apgar scores and cord pH values (data not shown).

No significant differences were seen in cord serum EPO levels between the buprenorphine-exposed group, substance-abusing controls and unexposed controls (Figure 6). In all study groups, a negative correlation (Spearman's correlation ($r=0.285$) existed between umbilical artery pH and EPO levels, and a positive correlation ($r=0.455$) between EPO levels and gestational age. No correlation existed between EPO levels and birth weight.

Serum concentrations of cTnT were lower among the substance-abusing controls ($p<0.0001$) (Figure 7). There were no correlations between cTnT levels and birth weight, pH or gestational age.

S100 levels between the study groups did not differ significantly (Figure 8). No correlation was seen between S100 levels and birth weight, pH or gestational age.

In all infants together and in each group separately, no correlations were found between cord serum concentrations of EPO, cTnT and S100.
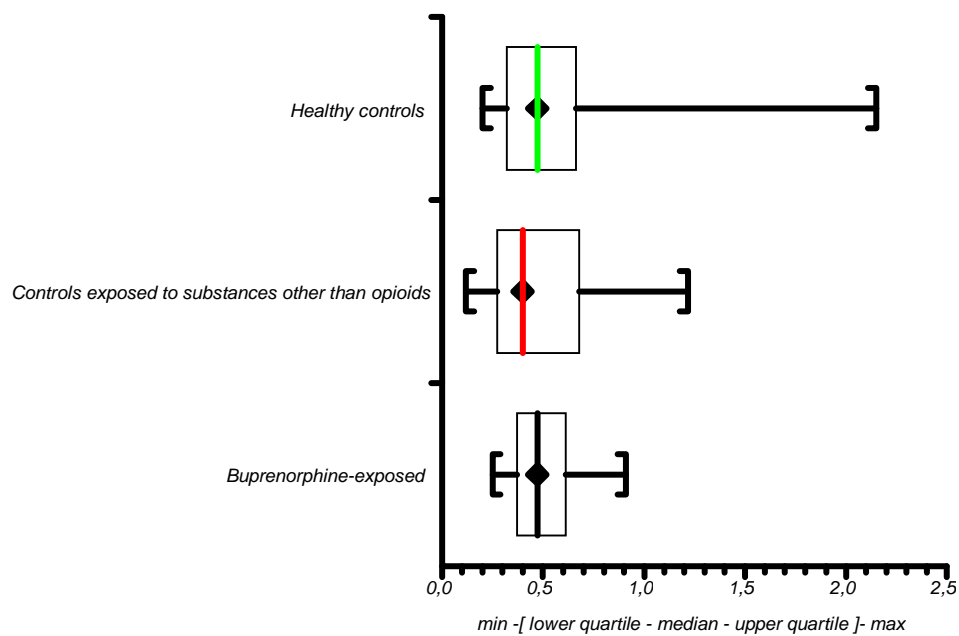
**Figure 6.** Erythropoietin levels (U/L) in cord blood in the three different groups.



*min -[ lower quartile - median - upper quartile ]- max*
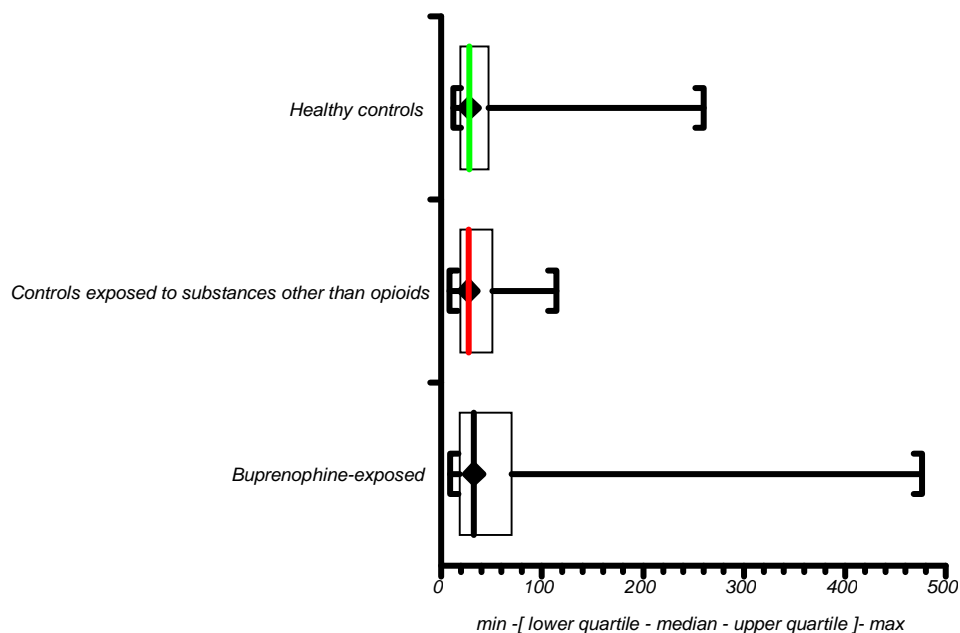
**Figure 7.** Cardiac troponin T levels (U/L) in cord blood in the three different groups.
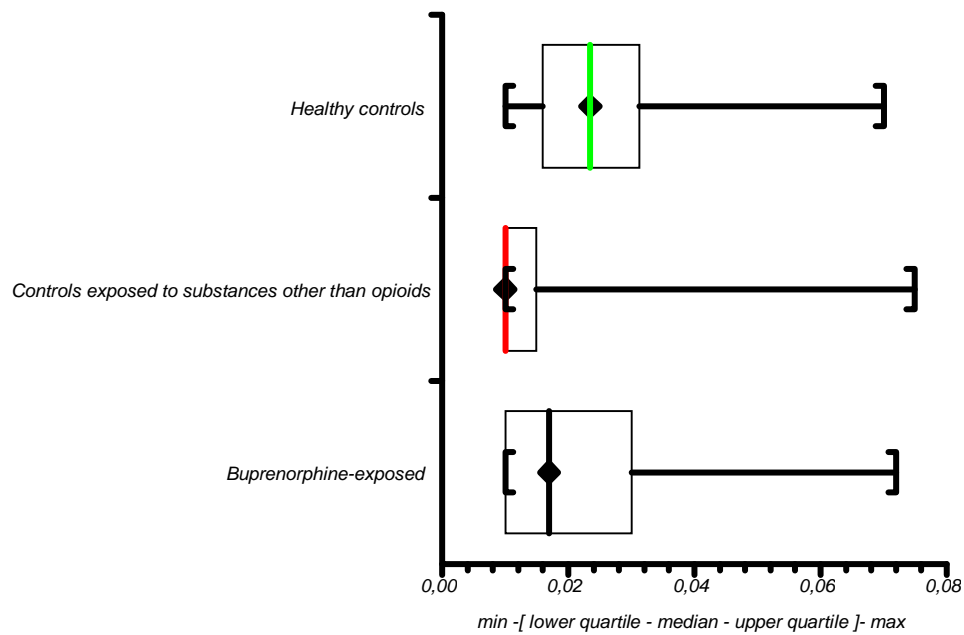


