Opioid maintenance treatment in pregnancy:

Maternal and neonatal outcomes

Gabrielle Katrine Welle-Strand

SERAF, Norwegian Centre for Addiction Research,

Institute of Clinical Medicine, Faculty of Medicine, University of Oslo

&

Department of Psychiatry and Substance Use, Norwegian Directorate of Health

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Acknowledgements

Abstract

Background

The life of a pregnant woman actively using drugs is far from the optimal, healthy life of a pregnant woman. Complications of maternal heroin use include premature delivery, indications of stress in fetal life, fetal growth retardation, neonatal withdrawal and increased fetal/neonatal mortality. For many years methadone maintenance treatment (MMT) has been recommended as the standard of care for opioid-dependent pregnant women. Methadone reduces the repeated intoxications and withdrawals for the fetus which follow maternal use of short-acting opioids. Compared to heroin use in pregnancy, MMT is associated with less drug use and better prenatal care. For the neonate, MMT is associated with neonates born closer to term, better fetal growth and reduced fetal mortality. However, neonatal abstinence syndrome (NAS) after methadone exposure in pregnancy appears to be more severe than after heroin exposure, and the possible long-term effects of exposure to opioid maintenance treatment (OMT) medications in fetal life are debated. Norway is a suitable country for studying the maternal and neonatal outcomes of pregnancies where the women are in OMT with methadone or buprenorphine. Most women are in OMT when they conceive and there is little use of legal or illegal drugs during pregnancy.

Study aims

The overall study aim was to explore the maternal and neonatal outcomes when women were in OMT during pregnancy. Further, the aim was to compare the neonatal outcome after exposure to methadone or buprenorphine in pregnancy and to evaluate the effect of breastfeeding on NAS. Lastly, the aim was to evaluate the extent to which women in OMT tapered their OMT-medication dose during pregnancy and how tapering influenced the neonatal outcomes.

Material and methods

The design is a mixed prospective/retrospective national cohort study of 139 pregnant women in OMT and their 161 neonates born between 1996 and 2009. The study has two retrospective and one prospective study part and also includes a case report. A standardized questionnaire was administered and medical information was collected from the hospitals and municipalities to confirm self-reported data from the interviews.

Results

Buprenorphine-exposed neonates had significantly larger head circumferences and tended to be heavier and longer than methadone-exposed neonates, after adjusting for relevant covariates. There were no differences in the incidence or duration of pharmacological treatment of NAS for the neonates between the medications. The use of any illegal drugs or benzodiazepines was associated with longer lasting pharmacological NAS treatment of the neonates. There were high initiation rates of breastfeeding (77%) for women in OMT, but also high rates of early cessation of breastfeeding. Breastfed neonates exposed to methadone prenatally had significantly lower incidence of NAS requiring pharmacotherapy and both the whole group of infants and methadone-exposed neonates needed shorter pharmacological treatment of NAS (p>0.05) than non-breastfed neonates. Two of the woman came off the OMT medication during pregnancy and another 15% tapered their OMT medication more than 50%. The birth weights of methadone-exposed neonates of women who tapered more than 50% were significantly higher than for the methadone-exposed neonates of the women tapering between 11 and 50%. No other significant differences were found between the tapering groups. The case report describes a well-functioning woman in OMT who tapers her buprenorphine dose from 24 mg in pregnancy week 14 to zero in week 31. Her blog describes how the withdrawal symptoms gradually increase in number and intensity. When she is off buprenorphine the woman has severe withdrawal symptoms and she chooses to go back on 4 mg of buprenorphine for the rest of the pregnancy.

Discussion and conclusion

In line with other studies, our results indicate that both methadone and buprenorphine are acceptable medications for use in pregnancy. If starting OMT during pregnancy, buprenorphine should be considered as the drug of choice, because of the more favourable neonatal growth parameters. Particularly methadone-exposed neonates seem to benefit from breastfeeding, with lower incidence of and shorter duration of pharmacotherapy of NAS compared with methadone-exposed infants who are not breastfed. The results add to the evidence regarding the benefits of breastfeeding for neonates prenatally exposed to OMT medications. Fewer than twenty per cent of women in OMT taper their medication substantially during pregnancy. Higher birth weights of methadone-exposed neonates of women who tapered substantially were the only significant difference found in neonatal outcomes. Studies are needed to document maternal well-being and fetal safety in maternal tapering of OMT medication during pregnancy. Pregnant women in OMT who taper their OMT medication should be monitored closely.

Norwegian summary

Bakgrunn

Livet til en gravid rusavhengig kvinne skiller seg i stor grad fra det ideelle, sunne livet til en gravid kvinne. Hvis den gravide bruker heroin er fosteret utsatt for stress og nedsatt vekst i fosterlivet og for tidlig fødsel, abstinenser etter fødselen og økt dødelighet for den nyfødte. Legemiddelassistert rehabilitering (LAR) med metadon har i mange år vært vurdert som den beste behandlingen for opioidavhengige gravide. Metadon reduserer de gjentatte ruspåvirkningene og abstinensene hos fosteret som følger av kvinnens bruk av korttidsvirkende opioider. Sammenliknet med bruk av heroin i svangerskapet, er metadonbehandling i graviditet assosiert med mindre bruk av rusmidler for kvinnen og hyppigere svangerskapskontroller. I tillegg er metadonbruk i graviditet assosiert med fødsler nærmere termin, bedre fostervekst og nedsatt dødelighet hos den nyfødte. Neonatalt abstinenssyndrom (NAS) etter metadonbruk hos kvinnen i svangerskapet synes å være mer langvarig enn hvis kvinnen bruker heroin. Eventuelle langvarige effekter av bruk av LAR-legemidler i svangerskapet er omdiskutert. Norge er et land som er egnet for å studere effekter av bruk av LAR-legemidler i svangerskapet for kvinne og hennes nyfødte. De fleste kvinnene er i LAR når graviditeten oppdages og kvinnene bruker lite legale og illegale rusmidler under graviditeten.

Forskningsspørsmål

Det overordnede målet var å studere resultatene for kvinnen og den nyfødte når kvinnen bruker LAR-legemidler i svangerskapet. Målet var videre å sammenlikne nyfødtfunn etter kvinnens bruk av henholdsvis metadon og buprenorfin i svangerskapet, samt å studere effekten av amming på NAS. Det var også et mål å undersøke i hvilken grad kvinnen trappet ned LAR-legemidlet i løpet av svangerskapet og hvilken effekt slik nedtrapping hadde på den nyfødte.

Materiale og metode

Studien er en nasjonal kohortstudie som er sammensatt av en prospektiv og to retrospektive deler, samt en kasuistikk. Den omfatter 139 kvinner som brukte LAR-legemidler i svangerskapet og de 161 nyfødte kvinnene fikk mellom 1996 og 2009. Et standardisert spørreskjema ble benyttet ved intervjuene av kvinnene. I tillegg ble det innhentet sykehusjournaler og medisinske opplysninger fra kommunen for å bekrefte selvrapporterte data fra intervjuene.

Resultater

Nyfødte som hadde vært eksponert for buprenorfin i fosterlivet hadde signifikant større hodeomkrets enn metadoneksponerte nyfødte og viste en tendens til høyere fødselsvekt og lengde, etter at det hadde blitt kontrollert for relevante kovariater. Det var ingen forskjell i forekomst av eller varighet på den medikamentelle behandling av NAS mellom LAR-legemidlene. Bruk av rusmidler eller benzodiazepiner under graviditeten førte til signifikant lenger varighet av NAS-behandlingen for de nyfødte. 77% av kvinnene ammet etter fødsel, men en stor andel sluttet raskt. Nyfødte som ble ammet og hadde vært vært eksponert for metadon i fosterlivet hadde signifikant lavere forekomst av NAS enn de som ikke ble ammet. Hele gruppen av nyfødte som ble ammet og de metadoneksponerte spesielt, trengte kortere behandling for NAS med legemidler (p>0.05) enn nyfødte som ikke ble ammet. To kvinner trappet seg helt ned fra LAR-legemiddelet i løpet av graviditeten og ytterligere 15% av kvinnene trappet ned over 50% av LAR-legemiddeldoseringen de hadde da de ble gravide. Fødselsvekten til metadoneksponerte nyfødte, hvor kvinnen hadde trappet ned over 50%, var signifikant høyere enn for metadoneksponerte nyfødte hvor kvinnen hadde trappet ned 11 til 50% under graviditeten. Kasuistikken beskriver en velfungerende kvinne i LAR som trapper ned sin buprenorfindose fra 24 mg i svangerskapsuke 14 til 0 mg i uke 31. I bloggen beskriver hun hvordan abstinensene øker gradvis i antall og intensitet. Hun er svært opioidabstinent når hun har trappet helt ned og velger etter 8 dager å gå tilbake på 4 mg buprenorfin for resten av graviditeten.

Diskusjon og konklusjon

Resultatene fra studien tyder på at både metadon og buprenorfin er akseptable legemidler å bruke under graviditet, i tråd med resultatene fra andre studier. Hvis LAR skal startes under graviditeten, bør buprenorfin vurderes som førstevalg, på grunn av bedre vekstparametere hos fosteret. Spesielt synes metadon-eksponerte nyfødte å profitere på amming med lavere forekomst av og kortere varighet av legemiddelbehandlingen for NAS enn metadon-eksponerte nyfødte som ikke ammes. Resultatene fra studien bekrefter fordelene ved amming for nyfødte som har blitt eksponert for LAR-legemiddel under graviditet. Mindre enn 20% av gravide i LAR trapper vesentlig ned på LAR-legemiddeldoseringen under graviditeten. Høyere fødselsvekt hos metadoneksponerte nyfødte hos kvinner som hadde trappet ned over 50% av utgangsdoseringen under graviditeten var den eneste signifikante forskjellen i nyfødtfunn mellom de forskjellige gruppene med nedtrapping/ikke-nedtrapping. Det trengs studier som dokumenterer kvinnens velbefinnende og fosterets sikkerhet når kvinnen trapper ned LAR-legemiddeldoseringen under graviditeten. Kvinner som prøver nedtrapping av LAR-legemiddel under graviditet må følges tett opp av helsepersonell.

List of papers

I. Welle-Strand GK, Skurtveit S, Jones HE, Waal H, Bakstad B, Bjarkø L, Ravndal E. Neonatal outcomes following in utero exposure to methadone or buprenorphine: A National Cohort Study of opioid-agonist treatment of Pregnant Women in Norway from 1996 to 2009. Drug and Alcohol Dependence 2013; 127: 200-206 [1].

II. Welle-Strand GK, Skurtveit S, Jansson JM, Bakstad B, Bjarkø L, Ravndal E. Breastfeeding reduces the need for withdrawal treatment in opioid-exposed infants. Acta Pædiatrica 2013; 102: 1060-1066 [2].

III. Welle-Strand GK, Skurtveit S, Tanum L, Waal H, Bakstad B, Bjarkø L, Ravndal E. Tapering from methadone or buprenorphine during pregnancy. Maternal and neonatal outcomes in Norway 1996-2009 (accepted European Addiction Research in March 2015) [3].

IV. Welle-Strand GK, M, Kvamme O, Andreassen A, Ravndal E. A woman's experience of tapering from buprenorphine during pregnancy. BMJ Case Report 2014. Doi:10.1136/bcr-2014-207207 [4].

Abbreviations and definitions

ADHD = attention deficit hyperactivity disorder

BMT = buprenorphine maintenance treatment

EKUP= enheten for kognitiv utviklingspsykologi = Cognitive Developmental Research Unit, Department of Psychology, University of Oslo

EMCDDA = European Monitoring Centre for Drugs and Drug Addiction

Europ-ASI = European Addiction Severity Index

FAS = fetal alcohol syndrome

FASD = fetal alcohol spectrum disease

Fundal height - is the distance from the pubic bone to the top of the uterus measured in centimetres and is a measure of the size of the uterus, fetal growth and development

GA = gestational age

GWS = Gabrielle Welle-Strand

IAS = Intrauterine abstinence syndrome, a suggested syndrome for fetuses' withdrawal from opioids in utero

IDU = injecting drug user

LAR= legemiddelassistert rehabilitering = medication assisted rehabilitation (MAR) = medication assisted treatment (MAT) = opioid maintenance treatment (OMT) = opioid substitution treatment (OST)

LOS = length of stay (in hospital)

MAW = medication-assisted withdrawal or methadone-assisted withdrawal - these terms are used mainly in publications from the USA and typically describe procedures which provide consecutively smaller doses of opioids to give a smoother transition from illicit opioid use to a medication-free state. The time-frame for such procedures typically ranges from a few days to 3-4 weeks.

MCMI III = Millon Clinical Multiaxial Inventory III

MOTHER project = Maternal Opioid Treatment: Human Experimental Research project

MMT = methadone maintenance treatment

NAS = neonatal abstinence syndrome

MBR= Norwegian medical birth registry

Opioid dose reduction or dose decrease – general terms where the dose of the prescribed opioid is reduced/decreased

OMT = opioid maintenance treatment; this is the preferred English term for the Norwegian treatment model based on methadone and buprenorphine

Opioid detoxification - is the most commonly used for short-term detoxification from opioids. In Norway this is usually performed at an in-patient institution, while in many other countries this will also be performed for out-patients. Therapeutic detoxification refers to special targeted programmes which patients enter voluntarily; while non-therapeutic detoxification includes all other options of detoxification/tapering.

OUS = Oslo University Hospital

RCT = randomised controlled trial

SCL-25 = Hopkins Symptom Check List - 25

SERAF = Senter for rus- og avhengighetsforskning = Norwegian Centre for Addiction Research, University of Oslo

SES = socio-economic status

SGA=small for gestational age

SIDS = sudden infant death syndrome

SIRUS = Statens institutt for rusmiddelforskning = Norwegian Institute for Alcohol and Drug Research

Tapering – this term most often describes a gradual and systematic reduction in the medication dose over time. In this thesis, tapering is used as the common term for all reductions in OMT-medication dose during pregnancy for the women in the study.

WHO = World Health Organization

Study background

My motivation for conducting research in the field of opioid maintenance treatment (OMT) and pregnancy has a long history. I started working as a medical doctor in an outreach street department in Oslo (Uteseksjonen) in 1987 and soon I developed a special interest in the drug-using women who became pregnant [5]. The cited study was an evaluation of seven pregnant women in their twenties, whom I encountered in my doctor's office in the outreach department. Six of the seven women were using drugs intravenously when their pregnancy was confirmed. Four of the women lost custody before their child was two years of age because they relapsed to drug use.

When the Norwegian parliament amended a new section (§ 6-2a) of the Social Service Act in 1996, it became possible to treat pregnant drug users compulsorily. I evaluated the first experiences of compulsory treatment at the detoxification department where I was working [6]. The report describes the characteristics and the results of the first 13 pregnant women who were treated according to amendment in the law.