**Figure 8.** S100 levels (mg/L) in cord blood in the three different groups.

*Aspects of neonatal abstinence syndrome of 58 infants with positive urinary buprenorphine at birth (Study V)*

In total, 46 (79%) infants had NAS and 38 (66%) required morphine replacement therapy for it.

The duration of morphine treatment ($n$=38) was 20±10 (SD) days (range 7–48 days). The mean age at the beginning of morphine treatment was 2.4±1.1 days (1–6 days). The length of hospital stay for the infants ($n$=58) was 25±19 days (3–125 days).

Both a high mean and a single high Finnegan score on the day of birth (day 0) predicted the length of morphine treatment (p<0.01 and p<0.05, respectively). High mean Finnegan scores on the first (day 1) and second days (day 2) of life correlated with the length of hospital stay ($p$<0.05).

The infants of mothers who reported having used intravenous buprenorphine had higher single and mean Finnegan scores on day 1 than those of the mothers who reported using sublingual BPR (10.6±4.3 (SD) *vs.* 7.5±2.9, $p$=0.003; 6.8±2.7 *vs.* 4.7±2.1, $p$=0.002, respectively).

The mean morphine dose of the infants whose mothers smoked more than 10 cigarettes daily ($n$=25, 43%) daily was significantly higher at the beginning (0.38±0.1 *vs.* 0.30±0.1 mg/kg/day, $p$=0.042) and remained significantly higher during the first and second days of treatment (0.38±0.1 *vs.* 0.31±0.1 mg/kg/day, $p$=0.038; 0.38±0.1 *vs.* 0.29±0.1 mg/kg/day, $p$=0.008, respectively).

The highest concentrations of infant urinary NBUP during the three days (days 0–2) correlated significantly with the length of hospital stay (Pearson's correlation coefficient ($r$=0.57, $p$<0.005) and duration of morphine treatment ($r$=0.46, $p$<0.008). The infants' highest urinary BPR concentrations during days 0–2 did not correlate with the length of hospital stay ($r$=0.15, $p$=0.3) or duration of morphine treatment ($r$=0.24, $p$=0.9).

The BPR dose on day 0 administered to the mothers correlated with the length of the infants' hospital stay ($r$=0.48, $p$=0.002) as well as with the morphine dose at the beginning of morphine treatment ($r$=0.49, $p$=0.049), but not with the infants' urinary BPR or NBUP concentrations on any day.

The infants who had benzodiazepines in their urine had a significantly lower mean Finnegan score on the first day of life ($p$=0.011) compared with those without benzodiazepines in the urine. Aspects of NAS are shown in Table 12, in which the infants of compliant and non-compliant mothers are compared.

A mother with poorly controlled diabetes mellitus type I, with no antenatal care, delivered a premature infant who had tetralogy of Fallot and severe periventricular leucomalacia. Microotia, hernia inguinalis and a muscular ventricular septal defect (VSD) were seen in another infant whose mother had compliance problems.

In total, 19 (33%) infants were placed in foster care.

**Table 12.** Aspects of NAS regarding the infants of compliant and non-compliant mothers.

|  | Infants of the compliant mothers $n = 28$ (%) mean ± SD (range) | Infants of the non-compliant mothers $n = 30$ mean ± SD (range) | Statistical significance $p$ |
|---|---|---|---|
| Morphine replacement therapy for NAS | 25 (89%) | 13 (43%) | < 0.001 |
| Duration of morphine treatment (days) | 18 ± 12 (7–48) | 10 ± 12 (7–42) | 0.009 |
| Length of hospital stay | 28 ± 13 (4–57) | 19 ± 13 (3–125) | 0.012 |
| Benzodiazepine- positive urine sample | 9 (32%) | 10 (33%) | NS |
| Infant discharged home | 8 (29%) | 3 (10%) | NS |

## DISCUSSION

*Importance of the present study*

To the best of our knowledge there is no published data on maternal health in the long run after a substance abuse problem during pregnancy. Our study provides a comprehensive overview of the long-term consequences of this issue, including the need of out-home-care as part of child-protection services in a fairly large sample and over a long follow-up time. This was possible because of the well-kept mandatory nationwide health and social welfare registers, which have been shown to have good coverage, missing only emigrants (*Gissler et al. 2004b*).

Overall, the published data on the pregnancies of women with substance-abuse problems in the Nordic health care system (*Kakko et al. 2008*), where high-quality antenatal care is easily accessible and affordable, is limited. Our study produced "real life" data from Finland in this setting.

The correlation between the severity of NAS and the neonatal urinary concentration of norbuprenorphine in the first three days of life is a novel finding. This is also the first study combining standard clinical parameters of perinatal wellbeing (cord blood pH, Apgar score, admission to a NICU) and three biochemical markers of perinatal hypoxia (EPO, TnT, S100) in newborns exposed prenatally to opioids.

*Study limitations*

As regards the retrospective register studies the possible inconsistent and incomplete reporting and data recording as well as the need to keep the assessed parameters simple is problematic. The variance in the follow-up time of the mothers and their offspring is a limitation, but it allowed us to have a fairly large sample size. In Study I only primary diagnoses in connection with in- and out-patient care were assessed, since the quality of secondary diagnoses was shown to be compromised in the registries used (*Gissler et al. 2004b*, *Aro et al. 1990*). In the medication purchase part of Study I the end point was the dispensation of drugs, not knowing if the drugs were actually taken and by whom.

Because of the tendency towards under-reporting of substance abuse during pregnancy (*Lester et al. 2001*, *Göransson et al. 2004*) we may not have identified all the eligible candidates for Study III. Nevertheless, it is likely that we found the majority of heavy BPR users for our prospective study, as we prospectively followed up 36 of the 38 infants needing morphine replacement therapy for NAS in Study V. The relatively small number of study

subjects in the prospective studies (III, IV and V) is a limitation, although the published data in this setting is scarce (*Jones et al. 2010*, *Jones et al. 2008*, *Winklbaur et al. 2008*).

All the buprenorphine-using mothers in Studies III, IV and V could be suspected of under-reporting additional substance abuse, including the use of street BPR. This issue comes up regularly in studies of substance abuse problems (*Auriacombe et al. 2004*, *Kakko et al. 2008*, *Jones et al. 2010*, *McCarthy et al. 2008*, *Simojoki et al. 2008*).

More appropriate control populations in Study IV would have been non-smoking BPR users or methadone users, but such control groups were not available, since all but one BPR user smoked and the number of methadone-maintained pregnant women was less than five during the study period. In addition, the healthy controls could have been smokers, but then the probability of them misusing additional substances may have been higher.

As regards Study V the maternal and neonatal urine samples were not obtained at the same hour after delivery as a result of many practical reasons, including normal variability in the timing of the first voiding of the neonate (*Vuohelainen et al. 2007*). Neither were urinary BPR and NBUP concentrations corrected for urinary creatinine concentrations to reduce variability in the concentrations due to different states of hydration (*Kacinko et al. 2009*). Urinary BPR and NBUP concentrations were measured in semi-quantitative analyses with many maternal samples exceeding the upper limit of detection, which could have confounded the correlation between NAS and the highest BPR and NBUP concentrations.

As health care systems differ in different countries, as do the characteristics of women who have substance abuse problems (*Unger et al. 2010*), our results may not be applicable in different populations.


*Maternal long-term outcome after a substance abuse problem during pregnancy*

Studies on parturients have shown that they are healthy and their mortality rate is lower than the expected age-specific mortality rate (*Gissler et al. 2004a*, *Jocums et al. 1998*). Women with infants also tend to take better care of their health and reduce risk-taking, at least if the pregnancy is intended (*Dott et al. 2010*). Whether this is true in this special setting is not known – the mortality rate in Study I was unexpectedly high, 38-fold greater compared with the controls.

An increased mortality rate in women with moderate-to-heavy alcohol consumption has been established in earlier studies (*Bradley et al. 1998*, *Fuchs et al. 1995*). For example, binge drinking is strongly linked to intentional and unintentional injuries, aggression and mortality (*Rehm et al. 2009*, *Rehm et al. 2006*, *Cherpitel et al. 2008*, *Rehm et al. 2003*, *Rehm et al.*

*2007a*), and illicit substance abuse is linked to accidents and suicide (*Rehm et al. 2006*, *Cherpitel et al. 2008*, *Mertens et al. 2005*, *Popova et al. 2007*, *Adrian et al. 2007*, *Adrian et al. 2003*, *Mertens et al. 2003*), but these studies did not take into account the modifying effect of motherhood. The 114-fold greater risk of violent and accidental death and the 100-fold greater risk of death from alcohol-related diseases seen in our study most likely reflect the fact that these women were not able to quit their problematic alcohol and/or substance use while having young children. We do not know if these women received appropriate addiction treatment. As the number of opioid-using women was small in this study, the possible life-saving effect of opioid substitution treatment could not be established. In addition, a frequently involved intimate partner with a substance abuse problem may have contributed to the risk of violent death (*Chermack et al. 2010*). Possibly, insufficient social support and networking may have led to exhaustion and despair of the mother.

In general, a high intake of alcohol is associated with severe morbidity, lower productivity at work and frequent social and family problems (*Rehm et al. 2006*, *Mertens et al. 2005*, *Lupton et al. 2004*, *Rehm et al. 2007b*). All of these issues were present in our study as well. Co-morbidity of alcohol and drug abusers has been reported as triple when compared with all hospital patients in general (*Adrian et al. 2007*). Chronic diseases and causes-of-death such as liver cirrhosis, depression, cancers and cardiovascular diseases have been attributed to alcohol misuse (*Rehm et al. 2009*, *Rehm et al. 2006*, *Cherpitel et al. 2008*, *Mertens et al. 2005*, *Mertens et al. 2003*). We did not observe higher cancer or cardiovascular disease rates among our cases. This may be related to the relatively young age of these women – mostly premenopausal – and the relatively short follow-up period. Nonetheless, the cases more often purchased medication for cardiovascular system diseases compared with the controls. One explanation could be that the medication was used to control withdrawal symptoms, e.g. high blood pressure and palpitations.

Mental health problems are commonly linked to substance abuse (*Rehm et al. 2006*, *Mertens et al. 2005*, *Popova et al. 2007*, *Adrian et al. 2007*, *Adrian et al. 2003*, *Mertens et al. 2003*). Consistently with previous studies, nearly half of the cases had in-patient (46%) and out-patient (47%) care episodes for mental and behavioural disorders. They also significantly more often received reimbursements for drugs in both basic and special refund categories for psychiatric disorders, e.g. antipsychotics, anxiolytics and antidepressants. Anxiolytics, hypnotics and sedatives were purchased more often by cases compared with controls. These medication classes consist mainly of different kinds of benzodiazepine, which commonly form part of a polysubstance abuse pattern. They are inappropriately prescribed for many

patients for long-term use, including patients with co-morbid alcohol and substance abuse (*Ashton 2005*, *Ashton 1989*). The validity of excess prescribing of opioid painkillers to cases can also be questioned in the absence of an excess of cancer diagnoses (*Skurtveit et al. 2010*). Unfortunately we were not able to assess the non-medical use of prescribed drugs in this study. Overall, the finding of common use of prescribed drugs among cases reflects their urgent need for professional help.