In 1998, I started working as a doctor in the newly established OMT programme in Oslo, and soon I met the first pregnant methadone patient. From the very beginning, there has been a lot of general, political and professional debate around how to treat pregnant women in OMT. I took the initiative to develop a standardized questionnaire, to evaluate all Norwegian women who gave birth while they were enrolled in OMT [7]. We also developed the first guidance for treating pregnant women in OMT, based on knowledge generated from research in different parts of the world [8].

In 2002 and 2004 I evaluated 56 neonates born to mothers in OMT in Norway between 1996 and 2003. The evaluation was part of my job as a medical doctor in OMT with a national responsibility for overseeing pregnancies in OMT/families with children in OMT. Some of the early results were later published as part of an international cooperation [9].

Working with pregnant women and mothers and fathers in OMT meant extensive cooperation with many different professionals and institutions. Monica Sarfi, a child psychologist, and I started to discuss a research co-operation, focusing on pregnancies in OMT and on both neonatal and longer-term results for the women and their children. We applied for research funds in 2004, and both got funding to start our study on pregnant women in OMT and their neonates/small children.

I have been working for the Norwegian Directorate of Health since 2006 and have been dividing my time between governmental work and my PhD-study since 2007. I was in charge of the development of the "National Clinical Guideline on Opioid Maintenance Treatment in Pregnancy and the Follow-up

of the Children and Families until School Age", which was issued in 2011 [10]. I have also been fortunate to cooperate with clinicians and researchers from many different parts of the world, especially through the co-chairing of the WHO Guideline Development Group making "Guidelines for the identification and management of substance use disorders in pregnancy", which were issued in the spring of 2014 [11].

My research interest in the field of addiction and pregnancy started with a concern for the pregnant women and their children whom I encountered in different clinical settings. I went on to systematize my clinical experiences and continued some years later to establish research collaboration with others. The research cooperation has later developed into a multidisciplinary research group at the Norwegian Centre for Addiction Research (SERAF) at the University of Oslo, focusing on research on pregnant women in OMT and a long-term follow-up study of a prospective cohort of women in OMT and their children.

1. Introduction

1.1 Illicit opioid use and opioid dependence

There were approximately 1.4 million problem opioid users in the European Union (EU) and Norway in 2007 [12]. This number has been relatively stable in recent years. In 2008, the Norwegian Institute for Alcohol and Drug Research (SIRUS) estimated that the total number of problematic heroin users was between 6 600 and 12 300 [13]. Patients in OMT without the use of illegal opioids/injections are not included in these numbers. In 2009, SIRUS estimated that the total number of injecting drug users (IDU) in Norway was between 8 700 and 12 300 [14]. Most of these individuals (85%) used heroin as the main drug. Opioid dependence is a medical condition, but represents a complex state with medical, psychological and social elements. Opioid dependent individuals often use other substances as well, both legal and illegal [15-17]. Opioid dependent individuals have increased mortality rates and increased somatic and psychiatric morbidity, as well as social problems [18-24].

1.2 Treatment of opioid dependence

Opioid dependence is a complex health condition that often requires long-term treatment and care. First of all, it is important to keep the patients in treatment over time in order to reduce mortality and morbidity. Likewise, it is important to reduce the social consequences of opioid dependence and improve the quality of life and social integration of the people affected. The goal of treatment is to reduce the use of illicit and legal drugs, to reduce criminal activity, to promote integration into education/work and society and to improve the patient's quality of life.

There are, in principle, two primary goals for the treatment of opioid dependence; either complete abstinence from all opioids and illegal drugs or opioid maintenance treatment [25]. On a national level, both abstinence-oriented treatment and OMT should be available, since treatment of opioid dependence should be individualized and tailored to meet the patient's treatment needs at any given time [26].

1.2.1   Abstinence-oriented treatment

Abstinence-oriented treatment is performed in a variety of ways. Opioid detoxification will often be the first step in the treatment, most often involving either alpha-adrenergic medications or opioid agonist medications at tapered doses [27]. Opioid detoxification will often be followed by either out-patient follow-up or in-patient treatment over a variable period of time. Opioid antagonist treatment

may be part of this treatment in order to prevent relapse to opioid use, most often as a sustained release formulation [28].

Van den Brink and Haasen performed a review in 2006 of treatment options for opioid-dependent patients [29]. Their conclusion was that the outcome of abstinence-oriented programmes remains poor and that such programmes are effective for only a few motivated patients with stable living conditions and adequate social support.

The main challenge with abstinence-oriented treatment of opioid dependence is the low retention in treatment and the fact that many patients will relapse to the use of opioids and other drugs after shorter or longer periods [17]. This will lead to an increase in opioid overdose cases, as well as to an increase in somatic and psychiatric morbidity and all the other consequences of opioid dependence. The World Health Organization therefore recommends that most patients should be advised to use opioid agonist maintenance treatment in their "Guideline for the psychosocially assisted pharmacological treatment of opioid dependence" from 2009 [30].

1.2.2   Opioid maintenance treatment

Opioid maintenance treatment (OMT) with methadone was started in New York in the 1960's [31, 32]. Because of the promising results, the treatment was scaled up quickly, both in the USA and in other parts of the world. The coverage of treatment, that is the proportion of those in need who receive treatment, the overall goals of OMT, and how the treatment is delivered, varies from country to country and also within countries [33-36].

In Europe, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) estimated that 734 000 opioid users received OMT in 2012 [37]. Methadone was prescribed to approximately two-thirds of the patients and approximately 20% were treated with buprenorphine [37]. The coverage of OMT ranges from 10% in Latvia, Slovakia and Poland to more than 60% in Malta and Luxembourg. According to EMCDDA, the coverage of OMT in Norway was 43% in 2012 [37].

In the beginning, methadone, a full opioid agonist, was the only medication available for OMT. Just before the turn of the millennium, buprenorphine, a partial opioid agonist, was introduced. In WHO's treatment guideline from 2009, methadone was recommended as the first line medication [30]. A recent Cochrane review comparing buprenorphine and methadone as medications for opioid dependence, concludes that methadone is superior to buprenorphine in retaining people in treatment, and that methadone equally suppresses illicit opioid use [38]. The Norwegian National Treatment Guideline for OMT from 2010, however, recommends buprenorphine as the first line medication in OMT, primarily because of safety considerations [39].

OMT should always include both pharmacological treatment and a variety of psychosocial measures tailored to meet the individual patient's specific treatment needs [30, 35]. The psychosocial interventions should include cognitive and behavioural approaches and measures including vocational training and social integration.

Different terms are used in this field to describe procedures for opioid dose reductions. Tapering most often describes a gradual and systematic reduction in the medication dose over time. In this thesis the term tapering is used as the common term for all reductions in the OMT-medication dose during pregnancy for the women in the study.

The literature on tapering OMT medication for non-pregnant patients is not abundant. Kornør did a literature review covering the period from 1966 to 2003 [40]. A total of 14 studies were included in the review. She reported a great variation both in the definitions of abstinence and abstinence rates. Kornør found a pooled abstinence rate of 48% and 22% for therapeutic and non-therapeutic detoxification, respectively, with a follow-up period from one to 103 weeks. Factors associated with the highest frequency of abstinence at follow-up were voluntary participation followed by younger age, shorter duration of dependence prior to OMT, less substance use during treatment and longer time in OMT. A recent retrospective study of 14 602 patients initiating a taper in MMT in Vancouver showed that only 4.4% of the patients initiating a taper succeeded [41]. The study demonstrated that being male and being young, having good treatment adherence, lower methadone dose at the initiation of tapering, longer tapers and gradual stepped tapering schedules were associated with higher odds of success. Other studies find similar low figures for completed tapering among OMT patients [42-44]. There is a potential risk of increased mortality after termination of OMT [22, 44-47].

1.2.3 Organization of OMT in Norway

Methadone maintenance treatment (MMT) in Norway started as two smaller projects based in Oslo in 1991 and 1994. In 1997 the Norwegian Parliament decided that OMT should be available in all of Norway and the treatment was rapidly extended in the subsequent years [48]. From the beginning, the general inclusion criteria were very strict, with a minimum age of 25 years, 10 years of opioid dependence and prior treatment without the use of opioid medications. In 2000, the inclusion criteria for OMT were somewhat modified; the length of opioid dependence prior to OMT was reduced to 5 years. With the National Treatment Guideline for OMT in Norway, which was issued in 2010, the inclusion criteria moved more into line with international recommendations [30, 39]. Buprenorphine was introduced as an OMT medication in Norway in 2001. OMT was expanded rapidly after 1998, with approximately 500 new patients every year until 2013. At the end of 2013 there were more than 7000 patients in OMT in Norway and approximately 50% of patients were using

methadone and buprenorphine, respectively [49]. Approximately one third of the patients in OMT in Norway are women and most of them are of reproductive age.

In Norway, OMT is organized as a co-operation between the patient, the specialist health care system, the general practitioner and social services. A coordinating group is organized around each individual patient, consisting of the patient and the professionals with responsibility for different parts of the treatment/follow-up. Methadone and buprenorphine are delivered by the same health care professionals in the same clinical settings and are regulated by the same national treatment guideline [39].

The annual OMT status surveys from the National Centre for Addiction Research (SERAF) and Oslo University Hospital (OUS) are based on individual data from approximately 80 % of the patients in OMT [50]. These reports give detailed and aggregated information about the medications in OMT, the use of legal and illegal drugs, somatic and psychiatric comorbidities, different aspects of psychosocial life and the rehabilitation process for OMT patients in different parts of Norway [49, 51-53].

1.3 Opioid dependence in pregnancy

1.3.1 Consequences for the pregnant woman

Pregnant women actively using drugs are at risk of malnourishment and they often lack adequate housing [54, 55]. Many pregnant drug-using women have drug-using partners and have lost custody of older children. To finance their use of drugs, many women engage in prostitution and/or criminal activities. A large proportion of the women have co-existing somatic and psychiatric disorders, for which they seldom receive proper treatment [24, 56-59]. In addition, a woman using opioids seldom uses heroin alone; she will often use a mixture of legal and illegal drugs and medications and almost always smoke cigarettes as well [60].

Women actively using drugs often discover their pregnancies late, come late for the first prenatal visit and have a tendency to miss later obstetric appointments [60]. The life of a pregnant woman using drugs is usually far from the optimal, healthy life for a pregnant woman.

1.3.2 Consequences for the neonate

The use of short acting opioids like heroin during pregnancy leads to fluctuating opioid concentrations in the maternal blood and therefore also in the fetal blood, and may result in fetal

withdrawal or overdose [61]. Besides this, the fetus will be exposed to any other legal and illegal drugs the pregnant woman is using, and nearly always to tobacco as well [62]. Alcohol consumption in pregnancy is particularly harmful for the developing fetus. Alcohol use in pregnancy can cause a range of congenital malformations and developmental problems ranging from the full fetal alcohol syndrome (FAS) to a broad range of different deficits known as fetal alcohol spectrum disease (FASD) [62, 63].

The fetal complications of maternal heroin use were described in the USA in the 1970's and included premature delivery, indications of stress in fetal life, neonates which were small for gestational age (SGA), neonatal withdrawal and increased fetal/neonatal mortality [64-66]. Neonatal abstinence syndrome will be covered under 1.4.4.

1.3.3   Possible long-term effects of illegal opioids in pregnancy

We will try to separate possible long-term effects of illegal opioids in pregnancy from the long-term effects of exposure to OMT medications in pregnancy. The latter will be covered in 1.4.5. Only a few examples will be given of studies in these sections, as this is not the main topic of this thesis.

Ornoy from Israel followed four groups of children into adolescence: 83 children born to heroin-dependent mothers, 76 children born to heroin-dependent fathers, 50 children with environmental deprivation and 50 normal children [67-69]. The first paper studied 5 to 6 year old children and the authors concluded that the specific role of heroin exposure in-utero in the determination of the developmental outcome of the children seems to be less important than the home environment. The second paper studied 6 to 12 year old children and the authors concluded that the children of heroin-dependent parents suffered from a high rate of hyperactivity, inattention and behavioural problems. The cognitive developmental and learning abilities were influenced to a large extent by their environment. The last paper studied 12 to 16 year old children and the results indicated that being exposed to drugs at the prenatal age, and/or growing up in a low SES (socio-economic status) environment puts the child at risk for poorer cognitive development, for increased risk of behavioural problems (according to the parents) and for ADHD-related (Attention Deficit Hyperactivity Disorder) problems.

The Maternal Lifestyle Study is a large, multisite, longitudinal investigation of cocaine- and opioid-exposed infants from the USA. The authors concluded at the three-year follow-up, "In the largest at-risk sample observed longitudinally to date, infants' prenatal exposure to cocaine and opioids were not associated with mental, motor or behavioural deficits after controlling for birth weight and environmental risks" [70, 71].

In a Norwegian prospective, longitudinal study 78 children who were prenatally exposed to illegal opioids, other illegal substances and alcohol were compared to a normal comparison group of 58 children. The majority of the children in the study group were placed early into foster or adoptive homes. Significant differences were found between the substance-exposed group and the comparison group at ages 1, 2, 3 and 4 ½ years [72-75]. The mean cognitive scores were within normal limits at age 4 ½ years, but the substance-exposed children had a particular weakness in the area of visual-motor and perceptual abilities. "The results suggest that even if children experience adequate caregiving, the accumulation of biomedical risk factors associated with prenatal drug exposure is a potential determinant of developmental problems". Morphometric cerebral characteristics have later been studied in a subgroup of the children in the study group and the comparison group [76].

1.4 Treatment of pregnant opioid dependent women

1.4.1   Abstinence-oriented treatment

There are few studies on abstinence-oriented treatment of opioid-dependent pregnant women. Although abstinence throughout the course of pregnancy is the ideal clinical outcome, it is often not realistic for the pregnant women [77]. Many women relapse to the use of opioids and other substances after detoxification [78, 79]. The few international studies which exist mainly focus on short-time outcomes of the pregnancy such as the use of opioids by the women and neonatal outcome.

Treatment options for heroin-dependent pregnant women in Norway

Until the late nineties, the treatment for pregnant, opioid-using women in Norway usually included detoxification and referral to in-patient treatment at institutions specialized in treating pregnant drug-using women and their young children [80]. The use of medications to relieve withdrawal symptoms was limited to short periods during the detoxification and opioid medications were usually not an option. There are also some special child welfare clinics around the country focusing on close follow-up of the women in pregnancy and similar close follow-up of the children and mother through childhood. Hjerkinn's study of women and children attending such a clinic in South Norway showed that women, who continued to use substances during pregnancy, were more likely to lose custody of their children [81-84]. The women in the study used many different substances including alcohol and

cannabis. Wiig's qualitative study from 2014 describes the lives and experiences of women becoming mothers who are treated in a family ward at the Borgestad clinic [85].