Diagnoses of infectious diseases are commonly linked to substance abuse (*Rehm et al. 2006*, *Mertens et al. 2005*, *Popova et al. 2007*, *Adrian et al. 2007*, *Adrian et al. 2003*, *Mertens et al. 2003*) and were overrepresented among our cases compared with controls as regards in-patient as well as out-patient care. Chronic use of alcohol suppresses the immune system, increasing the risk of a variety of infections (*Szabo 1999*, *Szabo et al. 2009*). In addition to the infection risks related to injected drug use, such as risks of HIV, hepatitis B and C, endocarditis, septicaemia and cutaneous infections (*Gordon et al. 2005*, *Cherubin et al. 1993*), this may reflect increased susceptibility in general, with poor nutritional habits and hygiene.

Women with a history of regular alcohol and substance use are more likely to seek gynaecological care for chronic and acute medical problems than women with no such history (*Gupman et al. 2002*). Our cases had more out-patient visits for menstrual cycle aberrations. This is in accordance with the results of previous studies indicating, for example, that opiate use is associated with irregular menses, oligomenorrhoea, and amenorrhoea (*Harlow et al. 2003*). Women with injection drug abuse exhibit a particularly high prevalence of risky sexual behaviour (*Kivelä et al. 2009*, *Cook et al. 2006*), human papilloma virus infection and bacterial vaginosis (*Plitt et al. 2007*, *Plitt et al. 2005*). Our cases displayed other issues affecting reproductive health as well. They had more spontaneous and induced abortions. The type of substance used and the pattern of use may contribute to the risk of miscarriage (*Bradley et al. 1998*, *Lacroix et al. 2004*, *Strandberg-Larsen et al. 2008*, *Ness et al. 1999*, *Kline et al. 1991*). In the literature, alcohol and/or substance abuse have been associated with a variety of pregnancy complications, e.g. intrauterine growth retardation, major congenital anomalies, placental abruption and antenatal haemorrhage (*Bell et al. 2008*, *Lupton et al. 2004*, *Tikkanen et al. 2006*, *Cox et al. 2008*, *Okah et al. 2005*, *Smith et al. 2006*). However, the cases displayed less in-patient care for pregnancy and childbirth compared with the controls. This may have been a result of ambivalence towards pregnancy which prevented them seeking professional help, or it may be related to our extensive easy access antenatal care system in Finland (*Raatikainen et al. 2007*). As only 2.9% of the cases (and 1.2% of the

controls) had insufficient antenatal care (defined as attending less than five antenatal care visits), the majority of these women were identified early in the index pregnancy, and were offered a wide spectrum of treatment and psychosocial support during the antenatal period. Two thirds of them responded to this kind of antenatal care (*Halmesmäki 1988*, *Kukko et al. 1999*).

Disability pensions and rehabilitation awarded by the Social Insurance Institution (SII) are always related to medical conditions, and there was a high prevalence of both among our cases. In our study a disability pension was awarded to 16.8% of the cases, reflecting the severity of their medical condition. The corresponding figure for the controls was 2.2% (OR 8.8, 95% CI 6.0–13.0). We were able to analyze only pensions granted by the SII. On the other hand this was also the interest of the study, as these pensions are granted to persons with no or a minor working history. For example, in 2007, the SII paid 87% of all pensions granted because of mental disorders in women aged 16–49, and in Finland in 2006, 1.8% of women aged 15–45 were on disability pension (*Social Insurance Institution in Finland 2008*). This shows that our numbers of pensions were very representative, as 69% of pensions granted to our cases were a result of mental and behavioural disorders.

The unemployment rate was over two times higher among cases than controls. As expected, the number of persons receiving unemployment subsidies granted by the SII (granted for persons with no or minor working history) was much higher among the cases. This probably reflects their early marginalization, ending up on rehabilitation subsidy or disability pension.

The prognosis of these women is poor compared with women without significant alcohol and/or substance misuse problems identified during pregnancy, regardless of their socioeconomic or marital status.

*Out-of-home custody child care*

Maternal substance abuse represents a risk as regards their children's wellbeing (*Topley et al. 2008*, *Macrory et al. 2007*, *Hans 2002*). There are differences between countries and within Finland in the criteria and management of child protection services (CPS) (*MacMahon 1997*, *Ondersma et al. 2001*) in substance-abusing populations, and in our area social problems were pronounced among the study populations of Studies II, III and V. In Study III, seven (10%) of the neonates were taken into care from the maternity hospital and in Study V, in total 19 (33%) infants were placed in foster care. This is quite the opposite of the situation reported in a French study on opioid-dependent women, where only 4% were placed in foster care from the maternity hospital (*Lejeune et al. 2006*). In a British study on opioid users the number was

9.5% in an area with marked social deprivation (*Dryden et al. 2009*). Predictably, the short-term social outcome in our study tended to be better in the compliant group than in the non-compliant group. No infant requiring medication for NAS born to a non-compliant mother was discharged home, in accordance with the results of an Australian study reporting that infants of mothers using illicit drugs were more likely to enter foster care than infants of mothers who were compliant with a methadone programme (*McGlade et al. 2009*).

Several pre- and perinatal factors were associated with later offspring out-of-home care as a part of CPS in our high-risk population (Study V). Daily maternal alcohol use both before and during pregnancy was significantly associated with long-term but not early custody of the child. This seems illogical, but it may be a result of significant underreporting of alcohol use. This was suspected in the whole cohort (*Sarkola et al. 2000*), as the number of drinks reported to have been taken was relatively small, and the amount of missing data was relatively high both before and during pregnancy. Earlier investigators have reported an association between parental/maternal alcohol use and child maltreatment, although the frequency of prenatal alcohol use was not defined (*Sidebotham et al. 2001*, *Kotch et al. 1999*). In this regard our finding on daily alcohol use and risk of out-of-home care as part of CPS is novel, although the association may be linked to drinking habits (i.e. binge-drinking) in our society (*Mäkelä et al. 2001*).