In Norway there has been, and still is in principle, zero tolerance to the use of illicit drugs and alcohol during pregnancy. If a professional knows that a pregnant woman is using harmful legal or illegal substances, he/she has to ensure that the woman stops using drugs, either through voluntary measures on the part of the woman or by the use of the Norwegian Social Service Act. A section of this Act makes it possible to detain pregnant women using drugs or alcohol [86]. This Act was amended in 1996. Between 20 and 50 women nationally are treated according to this Act every year. Presently this is § 10-3 in the Norwegian Municipal Health and Care Services Act.

1.4.2   Opioid Maintenance Treatment in pregnancy

Since the 1990's MMT has internationally been the recommended standard of care for opioid-dependent pregnant women [30, 54, 87]. The administration of the long-acting opioid methadone minimizes the peak and trough opioid levels in maternal serum which occur with the repeated use of short-acting opioids like heroin. This reduces the possible harmful repeated intoxications and withdrawals for the fetus which result from maternal use of short-acting opioids [61].

OMT in pregnancy should be combined with individualized psychosocial follow-up and easy access to prenatal care [55, 88].

1.4.3   OMT in pregnancy – effects for the woman

The objectives for OMT in pregnancy are to prevent the complications of using illicit opioids and other drugs of abuse, to encourage engagement in addiction treatment and prenatal care and reduce the other harms associated with an active drug-using life [54, 61].

Comparisons between pregnancies where women had used heroin and where women had used methadone were published in the 1970's in the USA. Compared to heroin use in pregnancy, methadone maintenance treatment (MMT) in pregnancy was associated with less drug use and better prenatal care for the women [60, 89].

At the Norwegian Centre for Addiction Research (SERAF), a prospective cohort of pregnant women in OMT was established in 2005-6 comprising 38 women (26 in MMT and 12 in BMT=buprenorphine maintenance treatment). The cohort is the prospective part of our study cohort and was first described by Bakstad [90]. A comparison group of 36 "normal" pregnant women was also established [91]. In the comparison group all the women were employed, none of them were single mothers and

none of them smoked during pregnancy. In many ways the comparison group can therefore be seen as a contrast group, as the women in the two groups differ in many background characteristics [91].

Lund described the background characteristics and the substance use of the women and their partners in the prospective cohort in two papers [92, 93]. The women reported a long history of use of different substances and sixteen of their partners also had a history of substance use. The use of substances during the last month of pregnancy and one year after pregnancy was low for the women, although there was some increase in the use of legal substances one year after the pregnancy. At the four year follow-up, the use of illegal substances remained low and the use of legal substances was similar to the one-year follow-up. The women reported a high degree of depression, anxiety and problems concentrating in their earlier life and so did their partners [24]. Further, the women reported high levels of previous emotional, physical and sexual abuse. The degree of total psychological distress for the women the last month of pregnancy and one year later was 49% and 33%, respectively and was predominantly linked to problems with concentration/understanding and remembering. At the four-year follow up, the women reported a significantly higher degree of psychological problems, but also at that stage mainly linked to concentration/understanding and remembering [93]. 89% of the children attended kindergarten and 73% of the families had follow-up from child protection services when the children were four years.

Lund has also written a paper on prescription drug use among women in OMT, based on data from the Medical Birth Registry and the Norwegian Prescription Database [94]. Benzodiazepine anxiolytics, opioid analgesics and benzodiazepine hypnotics were prescribed in 21%, 15% and 13% of the pregnancies, respectively. The prescription of these kinds of drugs was reduced from the time prior to pregnancy to the last trimester of pregnancy. Only five % of the women in OMT were prescribed antidepressants.

1.4.4 The opioid-exposed neonate

Early studies from the USA showed that, compared to heroin use in pregnancy, methadone maintenance treatment (MMT) in pregnancy was associated with neonates born closer to term, better fetal growth and reduced fetal mortality [66, 89, 95]. However, the neonatal withdrawal from methadone appeared to be more severe than from heroin, as judged by the amount of medication needed to control symptoms and the duration of pharmacological NAS treatment.

Neonatal abstinence syndrome (NAS) consists of a multitude of signs and symptoms in a neonate following an abrupt discontinuation of the exposure to one or several substances after delivery. NAS is characterized by hyperactivity of the central and autonomic nervous systems [96]. The term NAS is

primarily used to describe the neonatal withdrawal after in-utero exposure to opioids. However, substances like alcohol, benzodiazepines, nicotine and antidepressants can either produce NAS or accentuate NAS produced by prenatal exposure to opioids [97, 98]. Forty to ninety percent of neonates who have been opioid exposed during pregnancy develop NAS after birth [99-101]. NAS includes symptoms from various organ systems and if untreated can potentially be fatal. Different scoring systems have been developed for assessing and treating neonates with opioid withdrawal symptoms, but the Finnegan scale and Lipsitz scale are the most commonly used [102, 103]. The neonatal treatment of NAS usually consists of an opioid medication given to the neonate and tapered gradually to zero under close supervision, as well as different, non-pharmacological interventions tailored individually to the infant depending on the condition of the neonate and the development of NAS [100, 101].

The mechanisms which underlie NAS depend on many different maternal and fetal factors and are only partly understood [97]. Even in the early days of MMT in pregnancy, the researchers were puzzled by the fact that the maternal dose of methadone at delivery was not associated with the severity of NAS in the neonate [104]. A lot of studies have subsequently focused on this relationship. Some studies have supported the idea of an association between the methadone dose at delivery and the incidence and duration of NAS [105-109], while other studies have not supported such an association [90, 110-112]. A review of 67 studies was published by Cleary from Ireland in 2010, of which 29 studies were included in a meta-analysis. Cleary concluded that the severity of NAS did not appear to differ whether the woman was on a high or a low dose of methadone at delivery [113]. Studies so far have not found any association between buprenorphine dose at delivery and severity of NAS [90, 114-116].

The use of any drugs in addition to the methadone treatment has been associated with longer duration of pharmacological treatment of the neonate for NAS [112, 117].

Opioid-exposed children born preterm have a lower incidence of NAS and shorter pharmacological treatment than opioid-exposed neonates born at term [118, 119]. This may be due to the immature metabolizing systems for opioids, immaturity of the neonates' neural systems for opioid action or other explanations.

The literature reports varying results concerning the incidence and length of pharmacological treatment for NAS in neonates. It seems that randomised control trials (RCTs) generally find shorter treatment duration for NAS [114, 120, 121] than cohort studies [122, 123]. This may be because the RCTs include carefully selected participants with little comorbidity and little use of illegal drugs. The protocols for diagnosing NAS in RCTs are carefully planned and the scoring of NAS is often blinded.

However, there are most probably also cultural, economic and other factors explaining the varying incidence and length of pharmacological treatment of NAS in different studies/countries.

1.4.5   OMT in pregnancy – possible long-term effects for the child

The early longitudinal studies on children exposed to methadone in pregnancy from the USA which include several variables in the analyses showed that the drug-exposed infants did not differ from a high-risk comparison group on follow-up outcomes [124, 125].

Konijnenberg from SERAF's study group in Oslo performed a review on the potential effects on cognitive development of prenatal exposure to methadone and buprenorphine [126]. She found conflicting research findings, mainly because there are many factors that may affect the developmental outcome of prenatally exposed children. She reported that, although several studies have found that children exposed to OMT medication score lower on tests of cognitive function compared with control groups, few studies have investigated the mechanisms underlying these differences.

Baldacchino from Scotland undertook a systematic review and meta-analysis of neurobehavioural consequences of chronic intrauterine opioid exposure in infants and preschool children [127]. He identified only five studies which quantitatively reported on neurobehavioural function of the children. The meta-analysis showed no significant impairments for cognitive, psychosocial or observed behavioural outcomes when comparing opioid-exposed and non-exposed children.

In a recent review Ross focuses on both animal models and available clinical and imaging data [62]. The prevalence of cognitive impairment produced by prenatal methadone exposure has been questioned because of methodological concerns. The variations found in some studies may be in part due to socioeconomic status and other variables. When it comes to prenatal buprenorphine exposure, although less studied, Ross states that the risk to the fetus may be less than with prenatal methadone exposure.

McGlone with colleagues from Glasgow have studied a group of children prenatally exposed to methadone and a multitude of different legal and illicit substances. They find abnormal visual electrophysiology in the 6-month old infants which are associated with abnormal clinical visual assessment [128]. A recent study by the same research group shows that the neurodevelopment at 6 months was lower for the drug-exposed group of children compared to a control group. The results for the children who were exposed to opioids alone were significantly better than for the children who were exposed to multiple substances [129].

In the SERAF follow-up study of 38 children who have been exposed to OMT medication during pregnancy and a comparison group of 36 low-risk children, the children have been followed prospectively from the pregnancy until the age of eight years [90]. No statistical difference was found by Sarfi in the patterns of sleep-wakefulness in three-month old infants between the two groups [130]. At 6 months of age, Sarfi studied dyadic interaction between the infants and their mothers in the study and comparison group. The only significant impact on the quality of the mother-infant relationship found was the maternal style. "Good maternal style" is characterized by high maternal sensitivity and low maternal intrusiveness. No significant difference in dyadic interaction was found between the OMT group and the comparison group. Sarfi's study of the infants at 12 months and 2 ½ years and their mothers showed significant differences between the groups in perceived child problems in toddlerhood [131]. In a regression model, the mothers' self-reported psychological stress symptoms in terms of depression and anxiety predicted child behaviour problems.

Konijnenberg and Melinder from the Department of Psychology at the University of Oslo investigated the children in the SERAF follow-up study when the children were 4 ½ years. They conclude in a recent publication that, although the children of women in OMT did not appear to have attention deficits in daily life, they may have difficulties with visual selective attention [132]. The same authors have also detected deficits in goal-directed eye movements and smooth pursuit for the OMT-medication-exposed neonates at 4 ½ years [133, 134]. They conclude that the study demonstrates the need for training of cognitive abilities in children of women in OMT, starting in pre-school age. They also underline the differences between the mothers of the two groups concerning education and employment rates and other possible factors (such as maternal use of tobacco, other legal and illegal drugs in pregnancy, family situation) which could have influenced the results. Konijnenberg test out three risk models in her latest publication and the findings suggest that behaviour problems of children of women in OMT may not be a direct exposure effect [135]. She writes that this underscores the importance of taking multiple factors into consideration when studying the effects of prenatal OMT exposure on child behaviour.

The conclusion is that long-term follow up studies of children who have been exposed to OMT medications in pregnancy are sparse and that there are several methodological problems linked to this kind of research. There are a multitude of factors which can affect the development of the fetus during pregnancy and the OMT medication is only one of these variables. The other variables include genetic factors, the sex of the child, nutritional factors, maternal stress, the women's use of legal and illegal drugs and nicotine, the woman's physical and psychiatric health and other factors. Further, after the neonate is born, there are a large number of factors influencing the development of the growing child. These variables include genetic factors, the sex of the child, the caregivers' physical

and mental health, the child's psychosocial up-bringing, the education and income of the parents, the use of nicotine, drugs and alcohol by the caregivers, if there is any physical or psychological abuse of the child and several other factors. The treatment and total follow-up the child and the family receive and how this treatment is perceived by the family also play an important role in the development of the child and the family. The different variables also interact and they may mediate or moderate effects on the development of the child. The development of the child at any given age is a result of all the different factors and how they interact over time. The older the child becomes, the more difficult is it to attribute any one or only a few factors, to the developmental condition observed in the child [136].

Many of the existing studies are primarily on pregnant women in OMT who often have used a large number of legal and illicit substances in addition to their OMT medication.

One of the problems with conducting long-term follow up studies on children exposed to OMT medication and their families is finding relevant comparison groups. Ideally, the groups of children to be compared should only differ in the variable we want to study, namely the exposure to OMT medications during pregnancy. In a relatively wealthy country like Norway, it is especially challenging to find relevant comparison groups, as illustrated by the SERAF follow-up study.

1.4.6   Organization of OMT in pregnancy in Norway

When a patient in OMT becomes pregnant, her coordinating group will be supplemented with professionals responsible for treatment and follow-up in pregnancy. As soon as possible, the total somatic, psychiatric and psychosocial situation for the woman and her partner should be carefully assessed, and a treatment plan should be developed, focusing on both short-term and longer-term follow-up and priorities. Urgent treatment needs, like detoxifying the woman from any legal and illegal drugs of abuse, should be addressed immediately. The woman and her partner should receive thorough and consistent information about the different aspects of OMT in pregnancy. The follow-up of the pregnant OMT patient will be intensified and the cooperation between the professionals from the drug treatment services and those responsible for the pregnancy follow-up will be established.

Figure 1 gives an overview of the total numbers of neonates born to women in OMT in Norway from 1996 until 2013. The numbers are based on the figures from SERAF (especially for the earlier years) and from the Medical Birth Registry (from approximately 2005). There is compulsory registration of a number of variables/outcomes for all births in Norway. The variables include information about all medications the woman has used during pregnancy.

Fig 1. *Numbers of neonates born to women in opioid maintenance treatment (OMT) in Norway 1996 – 2013. Based on information from the Medical Birth Registry (MBR) and the National Centre for Addiction Research (SERAF)*
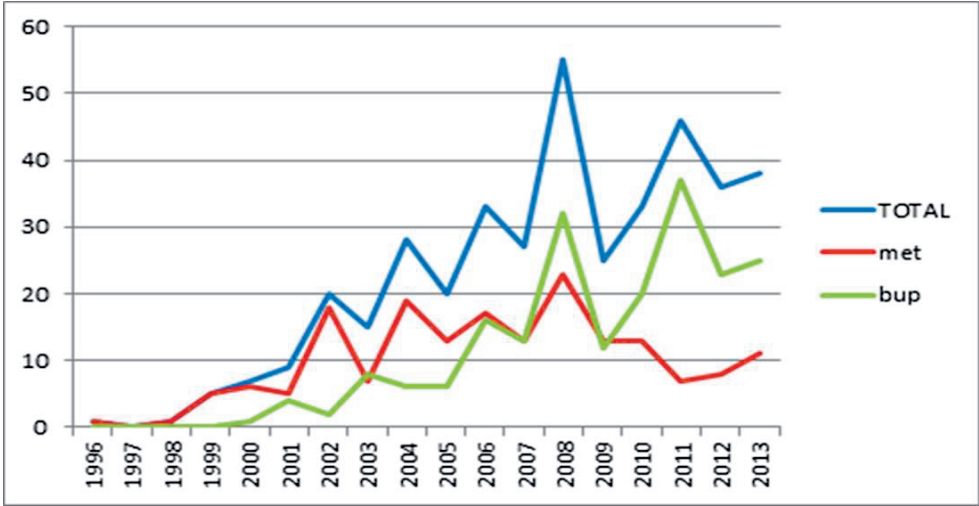
Total = total number of neonates born to women in OMT, met = number of methadone-exposed neonates, bup = number of buprenorphine-exposed neonates

1.5 The current study – research gaps

Norway is a suitable country for studying the maternal and neonatal outcomes of pregnancies where women are in OMT with methadone or buprenorphine as medications. First of all, the co-operation between different parts of Norway concerning treatment and follow-up policies for OMT in general, and OMT-exposed pregnancies specifically, is good. There is a national network of OMT leaders/OMT professionals where treatment strategies, implementation of research results, planned national research/evaluations and policies are discussed twice a year. In 2001, a national guidance was published, giving advice on how to treat pregnant women in OMT [8]. The existence of national co-operation also makes it easier to attract women from all over the country to participate in research.