During the study period (Study II) opioid abuse was rare and this may explain the lack of an association with out-of-home care as part of CPS. However, positive results in prenatal urine toxicology screening, regular health care contact for substance abuse problems, maternal care in connection with substance abuse after delivery and a partner with a substance abuse problem were associated significantly with out-of-home care, consistent with the results of previous studies on prenatal cocaine exposure (*Leventhal et al. 1997*, *Neuspiel et al. 1993*) and children ending up in foster care (*MacMahon 1997*, *Takayama et al. 1998*).

Daily smoking during pregnancy was common in our study population (78%) and a relatively strong indicator of later custody. We could identify only a few earlier studies addressing smoking during pregnancy and its association with infant maltreatment (*Wu et al. 2004*) and foster care (*Kalland et al. 2006*), but in those studies no information on frequency of prenatal smoking was provided. Furthermore, daily smoking during pregnancy could be a marker of a broader disposition of dependence which might be a significant risk factor as regards subsequent out-of-home care.

Well-known risk factors associated with child maltreatment include inadequate housing, low level of maternal education, unemployment, a large number of previous children, earlier

involvement of CPS among family members and unplanned pregnancy (*MacMahon 1997*, *Sidebotham et al. 2006*, *Sidebotham et al. 2001*, *Kotch et al. 1999*). The same risk factors were identified in our material. Predictably, the highest risk ratios as regards both early- and long- term custody were associated with maternal characteristics linked to substance abuse such as in-patient substance abuse treatment after delivery, homelessness or being institutionalised, and not being in work.

Some earlier investigators have identified an association between child maltreatment and neonatal characteristics such as low birth weight and/or prematurity (*Wu et al. 2004*, *Sidebotham et al. 2003*), while studies focusing on substance-abusing populations have not (*Leventhal et al. 1997*, *Neuspiel et al. 1993*). In our study these neonatal characteristics were not related to the risk of later out-of-home care. We found, however, associations between early- and long-term custody and neonatal factors more directly related to alcohol and substance abuse, such as NAS and its treatment, intensified postnatal surveillance and/or treatment in a NICU, delayed discharge of mother and newborn from hospital and the child not discharged with the mother. Substance abuse and the related lifestyle may lead to excess perinatal morbidity, and greater involvement of CPS occurs in connection with children with disabilities, who are at a greater risk of being maltreated (*Hibbard et al. 2007*).

The status of the mother-child dyad at the time of out-of-home care decisions was not known, as the national CPS register does not contain data on specific reasons for out-of-home care decisions. There are no uniform criteria for such decisions, but each one should be based on clear evidence of significant child maltreatment provided by multiple sources.


*Buprenorphine and pregnancy outcome*

Buprenorphine has been described as being well-tolerated by both mother and foetus (*Johnson et al. 2001*, *Schindler et al. 2003*, *Jones et al. 2010*, *Lacroix et al. 2004*, *Lejeune et al. 2006*, *Johnson et al. 2003*, *Fischer et al. 2000*). This was the case in our study also, since we did not find any major pregnancy complications, birth defects or increase in perinatal mortality (Study III).

The BPR doses and patterns of use were recorded as self-reported. Under-reporting of substance abuse by the mothers was suspected (Lester et al. 2001), in addition to what the weekly urine drug screens revealed (Appendix 2). Top-up use of BPR while on BMT is hardly discernible because of the high inter-individual variability in the serum levels of BPR at the same BPR dose (*Kuhlman et al. 1996*, *Kuhlman et al. 1998*).

We encouraged decreasing doses, or even withdrawal, which seemed not to harm the foetus, in Study III. The success of the mothers in the compliant group in reducing their use of BPR prior to delivery varied considerably: some of the mothers were too eager to reduce their BPR dose, which resulted in relapse or necessitated dose increase. This may reflect the severity of their addiction, since some of them had never sought help for their addiction problem before, as well as to some extent the failure of our support system at the beginning of learning curve. The BPR dose used by the non-compliant group was lower on the day of labour compared with that in the compliant group (Figure 5). The possible effort to wean before labour to avoid child welfare issues may have kept the doses smaller. It is also probable that the non-compliant group used BPR in more cost-effective way, intravenously (*Alho et al. 2007a*, *Kuhlman et al. 1996*), because of the relatively high street price and varying availability.

In Study III the mean birth weight after prenatal BPR exposure was lower compared with data in the national statistics (*Stakes 2005*) although it was within the national growth curves (*Pihkala et al. 1989*). Excessive smoking partly explains the weight difference (*Shankaran et al. 2004*, *Bernstein et al. 2005*), as 97% of our patients smoked tobacco. The dose-related effect of smoking on birth weight has also been recognised in opioid-dependent women (*Winklbaur et al. 2009*). Opioid use as such has been related to low birth weight and a symmetric type of growth restriction, although the causality has been controversial (*Kaltenbach et al. 1998*, *Kandall et al. 1999*, *Shankaran et al. 2004*, *Hendrix et al. 2008*, *Bada et al. 2002b*). In Study V the mean weight and head circumference were below average values (-0.7 SD and -0.5 SD, respectively (*Pihkala et al. 1989*). In an Australian study growth restriction in pregnancies of opioid users was related to low maternal body mass index (BMI) rather than to opioid dosing or nicotine use. It was speculated that low BMI may be an indirect marker of other genetic, nutritional and/or social determinants of intrauterine growth restriction (*Liu et al. 2010*). In animal studies BPR administration has lowered maternal weight gain. This anorexic effect of opioids on maternal nutrition is suggested to be one mechanism of action behind impaired foetal growth (*Hutchings et al. 1995*). In our study seven infants with birth weight less than mean -2 SD (*Pihkala et al. 1989*) were born to the non-detoxified women, and five of these to the non-compliant women. In an American study on treatment compliance with drug use intervention therapy sessions provided at the prenatal care clinic, the compliant mothers gave birth to infants with higher birth weights than non-compliant mothers (*Jones et al. 2002*), and the most marked growth restriction related to opiate use has been in connection with additional polydrug use (*Gillogley et al. 1990*). This emphasizes the importance of a stable lifestyle achieved by way of OMT with no additional

substance abuse (*Lacroix et al. 2004*, *Brown et al. 1998*, *Lejeune et al. 2006*, *McCarthy et al. 2005*). Unfortunately, this was achieved by less than half of our mothers.