Secondly, almost all the women are already in OMT with either methadone or buprenorphine when they conceive. This means they are already stabilized on their OMT medication and have climbed a varying number of steps on their rehabilitation ladder before becoming pregnant. Since there are strict professional attitudes and laws regulating the use of legal and illegal drugs in pregnancy in

Norway, the use of alcohol and illegal drugs in pregnancy is low after the determination of pregnancies for women in OMT. Further, the use of both methadone and buprenorphine as OMT medications, have all the time been guided by the same national guidance and have been delivered by the same health professionals in any part of the country.

1.5.1 Methadone or buprenorphine in pregnancy

Until the late 1990's, methadone was the only opioid medication generally used for the treatment of opioid-dependent pregnant women. The first published reports on the use of buprenorphine for pregnant opioid-dependent women, came from Austria [137, 138], and were later followed by reports from the USA [138]. The studies reported that buprenorphine-exposed neonates were born close to term, with relatively normal growth parameters and mild to moderate NAS. The first RCTs comparing methadone and buprenorphine in pregnancy were published by Jones from Johns Hopkins University in Baltimore [121] and Fischer in Vienna [114]. The results suggested that both buprenorphine and methadone were acceptable medications for use in pregnancy and that buprenorphine might lead to a lower incidence and shorter duration of pharmacological treatment of NAS.

Clinical studies comparing MMT with BMT yielded differing neonatal outcomes. A French multicentre study of 259 opioid-dependent pregnant women from 2006 did not report any significant differences in either NAS parameters or growth parameters [115]. A Swedish study from 2008 of 82 pregnancies in opioid-dependent women, however, reported significantly lower incidence of NAS and higher birth weights of infants exposed to buprenorphine in pregnancy than of infants exposed to methadone in pregnancy [139]. A second French study of 135 opioid-exposed pregnancies reported results similar to the Swedish study [140]. However, in all these three studies, MMT and BMT were provided in different treatment settings.

The Maternal Opioid Treatment: Human Experimental Research (MOTHER) study, an international, multicentre RCT of 175 pregnant women, found no difference in the incidence of NAS between the two medications [141]. The duration of NAS treatment was significantly shorter for the buprenorphine-exposed neonates than for the methadone-exposed neonates. There was, however, a significantly higher drop-out rate from treatment in the BMT group than from the MMT group. Jansson reported fetal neurobehavioural effects (fetal heartrate and movements) of exposure to methadone or buprenorphine as part of the MOTHER study for 17 participants [142]. In this preliminary report, she found that buprenorphine led to less depression of fetal neurobehaviour. She concluded that buprenorphine might be a better choice for the treatment of opioid dependence during pregnancy.

Although these studies seem to report better neonatal outcomes for buprenorphine exposure than for methadone exposure in pregnancy, the neonatal results seemed to vary quite a lot between studies. In most of the clinical studies, methadone and buprenorphine were delivered in different clinical settings. It was not clear whether the women receiving MMT and BMT were comparable when it came to background characteristics. When our study was initiated, there were few clinical studies comparing the maternal and neonatal outcomes of methadone and buprenorphine exposure in pregnancy.

1.5.2 Breastfeeding

Although opioid-exposed neonates are particularly likely to benefit from the advantages provided by breast milk and breastfeeding, breastfeeding among women in methadone and buprenorphine treatment has been a controversial issue among health professionals and hence not routinely promoted.

Human milk is the optimal nutrition for the neonate and breastfeeding is associated with a reduction in atopic dermatitis, asthma, obesity, type 1 and 2 diabetes and sudden infant death syndrome (SIDS) for the child [143]. For the mother, a history of lactation is associated with a reduced risk of type 2 diabetes, breast and ovarian cancer.

Both the World Health Organization and national governmental institutions, including the US Department of Health and Human Services and the Norwegian Directorate of Health, recommend that babies should be breastfed exclusively for the first six months of life [144-146].

Hospital initiation rates for breastfeeding in the general population in the United States are 75%, but the rates drop rapidly and at 3 months only 33% of mothers breastfeed exclusively [147]. In Norway, 85% of all the mothers breastfeed exclusively at one month, but the rate drops to 71% exclusive breastfeeding when the babies are three months old [148]. Women, who are young, have low socioeconomic status and who have low confidence in their own ability to breastfeed are less likely to breastfeed. Early cessation of breastfeeding is associated with maternal smoking, first child and low birth weight as well as with inconsistent advice from healthcare professionals [149-151].

The rates of breastfeeding for women in OMT vary between countries, but are relatively low. Breastfeeding was initiated in 24% of methadone-exposed neonates in Massachusetts [152], 28% of the methadone-exposed neonates in Scotland were breastfed [108] and in 45% of drug-exposed neonates in New South Wales (78% of the mothers were in MMT) [153]. Isemann from Ohio, however, found a 60% rate of initiating breastfeeding among MMT mothers at a university hospital [154].

Methadone is excreted into human milk in low concentrations [155-157]. Buprenorphine excretion into breast milk is less studied, but the concentrations appear to be low [158, 159]. The American College of Obstetricians and Gynecologists recommend breastfeeding for women using methadone or buprenorphine if the woman is HIV-negative and drug abstinent [61]. The American Academy of Pediatrics adds that the woman should be closely monitored in a drug treatment program and have significant social support when breastfeeding [160].

In 2006, Abdel-Latif reported that breastfed methadone-exposed infants had reduced NAS severity, the onset of NAS was delayed and the infants had a decreased need for pharmacological treatment of NAS, when compared with infants who were not breastfed [153]. Dryden from Scotland confirmed the reduced odds for breastfed methadone-exposed infants requiring treatment for NAS, compared with infants which were not breastfed [108]. O'Connor's study from Maine in the USA did not find significant differences in the severity of NAS and incidence of needing pharmacological treatment for NAS between buprenorphine-exposed breastfed neonates and neonates which were not breastfed [161].

There is a lack of studies reporting initiation and cessation rates of breastfeeding for women in OMT and a lack of studies reporting the effect of breastfeeding on NAS parameters for neonates who have been exposed to methadone or buprenorphine in-utero.

1.5.3 Tapering methadone or buprenorphine in pregnancy

The literature on tapering OMT medication during pregnancy is sparse. Most of the existing literature is linked to methadone-assisted withdrawal for heroin-dependent patients. In the early history of MMT, opioid addiction in pregnancy was treated either with in-patient detoxification programmes over 5-14 days or with MMT [162, 163]. The early studies demonstrated that most of the patients who underwent withdrawal, followed by rehabilitation, started using opioids again in pregnancy. Case studies also reported stillbirth incidences following detoxification in pregnancy [164] and marked fetal stress during methadone withdrawal [165].

Dashe (1998) from Texas studied 34 pregnant women who underwent in-patient detoxification in mid-pregnancy [78]. Detoxification was the only substance abuse therapy offered at the hospital and it was offered both to women reporting use of opioids and women in MMT. The median methadone dosage was only 20 mg when a 3–39 days detoxification period was started. Twenty-nine per cent of the women resumed opioid use and 12% of the women opted for MMT. Fifty-nine per cent of the women did not relapse. Luty from the UK (2003) performed a 21-day in-patient methadone withdrawal study of 101 pregnant opioid-dependent women [166]. Forty-two women completed the

detoxification. One miscarriage occurred during the first trimester and one premature delivery occurred in the third trimester. The complete obstetric records were available for only 24 of the women. Only one woman was abstinent from all opioid drugs at delivery.

Jones (2008) from Baltimore reported on five groups of participants receiving MMT and/or methadone-assisted withdrawal (MAW) in pregnancy [79]. 1) 67 women underwent a three-day MAW alone. 2) Eight women underwent three-day MAW followed by MMT. 3) 28 women underwent a seven-day MAW alone. 4) 20 women underwent a seven-day MAW followed by MMT. 5) 52 women were in continuous MMT. Patients in all three MMT groups remained in treatment longer, attended more obstetrical visits and more often delivered at the programme hospitals than patients in the MAW alone groups. At delivery, more than 50% of the women who had undergone MAW had positive urine toxicology for illicit drugs, while for the women in MMT the equivalent figures were 15-35%. Stewart (2013) in Texas reported on 95 pregnant women who elected in-patient opioid detoxification [167]. Fifty-three of the women had "successful" detoxification defined as no maternal illicit drug use at delivery, but this group also included women in active detoxification at delivery and women in MMT. The published studies reported above, have focused on methadone-assisted withdrawals over relatively short time periods for pregnant women who were using mainly illicit opioid drugs.

Cleary from Ireland published a study focusing on methadone dosing during pregnancy, which is not a study of tapering as such [168]. He reported that 40% of participants had reduced their methadone dose during pregnancy, while 35% had increased their methadone dose during pregnancy. Day reported from a retrospective case note review from a specialist "mother and baby team" in Birmingham in England [169]. The study included 129 cases over a 5-year period. During the review period, the preferred treatment strategy for women using heroin was MMT, with the option of slowly withdrawing the drug if the patient wanted to do so. In total 99 patients were prescribed methadone and 40 women commenced a reducing methadone regime, which 10 had completed by the time of delivery. Day reported one miscarriage, one stillbirth and two neonates who died soon after birth.

In Norway, most women are already in OMT when they conceive and most of them have been in OMT more than a year. If tapering of the OMT medication is to be performed during pregnancy, the American and Norwegian treatment guidelines recommend slow tapering in mid-pregnancy over a longer period of time [10, 170]. We have not been able to find any studies which have focused on this kind of slow and gradual tapering between pregnancy week 14 and 32.

There is a need to study slow tapering of OMT medication in mid-pregnancy for women in OMT using either methadone or buprenorphine and to study the effect of such tapering on maternal and neonatal outcomes.

1.5.4 Study questions

The following issues were of particular interest in our study since there were research gaps in the international literature where a study conducted in Norway could add valuable knowledge.

1. To compare the maternal and neonatal outcomes of methadone and buprenorphine in pregnancy. Methadone and buprenorphine have always been regulated by the same treatment guidance and delivered in the same clinical settings by the same health professionals in different parts of the country.

2. To study the effect of breastfeeding on neonatal abstinence syndrome (NAS) in methadone- and buprenorphine-exposed neonates. The rates of breastfeeding are high among the general population of Norwegian women and also among women in OMT who give birth.

3. To evaluate the effect of tapering/not tapering of OMT medication during pregnancy. This issue has been debated continuously among politicians and professionals since OMT was introduced in Norway. A considerable proportion of pregnant women in OMT try to taper their OMT medication during pregnancy.

2   Aims

2.1 Overall aim

The overall aim of this study was to explore maternal and neonatal outcomes when women are in MMT or BMT during pregnancy. Further, the aim was to investigate background characteristics of the women and other factors during pregnancy and shortly after birth which could affect the maternal and neonatal outcomes.

2.2 Aims for each paper

Paper 1: The aim was to compare the neonatal outcomes after prenatal exposure to either methadone or buprenorphine. Further it was to evaluate relevant covariates including the use of tobacco, legal and illegal drugs by the pregnant women.

Paper 2: The aim was to evaluate the incidence and duration of breastfeeding for women in OMT and to compare the characteristics of breastfeeding women to those who did not breastfeed. The aim was also to evaluate the effect of breastfeeding on the incidence and duration of neonatal abstinence syndrome (NAS), both for methadone- and buprenorphine-exposed neonates.

Paper 3: The aim was to evaluate the extent to which women in OMT tapered their OMT-medication dose during pregnancy and to compare the characteristics of the women who tapered their OMT-medication dose with the women who did not. The aim was also to study the influence of tapering on the growth- and NAS parameters of the neonates.

Paper 4: The aim was to describe how a well-functioning woman in BMT experienced tapering buprenorphine from 24 mg at 14 weeks gestation to zero in pregnancy week 31, based on the woman's detailed pregnancy blog and the medical records from her GP and local hospital.

3   Material and methods

3.1 Design

The design is a mixed prospective/retrospective national cohort study of 139 women in MMT or BMT during pregnancy who gave birth to 161 neonates in the period from 1996 to March 2009. The study also includes a case report.

3.2 Participants

A crude estimate, based on data from the Norwegian Medical Birth Registry (MBR) and SERAF, is that approximately 225 methadone- or buprenorphine-exposed neonates were born in Norway during the study period. Hence the study sample of 161 neonates comprises approximately 72% of the neonates born to women in OMT during the study period.

The 139 pregnant women/161 infants in the total national study cohort belonged to three different study parts. In the total cohort, 119 women had one child, 18 women had two children (including three twin pregnancies) and two women had three children during the study period. Eleven of the women had neonates in more than one of the study parts below.

The neonates were born at 19 different hospitals. Oslo University hospital (OUS) had 58 (36%) of the deliveries during the study period. Eight more hospitals had more than five deliveries and ten hospitals had fewer than five deliveries during the study period.

Part I. 1996 - 2003: This retrospective part comprised 51 women who gave birth to 56 neonates. The information about the participants was collected by the regional contacts in the OMT services and professionals in the municipalities. The study was part of my national responsibility for overseeing work with pregnant women in OMT, which was linked to my work at the OMT centre in Oslo [9].

Part II. 2005 – 2007: This was a prospective cohort of 38 women/38 neonates in OMT recruited through the regional OMT contacts in the last trimester of the pregnancy. Both the women and the children have been prospectively followed through research at SERAF and at the Cognitive Developmental Research Unit (ECUP), both at the University of Oslo. Part II included 4 women/4 neonates born in 2007; none of these were included in Part III.

Part III. 2004 and 2007 to March 2009: This was a retrospective cohort of 61 women who gave birth to 67 neonates. The women were recruited both through the regional OMT contacts, other addiction treatment facilities and through users' organizations.

Case report - the woman in the case report is included with her first pregnancy in OMT in Part III. The pregnancy described in the case report is not included in the national cohort study.

Table 1 gives an overview of the total number of neonates in our national cohort and the number of women/neonates included in each of the papers in this thesis.

Table 1. Overview of the number of neonates in the total national cohort and the number of participants (women/neonates) included in each of the papers

	Total cohort N (%)	Paper I N (%)	Paper II N (%)	Paper III N (%)
1996-2003	56 (35)	51 (37)	36 (29)	35 (28)
2005-2006	38 (24)	36 (26)	36 (29)	33 (27)
2004 and 2007-2009	67 (42)	52 (37)	52 (42)	55 (45)
Total numbers	**161**	**139**	**124**	**123**

3.3 Methods

In 1999, a standardized questionnaire was developed in order to evaluate all Norwegian women who gave birth while they were in OMT and their neonates [7]. The questionnaire was developed in close cooperation between medical doctors working in OMT and paediatricians from different hospitals in Norway. The questions were based on variables used in the international literature on methadone-exposed pregnancies. The questionnaire in Norwegian and a translated version of the questionnaire in English are enclosed (Appendix I and II).