The prematurity rate in our study (4.5%) was similar to the national figure (5.2%)(*Stakes 2005*). In Swedish and French prospective studies concerning pregnancy and opioid dependence prematurity rates have been 8.5% (*Kakko et al. 2008*) and 9–10% (*Gourarier et al. 2001*, *Lejeune et al. 2006*), respectively, while their national rates were under 6.6% in 2004 (*Europeristat 2004*). In an American study, supplementing while on MMT increased the risk of premature delivery (*Almario et al. 2009*). In addition, differences in sociodemographics, lifestyle and ethnicity (*Goldenberg et al. 2008*) of substance-abusing populations in different cultures influence the prematurity rate. Our low prematurity rate may reflect the success of our comprehensive care model (*El-Mohandes et al. 2003*, *Sweeney et al. 2000*, *Brown et al. 1998*, *Kukko et al. 1999*). The few cases of successful supervised BPR detoxification were not related to prematurity (*Comer et al. 2004*).

In the literature BPR does not seem to have the potential to cause major birth defects in humans (*Marquet et al. 1997*, *Johnson et al. 2003*), although the published material is scarce. The anomalies seen in our patients were confounded by additional illnesses and polydrug use (Study V). In the present study, it was not possible to assess the potential of prenatal BPR exposure to produce neurobehavioural deficits (*Bandstra et al. 2010*).

In animal studies, there have been difficulties in parturition speculated to be caused by the sedative effect of opiates (*European Medecines Agency 2009*). We did not encounter this, since the vaginal delivery rate (84%) was similar (83%) to that in the national statistics (*Stakes 2005*) despite the high induction rate (45%). We were liberal in inducing labour near term because of maternal exhaustion and anxiety, especially after successful diminishment of BPR dose at the end of pregnancy.

In our study two (3%) infants died. Their deaths were diagnosed as sudden infant death syndrome (SIDS) at autopsy. The national SIDS incidence was 0.019% in 2004 (0.025% in 2009). Both infants were born to smokers with compliance problems. Maternal smoking is one of the known risk factors of SIDS in epidemiological studies (*Moon et al. 2007*). In earlier studies an association between antenatal opioid use and an elevated risk of SIDS has been suspected (*Burns et al. 2010*, *Kandall et al. 1993*, *Kahlert et al. 2007*), but this has not been shown in large epidemiological studies. Several mechanisms behind SIDS have been speculated, such as altered autonomous respiratory and awakening responses to hypoxia (*Moon et al. 2007*). Since antenatally used opioids impair responses to ventilation challenges

and promote sleep apnoea in animals and infants (*Suguihara et al. 1991*, *Wallisch et al. 2010*), there may be an association between opioids and an increased risk of SIDS.

*Buprenorphine and biochemical markers of hypoxia (EPO, cTnT, S100)*

All the study infants were born in good condition, with no perinatal asphyxia as defined by standard clinical parameters: 5-minute Apgar score, cord pH value and need for intubation immediately after delivery (*Ruth et al. 1988*, *Thorngren-Jerneck et al. 2001*, *Ingemarsson et al. 1997*).

Ten of our subjects used additional substances according to the results of urinary drug screening tests, mostly benzodiazepines. It is possible that in addition to BPR-related ventilation depression, an additive or synergistic effect occurs between BPR and these additional substances to depress maternal ventilation. Misuse of BPR intravenously (*Simojoki et al. 2008*) may also cause hypoxic episodes by changing the buprenorphine/ norbuprenorphine ratio in plasma (*Kuhlman et al. 1996*). In an animal study, NBUP, the active metabolite of BPR, induced respiratory depression which was prevented by BPR (*Megarbane et al. 2010*).

We found no signs of hypoxia as defined by high cord blood EPO levels in infants exposed to BPR.

All our BPR users were smoking over 5 cigarettes per day during the second and third trimesters, but so were 81% of the substance-abusing controls and 8% of the healthy controls. In some studies smoking has been associated with significantly elevated EPO levels regardless of foetal growth (*Jazayeri et al. 1998*, *Gruslin et al. 2000*), but this was not the case in Study IV.

High cTnT concentrations indicate myocardial cell damage (*Clark et al. 2001*), but such concentrations were not seen in our subjects. The reason for this could be connected to our co-operative although drug-addicted study population with no major pregnancy or labour complications. There is, however, a case report of a severely opioid- and benzodiazepine-exposed preterm newborn whose drug withdrawal after birth resulted in myocardial ischaemia and significantly elevated levels of cardiac enzymes (*Biswas et al. 2005*). Whether this complication could emerge in association with antenatal drug withdrawal by the mother is not known, as none of our BPR-using women tried to undergo detoxification immediately before labour. Despite the fact that some of the substances abused may be cardio-toxic (*Butany et al. 2009*, *Pennings et al. 2002*), cTnT levels were lower in the substance-abusing controls than in the BPR-users.

Although the infants in this study were born in good condition and had normal S100 levels, 26/27 of the BPR-exposed subjects developed NAS. The clinical picture of NAS mimics hypoxic-ischaemic encephalopathy. Thus, we can only say that despite subsequent NAS, the CNS parameter S100 showed no elevation in these newborns. In a small series of neonates exposed prenatally to BPR, no hypoxic-ischaemic brain changes were seen in brain magnetic resonance imaging (*Kahila et al. 2007*).

The heterogeneous nature of the substances used by our substance-abusing controls limits the biochemical value of this work, but the control group with substance abuse potentially counteracts the confounding effect of substance abuse-related lifestyle on pregnancy outcome.


*Buprenorphine and neonatal abstinence syndrome (NAS)*

Neonatal abstinence syndrome is the main problem in the short term that is associated with BPR use in pregnancy (*Johnson et al. 2001*, *Schindler et al. 2003*, *Jones et al. 2010*, *Fischer et al. 2000*). In accordance with earlier reports (*Kayemba-Kays et al. 2003*, *Lacroix et al. 2004*, *Lejeune et al. 2006*, *Johnson et al. 2003*), a relatively high proportion (76–79%) of the infants in our study developed NAS, and the majority (57–66%) required morphine medication (*Finnegan 1984*) after a mean maternal BPR dose of 5 mg on the day of delivery. The high percentage of infants needing medication is in line with previous French data (*Simmat-Durand et al. 2009*, *Lejeune et al. 2006*), with a mean BPR dose of 5 mg, but slightly higher than in a US study of 58 BPR-exposed neonates with less than half (47%) of the infants needing morphine medication. In the US study no information on the mean BPR dose was provided (*Jones et al. 2010*). In a Swedish study by Kakko et al. on 47 infants, only 15% needed morphine treatment. They speculated that this was a result of appropriate BPR dosing. The mean BPR dose was 15 mg on the day of delivery (*Kakko et al. 2008*).

In Study III two of the infants were diagnosed and treated for NAS without having BPR in their urine. A possible explanation is the ability of other substances used by women during pregnancy to cause withdrawal symptoms, e.g. tobacco (*Law et al. 2003*). In a previous study, heavy maternal smoking (10 or more cigarettes per day) alone caused withdrawal symptoms in the newborn as assessed by Finnegan score (*Godding et al. 2004*). Newborns not exposed to opiates can score up to 7 (Finnegan score; 95th percentile = 8) during their first 3 days of life (*Zimmermann-Baer et al. 2010*). In addition, at the beginning of our study the personnel taking care of these children were at the start of their learning curves as regards use of the (semi-objective) Finnegan score (*Jones et al. 2010*), as the first BPR-exposed child was born in 2001.

In our study most of the infants treated for NAS remained in hospital for almost the entire neonatal period (mean 25±19 days (SD), range 3–125). This is in line with previous reports, although long hospitalization may reflect factors other than medical conditions, e.g. CPS aspects (*Kakko et al. 2008*, *Ebner et al. 2007*). The duration of morphine treatment was much longer (20±10 days) than in reports from Sweden, Austria and the USA where NAS treatment lasted for 4–9 days (*Kakko et al. 2008*, *Jones et al. 2010*, *Ebner et al. 2007*). This may partly be a result of differences in non-medical treatment of NAS, e.g. infant separation from the mother to go to a surveillance unit (*Saiki et al. 2010*).

Surprisingly, the infants of our compliant mothers had a longer duration of morphine treatment and stayed longer in hospital than did those of the non-compliant group. This is different to the situation in a French study, where the infants of non-compliant mothers had more severe NAS (*Simmat-Durand et al. 2009*). Our non-compliant group (Study V) may have included more occasional abusers of BPR, whose infants required no medication for NAS, and, on the other hand, some heavy abusers who dropped out of the enhanced out-patient service. The non-compliant women were more often street BPR-users, probably taking smaller doses, often intravenously.

A significant number of mothers also used other psychoactive forms of medication or addictive substances, according to self reporting and the results of urinary toxicology tests. This is in accordance with the results of previous studies showing that people on substitution treatment are likely to use other psychotropic and illicit substances as well (*Brown et al. 1998*, *Lejeune et al. 2006*, *Kacinko et al. 2008*), and polydrug use modifies the quality of NAS (*Lacroix et al. 2004*, *Lejeune et al. 2006*, *Bada et al. 2002a*). Concomitant use of opioids and benzodiazepines may delay the onset and lengthen NAS (*Sutton et al. 1990*, *Seligman et al. 2008*). In our study, prenatal exposure to BPR and benzodiazepines did not affect the length of morphine treatment or length of hospital stay, but it was associated with a significantly lowered mean Finnegan score for NAS on the first day of life.

Smoking 20 or more cigarettes per day during pregnancy while on OMT has been reported to intensify NAS and lengthen hospitalization for NAS treatment (*Choo et al. 2004*, *Winklbaur et al. 2009*). Smoking aggravated NAS in our study as well, as the infants of women smoking 10 or more cigarettes per day needed higher doses of morphine hydrochloride on the first and second days of treatment.

Whether the incidence and severity of NAS is opioid dose-dependent has been long debated. The published data are scanty as regards BPR (*Fischer et al. 2006*, *Simmat-Durand et al. 2009*, *Lejeune et al. 2006*, *Jones et al. 2005*). We found a correlation between maternal BPR

dose on the day of delivery and the length of hospital stay as well as with the morphine dose at the beginning of morphine treatment. One explanation could be our moderate dosing of BPR, the maximum dose being 16 mg. BPR has been shown to have dose-related effects on most physiological measures in the lower dose range (*Walsh et al. 1994*).

We studied maternal and neonatal urinary BPR and NBUP concentrations in relation to NAS, because both BPR and NBUP may suppress withdrawal signs (*Kuhlman et al. 1998*). Our results suggest that the concentration of NBUP, the active metabolite of BPR, rather than the concentration of BPR itself, is predictive of the length of hospital stay and duration of morphine treatment. This is in agreement with other data indicating higher urinary NBUP concentrations than urinary BPR concentrations after sublingual doses. It may also reflect the accumulation of BPR in the foetus (*Marquet et al. 1997*). NBUP has been shown to accumulate in foetal hair in significantly higher concentrations than BPR during daily BPR exposure (*Goodwin et al. 2007*). Thus, a high urinary NBUP concentration in the newborn may indicate a high BPR load and have implications for NAS treatment.