The questionnaire covered background characteristics about the women, previous pregnancies and information about the women's partners. A detailed description of the current pregnancy, with the use of all medications, cigarettes, alcohol and illicit drugs was covered. The prenatal care, social services follow-up and any in-patient treatment were also accounted for. The in-patient treatment during pregnancy included women with any treatment lasting more than 20 days in order to omit short stays in somatic hospitals. Information on urine drug screening was collected. Special emphasis was put on the use of OMT medication during pregnancy, including changes in dosages, attempts to taper the OMT-medication dose and the use of split dosages. Table 2 shows the questions about the

OMT-medication doses and tapering used in the questionnaire. The birth parameters, as well as the neonatal outcomes, and details about the NAS scoring and treatment, were also examined in the questionnaire.

Table 2. The questions about tapering of the methadone- or buprenorphine-medication dose for the pregnant women in OMT

1. What was the dose of methadone/buprenorphine when you realized that you were pregnant? 2. Did you attempt to taper the dose of OMT medication during pregnancy? (no/yes) 3. In which pregnancy week was the tapering started? 4. What was the lowest dose of your OMT medication during pregnancy? 5. In which pregnancy week did you stop the tapering? 6. What was the dose of methadone/buprenorphine at delivery? *Note: The information concerning changes of the OMT-medication dose was also confirmed by health professionals*

Table 3 shows the different neonatal outcomes measured in Paper I, II and III, respectively.

Table 3. The different neonatal outcomes measured in Paper I, II and III. The last two columns indicate the source of the data

	Paper I	Paper II	Paper III	Questionnaire	Record from hospital
GA at delivery	X	X	X	X	X
Preterm birth<37wks	X	X	X	X	X
Apgar 1 and 5 min	X				X
Birth weight	X	X	X	X	X
Birth weigth<2500g	X	X	X	X	X
Length	X	X	X	X	X
Head circumference	X	X	X	X	X
Incidence of NAS	X	X	X	X	X
NAS peak score	X				X
NAS treatm.duration	X	X	X	X	X

In January 2004 a few additional variables were added to the questionnaire (e.g. education, opioid dependence prior to OMT); hence this information is only available for Part II and III of the study.

3.4 Procedure

Part I.

The Centre for OMT in Oslo had a national responsibility for coordinating how the OMT treatment was delivered throughout the country. The Centre for OMT in Oslo also paid special attention to specific parts of the OMT, such as the treatment of pregnant women with methadone. I was given the responsibility of coordinating national initiatives linked to OMT and pregnancy.

In 2003, the Centre for OMT in Oslo decided to perform a national evaluation of the women who had been using methadone or buprenorphine during their pregnancy from 1996 to 2003. Prior to 2004, all patients starting OMT in Norway gave a written, general consent that information collected during their treatment could be used anonymously for research purposes. From 1999, the pregnancy questionnaire [7] was supposed to be filled in soon after delivery for all women who had been using OMT medications during their pregnancy. The questionnaires were filled in by the professionals responsible for the follow-up and were sent anonymously to the Centre for OMT in Oslo, where the first analyses were performed in 2004. In order to receive information about most of the pregnancies prior to 2004, the regional OMT contacts were reminded several times about the necessity of sending in the questionnaires.

Part II.

This prospective study cohort was planned during 2003. The research team consisted of a child psychologist, a master's degree holder and a medical doctor (GWS=Gabrielle Welle-Strand). The participants for the study were recruited through extensive information (lectures, written information and repeated personal contacts) from the research team to all the regional centres of OMT and to other relevant treatment facilities. The purpose was to recruit as many pregnant women in OMT as possible. The professionals were asked to forward written and oral information to as many potential participants as possible, and encourage the eligible women to contact the research team. The original plan was to recruit women only in 2005. However, as the estimated number of pregnancies in 2005 was too low, the recruitment period was extended to include 2006.

Written information about the project was sent to all eligible women, and a consent form was signed before the first contact was made. The research team organized, scheduled and conducted all the interviews with the women during the last trimester of the pregnancy. There were only two interviewers in Part II. The interviews took place as face-to-face interviews close to or at the women's place of residence. Besides the study questionnaire used for this thesis, the European

Addiction Severity Index (Europ-ASI) [171]and Hopkins Symptom Check List-25 (SCL-25) [172] and Millon Clinical Multiaxial Inventory III (MCMI III) [173] were filled in both by the woman and her partner, for other study parts. Approximately three months after delivery, a telephone interview was performed with the women to complete the questionnaire for the last part of the pregnancy, the birth, the neonatal- and post-partum period. The data from Europ-ASI, SCL-25 and MCMI III were used by other investigators in the research team.

Part III.

In order to have a larger total cohort on pregnancy and neonatal data, a second retrospective part was included in the study. Women who had babies in 2004, 2007 and 2008 were therefore included. The regional centres for OMT, other relevant treatment facilities and the user's organizations were contacted, in order to attract as many participants from these years as possible.

The women were informed by health professionals about the study and also received written information. The women who agreed to participate were sent a consent form, which was filled in before the interview took place. The interviews were mainly conducted by telephone, but some women were interviewed face-to-face. The women were encouraged after the interview to ask any questions that they might have about issues concerning pregnancy and OMT. All the interviews in Part III were conducted by GWS and the participants were also informed that they might contact the interviewer later if they had any further questions about OMT and pregnancy or related issues.

Ensuring the quality of the data in the questionnaire

In Part I, the health professionals responsible for the follow-up of the pregnant women, filled in the questionnaire after delivery based on their contact with the women and the medical records of the patients. This ensured the quality of the data concerning methadone/buprenorphine dosing, other medications, drug use in pregnancy and the neonatal outcomes. In Part II and Part III of the study, the women gave written consent so that the research team could send for:

1. Medical information concerning their OMT medication, including all changes in OMT-medication dosages and the results of urine tests from their GPs or other health professionals responsible for the follow-up. The research team received such confirming information for 73 out of the 88 women (83%).
2. Hospital records concerning the delivery, neonatal outcome and NAS treatment. This information was collected for 82 out of the 88 study participants (93%).

3.5 Ethics

The study was approved by the National Committee for Research Ethics and by the Data Inspectorate in Norway.

In Part I of the study, the data were collected by the professionals responsible for each participant and then the data were sent anonymously to the OMT Centre in Oslo. The participants did not have any direct contact with the researcher. The patients signed a contract at treatment entry which included a section on the use of their data for possible research purposes. Such a general consent for the use of patients' treatment data in research could pose an ethical dilemma. Some patients might have felt that they had to agree to this part of the contract to be included in OMT, even if this was not the case. The general agreement to research use of treatment data was later replaced by individual written consent to take part in particular research projects.

The participants in Part II and Part III of the study gave written consent to participate in the study. Further, most women in these parts of the study also gave separate written consent to send for medical information about their treatment in pregnancy, including OMT treatment and urine test results. Similarly, these women also gave separate written consent to send for records from the hospital concerning delivery, neonatal outcome and NAS assessment and NAS treatment.

The participants in Parts II and III of the study were mainly contacted by the professionals responsible for their follow-up. They received written information about the project. The written information letter/consent form gave detailed information about the purpose of the project, what kind of investigations was planned and when this was going to take place. The information also included the participant's rights to confidentiality, their right to access the information about themselves/their child and their rights to withdraw from the project, if they so wished. The information letter for Part II also included detailed information about collection of meconium and the prospective follow-up of the child and the family until the child was 24 months. Both information letters/consent forms included the right to contact the family again to ask if they would take part in follow-up studies after the end of this project. If the possible participants wanted further information about the project, the project group would be ready to give such information.

Did patients feel that they had to consent to research participation when asked by the professionals who performed their follow-up? Both in the information letter and in the consent form it was clearly written that participation in the research project was totally voluntary and that non-participation would not influence the treatment received. Further, it was underlined that participants could withdraw from the research project at any time, if they so wished.

In Part II of the project, the information letter included information about the research team's legal obligation to give information to the child custody services in cases where information about child neglect was revealed during the project. Many of the women had previous experience with child custody services, either as children/adolescents themselves and/or with their older children. This part of the information letter could have influenced some potential participants to say no to participation in the research.

In Part III of the study the majority of interviews were performed by telephone. Some of the participants did not like talking on the telephone and face-to-face interviews were arranged. The researcher always assured the participant that enough time was available both for the interview and for any questions the woman might have concerning the study or other issues related to OMT and pregnancy. If necessary the interview could take place over more than one day. In both Part II and III of the study, the research team offered the participants their expertise if they had questions or needed guidance concerning the follow-up of the pregnancy and their child after delivery. Many of the participants used this opportunity to ask questions they had. Quite a few participants contacted the research team on later occasions with further questions.

As discussed above, there are some potential ethical dilemmas when doing research on vulnerable groups of patients, such as women who have been using OMT medications in pregnancy [174]. On the other hand, researchers have an obligation to perform research on vulnerable groups. Otherwise there would be a lack of research data to inform treatment choices and treatment recommendations for vulnerable groups of patients in the future. Many of the interviewed women told the researchers that they wanted their experiences to be heard and they wanted to take part in the research in order to help future pregnant patients in OMT to have better treatment and follow-up.

3.6 Statistical analyses

All data analyses were carried out using SPSS for Windows, in versions 16.0 (Paper I), SPSS 19.0 (Paper II) or SPSS 22.0 (Paper III). Pairwise comparisons for continuous variables were done using independent t-tests or Mann-Whitney U-tests, if the variables were not normally distributed. Discrete variables were compared using $\chi 2$ tests for independence or McNemar's test for repeated measures on a single group. A significance level of 5% was chosen for all tests of significance.

Multivariate linear regression analyses were carried out to control for covariates in Paper I and Paper II. The main neonatal outcomes were entered into the regression analyses as dependent variables in turn. The association between the dependent variables (neonatal outcomes) was adjusted for the

relevant covariates in each paper. Both the unadjusted and the adjusted relationship for the main continuous neonatal outcome variables were calculated in Paper I and Paper II.

In Paper III we compared three different groups of women tapering the OMT medication more/less/not at all. Firstly, we conducted one-way ANOVA tests or χ2 tests, for continuous or discrete variables, respectively. Bivariate comparisons were only conducted if the ANOVA tests or χ2 tests were significant.

4 Results

4.1 Paper I

Buprenorphine-exposed neonates had significantly larger head circumferences and tended to be heavier and longer than methadone-exposed neonates, after adjusting for relevant covariates. The covariates included in our regression analyses were the mother's age, length of opioid dependence prior to OMT, low or high dose of methadone or buprenorphine at delivery, use of any drugs early or late in pregnancy, and the use of cigarettes late in pregnancy. There were no significant differences in the incidence or duration of pharmacological treatment of NAS between buprenorphine- and methadone-exposed newborns.

There was significantly more use of opiates in late pregnancy for women in MMT than for women in BMT. For other drugs or other periods of the pregnancy no significant differences in the use of drugs were found between the medication groups. For women in both MMT and BMT there was some use of drugs prior to the determination of pregnancy. For the women in MMT there was a significant decrease in the use of all drugs and alcohol from early to late pregnancy, while for women in BMT only the use of benzodiazepines and alcohol decreased significantly from early to late pregnancy. Women in both medication groups decreased the number of cigarettes smoked daily significantly from early to late pregnancy. Self-report in the interviews revealed more use of drugs than did urine drug screening when conducting validity analyses. Subgroup analyses also showed that women using any opiates, benzodiazepines, cannabis and/or amphetamines early or late in pregnancy, had significantly longer NAS treatment for their neonates, compared to neonates of women not using any drugs during pregnancy.

The only significant difference in background characteristics found was that women in MMT had longer opioid dependence prior to OMT than the women in BMT. Seventy to 80% of the pregnancies for the women in OMT were unplanned. The pregnancies were confirmed between gestation week six and seven. Approximately 90% of the women in both medication groups were in OMT prior to the pregnancy; with 18 months as the median length of OMT for both medication groups. The mean dose for methadone at delivery was 89.9 mg, for buprenorphine it was 13.3 mg.

Conclusions: The results indicate that both methadone and buprenorphine are acceptable medications for use in pregnancy. If starting OMT in pregnancy, buprenorphine should be considered the drug of choice, due to the more favourable neonatal growth parameters.

4.2 Paper II

Methadone-exposed neonates being breastfed had significantly lower incidence of NAS needing pharmacological treatment (53%), than methadone-exposed neonates not being breastfed (80%). Further, neonates of women in OMT who were breastfed had a significantly shorter duration of pharmacological treatment for NAS (28.6 days) compared with neonates of women in OMT who were not breastfed (46.7 days). Correspondingly, a similarly significant difference was found in the treatment duration of NAS for methadone-exposed neonates who were breastfed, compared to methadone-exposed neonates who were not breastfed.

No difference was found in the incidence of NAS for the whole group of OMT-exposed neonates linked to lactation status. Neither were there any differences in NAS incidence or treatment duration for buprenorphine-exposed neonates linked to lactation status.

When controlling for relevant covariates in linear regression analyses comparing the length of NAS treatment linked to lactation status, the following covariates were chosen: parity; the number of cigarettes the last month before delivery; the use of any legal or illicit drugs in the last month before delivery; and gestational age at delivery. The significant differences in NAS-treatment duration were unchanged both for the whole group of infants and for the methadone-exposed infants linked to lactation status.

A majority of women in OMT initiated breastfeeding after delivery, 74% of women in MMT and 80% of the women in BMT. The median length of breastfeeding was 12 weeks for women in MMT and 7 weeks for women in BMT.

We also compared the participants' demographic characteristics. Only preterm birth was associated with less breastfeeding. There were no significant differences linked to lactation status concerning OMT-treatment variables or the use of any drugs or cigarettes in pregnancy.

Conclusion: Breastfed neonates exposed to methadone prenatally had a lower incidence of NAS than those who were not breastfed. Both breastfed neonates exposed to OMT medication prenatally and methadone-exposed neonates in particular needed shorter pharmacotherapy for NAS than neonates who were not breastfed.

4.3 Paper III

Methadone-exposed neonates of women, who tapered more than 50% of their medication dose from determination of pregnancy until delivery, had significantly higher birth weights than neonates of women who tapered their methadone dose between 11 and 50% during pregnancy. No other significant differences were found concerning neonatal growth or NAS parameters between the different tapering groups of women. We did not find any association between unfavourable pregnancy outcomes, such as preterm birth or reduced growth parameters, and neonates of the women tapering the OMT medication the most.

Two women (2%), both on methadone, tapered their OMT medication completely during pregnancy. Fifteen percent of the women tapered their OMT medication dose more than 50% from the determination of pregnancy until delivery. Twenty-four percent of the women tapered their OMT-medication dose between 11 and 50% during pregnancy. Thirty-four percent of the women had unchanged dose during pregnancy. Twenty-four percent of the women increased their dose more than 10% from the determination to the end of the pregnancy. There were no significant differences between women in MMT and women in BMT in the degree of tapering during pregnancy. The women who tapered more than 50% during pregnancy spent a significantly longer time tapering than the women tapering between 11 and 50%.

When we compared the maternal characteristics, we found that the women who tapered more than 50% during pregnancy were significantly more likely to be non-smokers the last month prior to delivery than the women who did not taper. The women who tapered their OMT-medication dose the most did not use any opioids or benzodiazepines in the last month before delivery.

The mean methadone dose levels at delivery were 20 mg, 93 mg and 107 mg respectively, for the women who tapered more than 50% of their methadone dose (Group I), between 11 and 50% of their methadone dose (Group II) or did not taper their methadone dose at all during pregnancy (Group III). The corresponding buprenorphine dose levels for the women in BMT at delivery were 2.3 mg, 12.3 mg and 17.8 mg (Group I, II and III), for the three different tapering groups, respectively.

Conclusion: The only significant difference in neonatal outcome found was that methadone-exposed neonates of women tapering more than 50% of their medication dose during pregnancy had higher birth weights than neonates of women tapering between 11 and 50% during pregnancy.

4.4 Paper IV

The case report is based on a woman's detailed blog during her pregnancy and the medical records from her general practitioner and the local hospital. The woman is 32 years old, married and fully employed. She has been in OMT for seven years without any use of illegal or legal drugs. She is a mother of two children; one of them born during her OMT. In her second pregnancy she stopped smoking and never started again. In her third pregnancy, she decides to try to taper her buprenorphine dose to zero. She suggests the slow and systematic tapering protocol herself after studying and receiving advice in accordance with the Norwegian clinical guidelines on OMT and pregnancy [10]. The professionals performing the follow-up accept her suggested tapering plan which has a reduction of 0.2 mg buprenorphine per day. She starts tapering from 24 mg of buprenorphine in pregnancy week 14. She receives close follow-up from her GP and the local hospital during the tapering.

The woman's withdrawal symptoms increase gradually both in number and in intensity as her buprenorphine dose is reduced. In pregnancy week 31 she is off buprenorphine, but she hardly sleeps, feels mentally worn out and has all the signs and symptoms of severe withdrawal. She is also losing weight and the fundal height measure is not increasing as expected. After receiving conflicting advice from the professionals performing the follow-up and thorough consideration, she chooses to go back on 4 mg of buprenorphine.

For the rest of the pregnancy the woman is maintained on 4 mg of buprenorphine/day and she reports no further withdrawal symptoms. Her son is born in pregnancy week 38+3, his length is 50 cm, his birth weight 2950 g and the head circumference is 34 cm. The baby is observed closely for withdrawal signs, but does not reach the threshold score for pharmacological treatment of NAS. On day 10 after birth, the woman and her son leave the hospital for home. The baby is fed exclusively on breast milk for four months, thereafter he gets formula supplementation.

Conclusion: The woman in the case report tapers her buprenorphine dose from 24 mg in pregnancy week 14 to zero in week 31. The woman develops all the signs and symptoms of severe opioid withdrawal and there are signs indicating that the fetus is not in an optimal position, either. The woman chooses to go back on 4 mg of buprenorphine and her newborn son does not require pharmacological treatment for NAS.

5 Methodological considerations

5.1 Design

The study is designed as a national cohort study with two retrospective parts and one prospective part. Part I is retrospective, Part II has a prospective study design and Part III also has a retrospective study design. This rather unusual study design is a result of combining three study parts in order to reach a sufficient number of study participants. It is also the result of first performing a clinical evaluation of pregnant patients in OMT which then developed into a clinical research project focusing on pregnant women in OMT and their neonates.

In retrospective cohort studies the researcher looks at historical data to study the effect different interventions and variables have on the outcome variables during a certain period. In this study the period is the pregnancy and early neonatal period. The intervention is the use of methadone or buprenorphine by the women during pregnancy. The main challenge of the retrospective study design is the problem of identifying and controlling for possible confounding variables. Another challenge of a retrospective study design may be recall bias.

In a prospective study design the researcher follows the participants from before the period of intervention, and the study variables and outcomes are recorded as the study progresses.

There are some challenges in combining retrospective and prospective data in a common design. The researchers have to ensure as far as possible that the variables recorded during the different study parts are comparable. Also, the choice of variables available in the retrospective study might limit the use of variables in the prospective study. However, the inclusion of a prospective study part in a predominately retrospective study may also strengthen the total study design. The total study has a relatively high number of study participants, due to the combination of the three study parts. The relatively high number of study participants increases the power of the study and reduces the possibility of random errors and type II errors (see 5.6). However, the period for inclusion of participants in the study was from January 1996 to March 2009, which is a relatively long time period. The long inclusion period of participants was the cost of achieving a relatively large study cohort.

The thesis also includes a case report, which sheds further light on the study aim of our third paper, namely the issue of tapering OMT medication during pregnancy.

5.2 Selection bias

Selection bias might arise if the participants in a study not are selected in a random manner and that the participants are different from the non-participants concerning background characteristics, confounders, exposure and/or outcome. Selection bias also refers to the problem that pre-test (here before pregnancy) differences exist between the studied groups, which may interact with the independent variables and thus be (partly) responsible for the observed outcome.

The participants of this study were recruited either indirectly or directly through the professionals responsible for their OMT treatment, other addiction treatment facilities and user organisations throughout Norway. The study recruited approximately 65% of all women who used OMT medications during their pregnancies in the study period [1]. This means that approximately 35% of the women in OMT who gave birth during the study period were not in our study.

There is no systematic information about the women who were not included into the study, but they probably do not differ systematically from the women studied. In some parts of Norway, OMT is less centralized, and general practitioners and community professionals are in charge of the treatment. This could mean that some women in these areas might not have received information about the study. Further it is possible that the better-functioning women in OMT may only have contact with the health services in the municipality and may therefore have been less likely to hear about the study. On the other hand, there will clearly be women who were informed about the study, but for different reasons did not want to participate. They might have been afraid that sensitive data would be disclosed to the professionals responsible for the follow-up. Although, in the written information the potential participants received before signing the consent, the confidentiality of information was thoroughly stressed. We cannot rule out the possibility of selection bias, but it is hard to see that any systematic selection bias might have influenced the findings. If more better-functioning women were included in the study, the results would have been less confounded by the use of legal and illegal drugs.

Twenty women had more than one child in the study. In all three papers, the first pregnancy in OMT was selected if the woman had more than one pregnancy, in order to avoid dependence in the data created by the inclusion of siblings. In this manner, we avoided selection bias when choosing one of several pregnancies for the same woman.

The selection into the different comparison groups (methadone/buprenorphine, lactation status, and tapering status) for each of the three papers might have caused systematic differences in the background characteristics of the groups compared. Therefore the background characteristics of the

different groups compared were analysed, and by different statistical approaches, we tried to minimize this possible source of selection bias.

Another possible source of selection bias could be that the professionals in various parts of the country gave different advice on medical issues related to the group assignment in our different papers. This might have happened despite national guidance giving recommendations on different issues linked to pregnancy and OMT through most of the inclusion period for the study [8].

In Paper I, there may still be some selection of women into either BMT or MMT in the present study; also called confounding by indication. The women in MMT had significant longer opioid dependence before starting OMT than the women in BMT. The women in MMT used significantly more opioids in the last month before delivery than the women in BMT. Together, these findings might indicate that the women recruited into MMT represent a more substance-dependent group than the women in BMT. To reduce this possible confounding, the neonatal outcomes were modelled in turn in a multivariate linear regression analysis to adjust for covariates which could influence the outcome variables.

In Paper II there may also have been some selection. With regard to breastfeeding, some hospitals in Norway have been more reluctant about recommending and supporting breastfeeding for women in OMT. This might have had an influence both on the initiation rates of breastfeeding and also on the length of breastfeeding for some women in the study. The effect of this kind of selection bias would be that there would be less representation from regions/hospitals where professionals to a lesser degree recommend breastfeeding in the breastfeeding group in Paper II. This would mean an uneven representation in the breastfeeding/non-breastfeeding groups from different hospitals, but should not influence the resulting neonatal outcomes.

Likewise, there has been a long-lasting political and professional debate in Norway about tapering OMT medication in pregnancy. It is known that professionals performing the follow-up of pregnant women in OMT give different advice on the issue of tapering the dose of methadone and buprenorphine during pregnancy. This might have led to differences in group assignment in Paper III in various parts of country.

5.3 Information bias

Information bias refers to systematic errors that arise if the information that is collected is not correct or if the variables are misclassified. Recall bias is caused by the differences in the accuracy or

completeness of the recollections retrieved by study participants regarding events or experiences from the past. Recall bias is an issue in all research that involves interviews or questionnaires.

In this study, there were three different ways of collecting the data. In Part I of the study health professionals filled in the questionnaire. For some of the questions, this might have led to missing data, if the information asked for was not available in the participants' medical records. An example of this would be missing breastfeeding information and hence fewer participants in the breastfeeding part of the study.

In Part II of the study, the participants were interviewed face to face in the last trimester of pregnancy, and then by telephone once or several times after delivery. In addition, medical information about the OMT, including changes in dose of OMT medication during pregnancy and the results of urine tests, were collected from the health professionals performing the follow-up. Likewise, hospital records concerning delivery, neonatal outcome and NAS treatment were collected for the participants and their neonates. In this part of the study, the recall bias was probably very low since the interviews took place both during pregnancy and shortly after delivery.

In Part III of the study the women were interviewed retrospectively, mostly by telephone, a median number of 332 days after delivery. Again the medical information both concerning the follow-up in pregnancy (OMT medication variables and urine test results) and hospital records concerning the delivery, neonatal outcomes and NAS treatment were collected for almost all the participants/neonates. In this part of the study, there will probably be some recall bias for some of the variables, like smoking and breastfeeding data, especially for the women who were interviewed a long time after the birth of the child.

There might also have been some underreporting of sensitive data in all parts of the study, for example data about the use of cigarettes, alcohol and legal or illegal drugs during pregnancy. With regard to the use of legal and illegal drugs, however, the validity analyses performed indicated that self-report during interviews revealed more use of drugs than urine drug screening did [1]. Some information in the questionnaire relied entirely on self-report in the second and third part of the study, like information about the use of alcohol, cigarettes and the breastfeeding information.

There were only two interviewers in Part II of the study, who cooperated closely concerning the questionnaire. This helped ensure that the variables of the questionnaire were addressed in the same manner to all the participants, when the interviews were performed. In Part III of the study, one of the interviewers from Part II performed all the interviews. This helped ensure that the variables were addressed in the same manner in Part II and Part III of the study.

Another possible source of information bias in the study would be if the methods of assessing and treating NAS in the 19 different hospitals of the study were different. All the hospitals used a validated method of assessing and treating NAS. Most of the hospitals used a modified Finnegan score, while a few used the Lipsitz score. The hospitals had, however, varying experience in assessing and treating NAS, which could have led to differences between hospitals in the assessment and treatment of NAS. This might have led to variation in the recording of NAS treatment variables at different hospitals. Further, the assessment of NAS was not blinded; hence the professionals assessing and treating the neonates for NAS probably knew which OMT medication the mothers were on or whether the women had tried to taper their OMT-medication dose. This could have led to differential classification: If a professional thinks that buprenorphine leads to less NAS, there is a chance that she will give buprenorphine-exposed neonates lower NAS scores systematically than methadone-exposed neonates. Differential classification could also have occurred if the professional was in favour of tapering in pregnancy and knew which mothers had tapered their OMT-medication dose the most during pregnancy.

5.4 Confounding

In Paper I and Paper II of the study, possible confounding variables were identified and controlled for in a multivariate linear regression analysis. The relevant covariates were chosen on the basis of the literature and analyses of background characteristics of our study population. The covariates included in Paper I were the age of the woman at delivery, years of opioid dependence prior to OMT, low or high dose of OMT medication at delivery, number of cigarettes the month before delivery and the use of any drugs early and/or late in pregnancy. Most other cohort studies which have compared methadone- and buprenorphine-exposure on neonatal outcome, have not adjusted the results for possible confounders [175]. The covariates included in Paper II were parity, smoking during the month before delivery, the use of any drugs during the last month before delivery and gestational age at delivery. Hence, in Papers I and II the effect of possible confounding factors on the neonatal outcomes was reduced to quite a large extent by including the multivariate linear regression analyses.

There were, most probably, also some unexamined covariates in the papers. For Papers I-III there was no assessment of the socio-economic status (SES) of the women in the different groups, beyond length of education and having a partner. In Paper II the questionnaire had no information about the extent of breastfeeding, so there was no information about how many of the neonates were exclusively breastfed. In Paper III, there was no information about the reasons why some women choose to taper their OMT-medication dose. A woman who decides to taper the OMT-medication

dose herself probably has greater chances of tapering substantially [40]. Neither was there any measure of the well-being of the fetus or the women during the tapering process. It is more likely that a woman experiencing severe withdrawal will stop the tapering.

5.5 Type I error

Is there a chance that some of the apparently significant results were attributable to chance? This might be the case when multiple comparisons are carried out. Choosing a level of significance of five percent means that one out of twenty comparisons may come out with a significant result, when there in reality is none (false positive result).

This might have been the case in Papers I-III, but especially for Paper III, where we performed the largest number of comparisons. The reason for performing the ANOVA tests or χ2 tests (including all three comparison groups) before conducting bivariate analyses in this paper was to minimize the probability of Type I error.

5.6 Type II error

Type II errors can arise when the sample size is too small for one or more of the groups in the study. This might be the case for the buprenorphine groups in Paper I and II, the non-breastfeeding group in Paper II and also for the tapering groups in Paper III. Increasing the number of participants in each of these groups might have led to more significant differences in the outcomes between the different groups. Another way of minimizing Type II errors would be by performing meta-analyses based on several studies. In that case the number of participants in the different groups will increase.

5.7 Strengths of the study

There are, however, several strengths of the study.

First of all, the study is a national cohort study, which includes a relatively large proportion of the women who have been pregnant in the study period. The number of participants is relatively high, compared with many other studies where women have used OMT medications during pregnancy [175]. Women who use OMT medications during pregnancy are not necessarily easy to recruit to research.

Second, both methadone and buprenorphine have all through the study period been delivered by the same medical professionals in different parts of Norway. Since 2001 there has been a national guidance, giving evidence-based national recommendations on how to treat women who use methadone or buprenorphine during pregnancy [8]. In many of the countries where similar cohort studies have been performed, methadone and buprenorphine have been delivered in different treatment settings by different health professionals. The fact that both OMT medications are delivered in the same clinical settings by the same health professionals minimises the variance in additional treatment and follow-up. Variations could be how many days a week the women have to come to the clinic, the number of urine tests she has to deliver each month given a certain level of rehabilitation and the type and amount of additional treatment offered. These are clearly factors which might influence treatment outcomes.