**CONCLUSIONS**

The following conclusions can be drawn:

1. Women with substance abuse problems identified during pregnancy have an increased mortality rate (OR 38) during the following 6–15 years. In particular, the risk of death attributable to accidents and violence is increased (OR 114).

2. After adjusting for socioeconomic and marital status, women with substance abuse problems identified during pregnancy have increased co-morbidity rates in the areas of mental disorders (AOR 8.8), viral (AOR 23.5) and bacterial (AOR 6.1) infections, as well as injuries and poisoning (AOR 4.2).

3. Children born to women with substance abuse problems during pregnancy have a substantial (50%) chance during early childhood and a 38% chance by the age of two years, of being in out-of-home care as part of child protection services, according to CPS practice in the Greater Helsinki area. The risk is associated with factors identifiable during the pre- and perinatal period.

4. Buprenophine exposure during pregnancy does not affect the prematurity rate or the number of pregnancy and labour complications.

5. Prenatal buprenorphine exposure does not have a significant effect on erythropoietin, cardiac troponin-t or S100 levels in cord serum collected at birth.

6. Neonatal abstinence syndrome occurs in the majority of buprenorphine-exposed infants and most of them need morphine medication for the condition. Smoking over 10 cigarettes daily aggravates NAS.

7. An infant's highest urinary norbuprenorphine concentration during their first 3 days of life correlates with the duration of morphine treatment and the length of hospital stay.

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Appendix 1. Finnegan score

## VIEROITUSOIREIDEN ARVIOINTI (Finnegan 1986)          Nimitarra

Arviointi syötöillä; myös arviointivälin oireet lasketaan. Arviointiväli 2 tuntia jos ≥ 8 pistettä.

| PVM | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| KELLONAIKA | | | | | | | | | | | | | | |
| SYÖMISONGELMAT | 2 | | | | | | | | | | | | | |
| OKSENTELU | | | | | | | | | | | | | | |
| Pulauttelu | 2 | | | | | | | | | | | | | |
| Kaarimaiset oksennukset | 3 | | | | | | | | | | | | | |
| ULOSTEET | | | | | | | | | | | | | | |
| Löysät | 2 | | | | | | | | | | | | | |
| Vetiset | 3 | | | | | | | | | | | | | |
| KUIVUMINEN | 2 | | | | | | | | | | | | | |
| HAUKOTTELU (>3 kertaa) | 1 | | | | | | | | | | | | | |
| AIVASTELU (>3 kertaa) | 1 | | | | | | | | | | | | | |
| NENÄN TUKKOISUUS | 1 | | | | | | | | | | | | | |
| HIKOILU | 1 | | | | | | | | | | | | | |
| MARMOROITUMINEN | 1 | | | | | | | | | | | | | |
| KUUME | | | | | | | | | | | | | | |
| 38-38,5°C | 1 | | | | | | | | | | | | | |
| > 38,5°C | 2 | | | | | | | | | | | | | |
| NENÄSIIPIHENGITYS | 2 | | | | | | | | | | | | | |
| HENGITYSTIHEYS | | | | | | | | | | | | | | |
| > 60/min | 1 | | | | | | | | | | | | | |
| > 60/min ja retraktio | 2 | | | | | | | | | | | | | |
| HANKAUMAT | | | | | | | | | | | | | | |
| Nenä/polvet/varpaat | 1/1/1 | | | | | | | | | | | | | |
| KIMEÄ ITKU | | | | | | | | | | | | | | |
| Jaksoittainen | 2 | | | | | | | | | | | | | |
| Jatkuva | 3 | | | | | | | | | | | | | |
| SYÖTÖN JÄLKEINEN UNI | | | | | | | | | | | | | | |
| < 3 tuntia | 1 | | | | | | | | | | | | | |
| < 2 tuntia | 2 | | | | | | | | | | | | | |
| < 1 tuntia | 3 | | | | | | | | | | | | | |
| MORO-REFLEKSI | | | | | | | | | | | | | | |
| Yliaktiivinen | 2 | | | | | | | | | | | | | |
| Merkittävästi yliaktiivinen | 3 | | | | | | | | | | | | | |
| TÄRINÄT, VAPINAT | | | | | | | | | | | | | | |
| Vähän häirittäessä | 1 | | | | | | | | | | | | | |
| Paljon häirittäessä | 2 | | | | | | | | | | | | | |
| Vähän rauhassa ollessa | 3 | | | | | | | | | | | | | |
| Paljon rauhassa ollessa | 4 | | | | | | | | | | | | | |
| JÄNTEVYYS | | | | | | | | | | | | | | |
| Lisääntynyt | 2 | | | | | | | | | | | | | |
| Lihasnykäykset | 3 | | | | | | | | | | | | | |
| Yleistynyt kouristus | 5 | | | | | | | | | | | | | |
| KIIHKEÄ NYRKIN IMEMINEN | 1 | | | | | | | | | | | | | |
| YHTEENSÄ | | | | | | | | | | | | | | |

LÄÄKITYS (aloitetaan jos 3 kertaa peräkkäin ≥ 8 pistettä):

Appendix 2. Obstetric follow-up scheme for case pregnancies (Studies III–V)

| | Bioprofile<br><br>Foetal growth<br><br>Cardiotocogram weekly after 26 weeks of pregnancy | HIVAb<br><br>HBsAg<br><br>HCVAb, if positive HCV RNA viral load (XX) | Interview on recent substance use including tobacco smoking | Supervised urinary drug screening at every visit with the woman's permission |
|---|---|---|---|---|
| At 13 weeks of gestation | X<br>Nuchal translucency measurement | X | X | X |
| At 18–20 weeks of gestation | X<br>Foetal morphology | | X | X |
| At 24 weeks of gestation | X | | X | X |
| At 30 weeks of gestation | X | | X | X |
| At 36 weeks of gestation | X | XX | X | X |
| At term | X | | X | X |
| Day of labour | | | X | X |