Third, more than 90% of the women in the study were already in OMT treatment with either methadone or buprenorphine when they conceived. Median length of their OMT treatment was 18 months prior to the pregnancy. This means that most of the participants in the study had established a stable life-style, not characterized by illicit drug use, prior to the pregnancy. If a woman is included in OMT during the pregnancy, the neonate will most probably have had a period in early pregnancy where the fetus was exposed to many different legal and illegal substances with resulting fluctuations in the concentrations of the various drugs used.

Many of the women participating in our study had not been using any illicit or legal drugs for a long time prior to the start of the pregnancy. The use of all drugs by the study participants was well documented in the study and self-reported use of drugs and alcohol were confirmed with urine drug screening. The use of drugs and alcohol during pregnancy confound the neonatal outcome; both the growth and NAS parameters [89, 95, 112, 117].

In Norway, because of a well-developed welfare system, there is less poverty among women in OMT compared with many other countries where studies are performed. Even though women and families in OMT in Norway are generally poorer than other families, the differences are not as large as in many other countries.

In Papers I and II the continuous neonatal outcomes variables have been adjusted for relevant covariates which could have influenced the outcomes, hence reducing the effect of possible confounders.

Since there is a relatively high proportion of women in OMT in Norway who initiate breastfeeding, Norway is a suitable country for studying the effect of breastfeeding on the neonatal abstinence syndrome outcome variables.

Likewise, for different reasons, many women in OMT in Norway try tapering their OMT-medication dose during pregnancy. This makes Norway a suitable country for studying this controversial and understudied issue and to evaluate whether tapering of the OMT-medication dose might have an effect on maternal and neonatal outcomes.

Lastly, the inclusion of a case report in the thesis gives a realistic clinical example of how a well-functioning woman in OMT experiences tapering her OMT-medication dose during pregnancy. The case also illustrates many of the dilemmas linked to OMT in pregnancy and the challenges both the woman and the professionals face during the course of a pregnancy.

5.8 Internal and external validity

The validity of a study is often divided into internal and external validity. The internal validity is high if the systematic errors are minimized. A randomized controlled trial with a double-blind design is the gold standard of a study with high internal validity. Our study, which is a clinical cohort study with several potential systematic errors/biases as accounted for above, has limitations in its internal validity.

Usually, there will be a balance between the internal and external validity of a study. A study with high external validity means that the results of the study can easily be generalized to other situations and other study populations. In our study, we included as many of the women in Norway who were in OMT during pregnancy in the study period as possible. There are no reasons to think that the pregnant women in OMT who participated in the study were different from the pregnant women who did not participate in the study. Further, the relevant variables were included in the study and the results were adjusted for possible confounders as far as possible. This should mean that the study results can be generalized to other populations of pregnant women in OMT both in Norway and in other countries. The results of a meta-analysis [175] which included Paper I, indicates that the external validity of the study is relatively high. See further discussion of this in 6.1.

6.0 Discussion of the results

6.1 Paper I

The first finding was, after adjusting for relevant covariates, that buprenorphine-exposed newborns had significantly larger head circumferences and tended to be heavier and longer than methadone-exposed neonates. There was no significant difference in the incidence of NAS or in the length of pharmacological treatment for NAS between the neonates exposed to methadone and buprenorphine in utero. However, the *unadjusted* growth parameters were all significantly different, with buprenorphine-exposed neonates being heavier, longer and having larger head circumferences than methadone-exposed neonates. This indicates that the differences found in the non-adjusted growth parameters partly were explained by differences in the chosen covariates between the MMT group and BMT group of women.

Recently, Brogly published a systematic review and meta-analysis comparing the unadjusted neonatal outcomes after prenatal buprenorphine or methadone exposure [175]. The review included a total of 12 studies; four RCTs and eight cohort studies. Paper I was one of the included cohort studies [1]. A total of 515 buprenorphine-exposed and 855 methadone-exposed neonates were included in the meta-analysis. Brogly found significant differences between buprenorphine- and methadone-exposed neonates in favour of buprenorphine-exposed neonates for all the neonatal outcomes where Paper I results were included. All our unadjusted results, apart from the risk ratio for NAS treatment, were in the direction of better outcomes for buprenorphine-exposed neonates, in line with the combined results of Brogly's meta-analyses. The advantage of a meta-analysis is the larger number of participants, which means that type II error due to insufficient power is diminished. However, since the unadjusted results were used in the meta-analysis, it is probable that some of the differences found in the neonatal outcomes were explained by confounding factors, as demonstrated in our study. A recent large retrospective cohort study from USA, comparing 248 pregnant women in MMT to 361 women in BMT, finds similar favourable neonatal outcomes for the buprenorphine-exposed neonates compared to methadone-exposed neonates [176].

In many of the cohort studies included in the meta-analysis cited above [175] and in the recent cohort study, MMT and BMT were delivered in different treatment settings [115, 176-178]. For the four cited studies, BMT was provided through prescription and self-administration, while MMT was provided in a specialized medical clinic, mainly by supervised daily dosing of methadone. In our study both MMT and BMT were delivered by the same health care professionals in different parts of the

country and according to the same treatment recommendations. This makes it more likely that the treatment and follow-up for women in the two different medication groups was similar and reduces the likelihood of confounding.

Second, subgroup analysis in Paper I showed that women using any drugs (opioids, benzodiazepines, cannabis and/or amphetamine early or late in pregnancy) had significantly longer NAS treatment for their neonates compared to neonates of women not using any drugs during pregnancy. Other researchers have had similar findings: Seligman found that benzodiazepine use by the women predicted longer NAS treatment for methadone-exposed neonates [112], while Jansson reported significantly higher incidence of NAS for the neonates of poly-drug using methadone patients [117].

Third, in Paper I the use of benzodiazepines and alcohol were reduced significantly from early to late pregnancy both for women in MMT and BMT. Further, a significant reduction in the use of opioids other than the OMT medication, and of cannabis and amphetamine was found for women in MMT from early to late pregnancy. In the MOTHER study, however, the MMT and BMT participants did not differ during the course of the study concerning the rates of urine tests positive for cocaine, benzodiazepines and marijuana [120]. The professional opinion in Norway is that pregnant women should not use any illegal drugs or alcohol. Further, in Norway, there exists an Act making it possible to treat pregnant drug users compulsorily, if they use drugs which could harm their unborn babies [86, 179]. The Act states that voluntary measures should always be taken first. Probably, the combination of the use of voluntary measures and the possibility of detention, at least partly, explain the reduction in substance use during pregnancy for the women in the study.

Fourth, in Paper I the number of cigarettes smoked daily was significantly reduced for both women in MMT and BMT from early to late pregnancy. Maternal smoking in pregnancy has been associated with lower birth weights, smaller head circumference, intrauterine growth retardation, preterm births and increased morbidity [150]. Smoking has also been shown to play a role in the timing and severity of NAS in neonates prenatally exposed to methadone [98]. Chisolm, however, reported no change in cigarette smoking during pregnancy for either women in MMT or BMT in the USA [180]. There has been a lot of focus on the harms of smoking in pregnancy in Norway, and the daily prevalence of smoking at the end of pregnancy for the general population was 13.2% in 2002-2004 [181]. Chisolm has also published a study about smoking knowledge, attitudes and practices of patients and staff at a perinatal substance abuse treatment centre [182]. She found that half the patients wanted to stop smoking and that the patient desire to stop smoking was underrated by the staff. During the last month of pregnancy, more than 85% of the participants in our study smoked. There is still a great potential for improving pregnancy outcomes for pregnant women in OMT, with

efforts aimed at smoking cessation/reduction for the women, as well as efforts aimed at changing staff attitudes towards smoking among women in OMT.

To sum up: Paper I demonstrated more favourable neonatal growth outcomes for buprenorphine-exposed neonates than for methadone-exposed neonates in line with other studies and a recent meta-analysis. The study also showed shorter pharmacological treatment of NAS for the neonates of women who had not used any illegal drugs or benzodiazepines during pregnancy. In addition, the study demonstrated a significant reduction in the use of cigarettes, alcohol, benzodiazepines and illegal drugs during pregnancy for women in OMT.

6.2 Paper II

The first finding is that breastfed neonates exposed to methadone prenatally have significantly lower incidence of NAS requiring pharmacotherapy. Further both the whole group of infants and the methadone-exposed neonates who were breastfed needed shorter pharmacological treatment of NAS than neonates who were not breastfed. The shorter duration of pharmacological treatment for NAS for breastfed infants did not change when adjusted for relevant covariates in our regression analysis.

Bagley reviewed the literature on the role of feeding method on NAS outcomes and includes Paper II in her review [183]. She concluded that the seven studies indicate an overall decreased need for pharmacological treatment, a decrease in NAS scores and decreased length of pharmacological therapy and hospitalization for infants who were breastfed primarily or breastfed to any extent. Further, Allegaert included Paper II in a summarized table of three population studies in a comment to the editor in 2014 [184]: "Based on a pooled dataset of 400 neonates (54.5% breastfed), there is a significant reduction in the incidence of NAS (54% vs 77%)". The same trends are observed when the duration of NAS treatment is considered, 18 to 23 fewer days of NAS treatment for breastfed infants compared to formula fed infants.

Direct comparison with other studies evaluating the effect of breastfeeding on the incidence of NAS is difficult because they evaluate somewhat different study populations. Other authors have shown significantly lower incidence of NAS needing pharmacotherapy for groups of breastfed infants exposed to opioids compared with exposed infants who were not breastfed: Abdel-Latif found this for a group of infants exposed to opioids and other substances [153], Dryden found the same for neonates of a group of women in MMT where 80% were using illegal drugs [108] and Wachman found the same for a mixed group of methadone- and buprenorphine-exposed neonates [178].

The duration of pharmacological treatment of NAS for infants linked to lactation status is not uniformly documented in the literature. Isemann showed that breast milk feeding was associated with a shorter median duration of pharmacological therapy in both preterm and term infants [154]. Lim found a trend towards breastfed infants needing fewer days of pharmacological treatment of NAS compared to not breastfed infants [185]. Some authors have, however, shown shorter lengths of stay (LOS) at the neonatal unit after delivery for breastfed neonates, which can be seen as a proxy for the pharmacological treatment of NAS [153, 177, 178].

We did not find a similar reduction in the incidence of NAS for breastfed buprenorphine-exposed infants. The effect of breastfeeding on buprenorphine-exposed neonates has been less studied. O'Connor found no significant difference in the incidence of NAS for breastfed versus not breastfed buprenorphine-exposed neonates [161]. The length of pharmacological treatment for NAS was shorter for breastfed than for not-breastfed buprenorphine-exposed neonates in our study, but the difference was not significant. This might have been due to Type II error because of too small comparison groups. To our knowledge, no authors have so far documented a significant difference in the incidence or length of pharmacological treatment of NAS for buprenorphine-exposed neonates linked to lactation status.

The second finding in Paper II was a relatively high initiation rate of breastfeeding (77%) for women in OMT. Recently, O'Connor reported a similar rate of breastfeeding (76%) of buprenorphine-exposed infants in a study from a maternal-infant opioid dependence treatment programme in Maine, USA [161]. Likewise, in a recent large retrospective cohort study from Vermont, 75% of the neonates of women in BMT and 63% of the neonates of women in MMT received breast milk at discharge from hospital [176]. Apart from these comparably high initiation rate of breastfeeding, most of the reported initiation rates for breastfeeding for women in OMT seem to be quite low [152, 177, 186]. There may be two reasons why the initiation rates of breastfeeding are relatively high in our study: First, there is a high breastfeeding initiation rate among the general population of women in Norway [148]. Second, the women who gave birth while in OMT in Norway used almost no legal and illegal drugs in the last part of the pregnancy and during the neonatal period [10, 92], so they were eligible for breastfeeding.

Our study demonstrated a high rate of early cessation of breastfeeding. Eight weeks after delivery 53% of the women in MMT and 39% of the women in BMT were breastfeeding. The median length of breastfeeding was 12 weeks for women in MMT and seven weeks for the women in BMT. O'Connor found that 66% of those initiating breastfeeding were still breastfeeding six to eight weeks after delivery, a rate similar to the results in Paper II [161]. Wachman found an even higher cessation rate;

60% of those who initiated stopped breastfeeding after average 5.88 days [152]. Abdel-Latif reported a median duration of breastfeeding for drug-dependent women of 44 days [153].

The length of breastfeeding and the reasons why women in OMT stop breastfeeding early is clearly an understudied issue. A recently published paper studies the perceptions surrounding breastfeeding decisions and management for women in MMT [187]. The author interviewed seven pregnant women and four postpartum women in MMT. Three major categories were identified: 1) Fears, barriers and misconceptions about breastfeeding and methadone. 2) Motivation and perceived benefits of breastfeeding. 3) Sources of information, support and anxiety about breastfeeding generally and in MMT. This study has identified some important issues which need to be addressed in order to ensure that more women initiate breastfeeding and also useful information on how to encourage women in OMT to continue breastfeeding longer. From unpublished data in our study, we know that the breastfeeding rates vary between women giving birth at different hospitals in Norway. The women also reported that they got varying information and advice concerning breastfeeding from the health professionals.

The results in Paper II add to the literature demonstrating the benefit of breastfeeding on neonatal withdrawal for neonates exposed to OMT medication prenatally. Further, the study highlights the need for an increased focus on measures which can increase the initiation and continuation rate of breastfeeding among women in OMT.

6.3 Paper III

First, we evaluated to what extent the women in the study tapered their OMT-medication dose during pregnancy. Two women (2%), both in MMT, tapered their OMT-medication dose completely during pregnancy. Another nineteen women (15%) tapered their OMT-medication dose more than 50% and 30 women (24%) tapered their OMT-medication dose between 11 and 50% during pregnancy. Forty-two women (34%) had unchanged dose, while 30 women (25%) increased their OMT-medication dose by more than 10% during pregnancy.

The findings are comparable to Cleary's findings from Ireland [168]. He reported that 40% of the participants had reduced their methadone dose during pregnancy, while 35% had increased their methadone dose during pregnancy. Day reported from UK that of 99 pregnant women who were prescribed methadone, 40 women commenced a reducing methadone regime, which 10 women had completed by the time of delivery [169]. Apart from Cleary's and Day's studies , we have not been

able to find other studies with figures on dose reductions and/or dose increases of OMT medication during pregnancy.

The relatively few women (n=21) in our study who tapered more than 50% of their initial dose, might be a selected group of better-functioning women who voluntarily chose to taper. This is indicated by the finding that these women were significantly less likely to smoke during the last month before delivery compared to the women who did not taper, and that they did not relapse to the use of other opioids or benzodiazepines before delivery. Nosyk's retrospective study of 14 602 patients initiating a taper in MMT in Vancouver demonstrated that being young, having good treatment adherence, lower methadone dose at the initiation of tapering, longer tapers and gradual stepped tapering schedules were associated with higher odds of success [41]. Even though there are differences between tapering for non-pregnant OMT patients and pregnant OMT patients, there might be common demographics for the OMT patients who manage to taper to the greatest extent during pregnancy and non-pregnant OMT patients who taper their medication dose.

Second, a significant difference was found in the birth weights of the methadone-exposed neonates of the women who tapered more than 50% of their OMT-medication dose during pregnancy compared to the methadone-exposed neonates of the women who tapered between 11 and 50%. The results show that the women who tapered their OMT-medication most, significantly more often stopped smoking than the women who did not taper. This may have had an impact on the birth weight of the neonates of the women tapering the most. No other significant differences were found for neonatal growth or NAS treatment parameters between the different tapering groups.

The literature has not shown a consistent relationship between the dose of methadone [113, 188] or buprenorphine [116] at delivery, and the incidence and length of pharmacological treatment of NAS for the neonate. Looking at the incidence of NAS for the different tapering groups, there is a tendency for lower NAS incidence for the neonates of the women who tapered more than 50% of their dose during pregnancy, compared to the neonates of the women who tapered their OMT-medication dose less or not at all. However, the differences are not significant, in spite of the fact that the mean dose of methadone was 19 mg and the mean dose of buprenorphine was 2.3 mg at delivery for the women who tapered their OMT-medication dose the most during pregnancy. For the length of pharmacological treatment of NAS between the different tapering groups, no such tendencies were observed in the results.

No unfavourable pregnancy outcomes were found for the neonates of the women who tapered their OMT-medication dose substantially during pregnancy. Since our study only included live births of women in OMT, it is not known if any pregnancies were lost during the OMT women's attempts to

taper during pregnancy. Early abortions [79, 166] and stillbirths [79, 162, 164, 169] have been described in relation to MMT tapering in pregnancy in other studies.

The rationale for the current international recommendations against tapering of OMT medications in pregnancy has primarily been the high risk of relapse to heroin and other drugs of abuse [11, 61, 170]. In our study, no increase was found in the use of any drugs for the women who tapered their OMT-medication dose the most, compared to the other groups of tapering women. However, this finding must be viewed in the light of the restrictive Norwegian policy and laws towards the use of any drugs of abuse or alcohol during pregnancy.

Another possible effect of tapering OMT-medication dose during pregnancy is the risk of prenatal maternal stress. Human studies indicate that women with high stress and anxiety levels are at increased risk of spontaneous abortion and preterm labour and that prenatal stress also is associated with low birth weight and having a growth-retarded neonate [189, 190]. Further, prenatal maternal stress has also been shown to be associated with long-term behavioural consequences for the offspring, including attention and learning deficits, generalized anxiety and depression [191]. A woman who is tapering her OMT-medication dose during pregnancy is surely under a lot of stress [4].

Unfortunately, in Paper III, there was no measurement of the woman's withdrawal symptoms or well-being. Most probably, a woman tapering her OMT-medication dose substantially during pregnancy, will find her general health condition increasingly influenced by the withdrawal symptoms, the further her OMT-medication dose is tapered. Her attention will be directed towards the increasing symptoms of withdrawal as the delivery approaches, as the case report included in this thesis shows [4]. Probably, in a pregnancy where the woman tapers her OMT-medication dose substantially, the woman will have less strength to focus on other health-promoting issues like reducing or giving up smoking and preparing for the period after birth for the neonate and the rest of the family.

McCarthy from California describes an Intrauterine abstinence syndrome (IAS) in his paper from 2012 [192]. The study reviews the evidence for such a syndrome and claims that fetal withdrawal creates an adverse environment for the developing fetal brain which might have long-term health effects. The authors of the MOTHER study comment on McCarthy's review and write that McCarthy fails to define IAS in his review and claims that the literature review is selective [193]. However, McCarthy and the MOTHER study authors agree about the fact that that maternal withdrawal will lead to fetal withdrawal and that the withdrawal of the fetus during maternal withdrawal needs further attention. In our study, there was no measurement of fetal withdrawal or fetal well-being.

If a woman chooses to taper her OMT-medication dose during pregnancy, a gradual taper as recommended in the Norwegian and US national clinical guidelines will logically lead to less severe withdrawal symptoms both for the woman and the developing fetus [10, 170]. This will, however, imply that the fetus will be exposed to OMT medication for most of the pregnancy.

In conclusion, fewer than 20% of the women tapered their OMT-medication dose substantially during pregnancy. Tapering more than 50% of the initial OMT-medication dose was associated with significantly higher birth-weights of methadone-exposed infants. There was no apparent harm to the women or the neonates linked to tapering of the OMT-medication dose.

6.4 Paper IV

This paper gives an in-depth description of an employed, drug-abstinent woman's pregnancy in OMT and her systematic taper of the buprenorphine dose mid-pregnancy from 24 mg until she is off her medication in pregnancy week 31. She is in severe opioid withdrawal and there are signs that the fetus is not doing well either. The woman chooses to go back on buprenorphine 4 mg for the rest of her pregnancy.

The woman's blog was written continuously during her pregnancy, documenting everything she experienced while she tapered her buprenorphine dose. The detailed blog is valuable, because the woman not only writes down all the signs and symptoms linked to her pregnancy and tapering, she also describes the professional follow-up, the comments she receives from different professionals and her own thoughts and opinions about the pregnancy and how it develops. She also describes in detail how the tapering affects her daily life.

The tapering procedure the woman followed is in line with the recommendations for such tapering given in the US and Norwegian national clinical guidelines [10, 170]. The woman also had a major influence on the schedule for tapering; she suggested tapering her dose in small daily steps, rather than reducing the dose once a week. She describes the first symptoms of withdrawal which start in pregnancy week 17. Thereafter the number and intensity of the withdrawal symptoms gradually increase, until the woman has all the signs and symptoms of severe opioid withdrawal when she is off buprenorphine.

Even though the case report gives a detailed description of the symptoms and signs of withdrawal the woman experiences during pregnancy, it is a single case report, which might not be representative for other patients in similar situations.

From pregnancy week 29 to 31, the patient's body weight was reduced by 2.8 kg and during the same period her fundal height measure was not increasing as expected. Together these signs might indicate that the fetus is experiencing intrauterine growth retardation. In pregnancy week 31 + 2, the patient is off her buprenorphine medication, but she hardly sleeps, feels mentally worn out and has all the signs and symptoms of severe withdrawal. The patient is thinking a lot about using drugs, but writes in her blog that she is far from using any drugs. After 8 days without OMT medication, she is sent to the local hospital for a medical check-up. The patient receives opposing advice from the medical professionals: The gynecologist recommends her to stay off buprenorphine, while her OMT doctor recommends that she goes back on a small dose of buprenorphine. Getting conflicting recommendations from the professionals leaves the patient in confusion; whose advice should she listen to? In her blog, she describes in detail how painful the decision process is for her. Eventually, she decides to go back on 4 mg of buprenorphine. The patient's severe withdrawal was a condition of extreme maternal stress, which is associated with unfavourable short and long term outcomes for the fetus [189, 191].

The patient reports being confused and frustrated about getting conflicting advice from different professionals. It is important that the women in OMT receive consistent, evidence-based information about the different aspects of pregnancy and OMT from the different professionals performing the follow-up.

In conclusion, Paper IV gives a detailed clinical example on how a well-functioning woman in OMT tapers her buprenorphine dose mid-pregnancy from 24 mg to zero. The woman's withdrawal symptoms increase gradually in numbers and intensity, until she is off buprenorphine in pregnancy week 31. After 8 days without OMT medication, she chooses to go back on 4 mg of buprenorphine for the rest of the pregnancy.

7.0 Clinical implications

Several clinical implications arise from our study.

The results indicate that both methadone and buprenorphine are acceptable medications for use in pregnancy. Our findings support that if OMT is to be started during pregnancy, buprenorphine should be considered the drug of choice, because of the more favourable neonatal growth outcomes in our study. These findings have been confirmed by the recent meta-analysis which included our Paper I [175].

We also documented that any use of illegal drugs or benzodiazepines during pregnancy was associated with longer lasting pharmacological NAS-treatment for the neonates. This underlines the importance of pregnant women in OMT not using benzodiazepines, alcohol or illegal drugs. There are, of course, other reasons for the women to avoid using drugs. Abstaining from drug use will improve the women's parenting abilities and their ability to make optimal use of the follow-up they receive.

Our results show that the majority of women in the study continued to smoke during pregnancy, although they reduced the number of cigarettes they smoked daily. The focus on smoking cessation or smoking reduction should be intensified for women in OMT, for the benefit of both the neonates and the women themselves.

The study demonstrated that although many of the participants initiated breastfeeding, many of them stopped breastfeeding early. Apart from the general advantages of breastfeeding for neonates, the study adds to the literature demonstrating that breastfeeding has a positive effect on NAS. Pregnant women in OMT should be educated about the benefits of breastfeeding in general and for neonates exposed to OMT medication in particular. The women need close follow-up during the neonatal period, at the hospital and during the following months, to encourage and support them in their efforts to initiate and continue breastfeeding. Additionally, health care professionals need to be educated about the benefits of breastfeeding for neonates exposed to OMT medication and in evidence-based methods for promoting and supporting continuing breastfeeding among women in OMT.

The main recommendation from WHO and countries which have evidence-based recommendations about OMT medication and pregnancy is that women should stay on their OMT medication during pregnancy [10, 11, 170, 194, 195]. However, well-functioning women in OMT and others requesting such information should be informed about the possibility of tapering their OMT medication during pregnancy. The information should include how and when such tapering could be done. They should

also be informed that few women manage to taper their OMT-medication dose substantially during pregnancy. Women also need to be informed that even if they taper their OMT-medication dose substantially, they might still have a neonate who will develop NAS requiring pharmacological treatment. Tapering the OMT medication should be completely voluntary and the woman should know that the tapering can be stopped or reversed whenever the woman decides. If the woman tries to taper her OMT-medication dose, close professional follow-up needs to be established and the woman should have easy access to consistent professional advice when she needs it.

A woman in OMT who becomes pregnant should be carefully assessed taking into account her life-time and recent drug-use story, her history of addiction treatment including OMT, her somatic and psychiatric health, her use of medications and her total psychosocial situation. Her treatment plan should be regularly and carefully revised and individualized, taking into account her wishes and opinions regarding the treatment and follow-up during pregnancy and the neonatal period.

A pregnant woman in OMT needs close follow-up during the pregnancy and the period at the hospital including the delivery. The neonate, the woman and her partner will need close follow-up during the assessment and possible treatment of NAS in the neonatal period. The family will need continuous support and non-judgemental attitudes from all the treatment professionals involved in their follow-up.

All professionals involved in the follow-up of women in OMT should receive comprehensive training about OMT and the different aspects of OMT during pregnancy and the neonatal period.

Last, but not least, there should be continuous focus on the necessity of consistent, balanced and evidence-based information about the treatment options and follow-up for the women who become pregnant in OMT. A pregnant woman in OMT is in a vulnerable position. Getting conflicting information about important aspects of her treatment, will surely lead to unnecessary confusion and worrying on the part of the woman and her partner.

8.0 Future research

Generally, there is a need for more carefully designed prospective studies of OMT in pregnancy. This will make it possible to record all the necessary baseline variables for the pregnant women. Further, a prospective design will also make it possible to monitor continuously the pregnant woman's well-being/quality of life, her possible withdrawal symptoms, her use of OMT medication and other medications, her use of tobacco, alcohol and legal and illicit drugs, as well as the treatment and follow-up she receives from different professionals. A prospective design will also make it possible to monitor the fetus closely, allowing a better understanding of the fetus' reactions to the woman's OMT medication and possible alterations in dosing.

Even though the recent meta-analysis comparing methadone- and buprenorphine-exposed neonates is quite clear about the more favourable neonatal outcomes for buprenorphine-exposed neonates, some of the differences found might be due to selection bias/confounding [175]. Hence, carefully designed studies comparing MMT and BMT in pregnancy are still needed, where the possible confounding variables should be included in the analyses. Both medications are still needed in OMT, because opioid-dependent women need a choice of effective medications for their OMT. We still need a better understanding of the optimal treatment with either methadone or buprenorphine during pregnancy, both concerning dose reductions/increases and also the optimal dose intervals in pregnancy.

We need research focusing on breastfeeding amongst women in OMT. Primarily, we need to study how we can motivate more women in OMT both to initiate and to continue breastfeeding. It would be of interest to conduct studies focusing on factors which increase and reduce the chances of women commencing and continuing breastfeeding. The studies need to look at factors linked to the women themselves and also variables linked to professional recommendations about breastfeeding the women receive during their follow-up. Further, there is a need for more studies focusing on the effect of breastfeeding on neonatal abstinence syndrome, especially for BMT-exposed neonates.

Prospective studies on tapering OMT medication for pregnant women are needed. Ideally, a study should be designed where women who chose to taper their OMT medication could be compared to a group of women who chose not to taper. In such a study, there would need to be close monitoring of the fetuses and the women to ensure their continued safety and well-being, and to deal with any possible withdrawal symptoms during tapering.

There is also a need for qualitative research about OMT and pregnancy; how different treatment methods and professional follow-up/treatment and systems for patient involvement influence the outcomes.

Lastly, there is a need for longitudinal follow-up studies where children who have been prenatally exposed to OMT medications and their families are followed over a number of years, to study the effect of different treatment modalities and follow-up strategies. Ideally such longitudinal studies should be started in pregnancy, and somatic, psychiatric and psychosocial variables for the fetus/child and the parents should be registered on an ongoing basis. Longitudinal studies of this type would also shed light on possible long-term effects of exposure to the different OMT medications in pregnancy, as well as other variables and moderating and mediating factors which could influence the shorter- and longer-term outcomes.

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Errata I

Paper I.

There are two mistakes in our report of malformations, see 3.3. Unadjusted pregnancy, birth and neonatal outcomes, last paragraph:
1. *The child born with a gastroschisis was exposed to methadone, not to buprenorphine.*
2. *The other child reported as being born with spina bifida, was born with a hydrocephalus. The child with the hydrocephalus was exposed to buprenorphine in utero.*

Table 4: Unadjusted pregnancy, birth and neonatal outcome…..It should be stated that *p<0.05 for the difference in head circumference between methadone- and buprenorphine-exposed neonates in Table 4.* In the text this is stated correctly.

Paper II

RESULTS: Breastfeeding rates and duration: The correct figure should be that *80% of the women in BMT initiated breastfeeding after delivery.* In Table 1 the correct numbers for buprenorphine are given: 37 out of 46 women in BMT initiated breastfeeding (80%).

Errata II. Added in June 2015 (accepted by the committee)

Paper III

In Table IV under Background characteristics, 5.line: the correct wording should be: *Current pregnancy planned* (not unplanned as stated).

Appendix I

SPØRRESKJEMA VED GRAVIDITET/FØDSEL I LAR

X= vet ikke/vil ikke svare, N= spørsmålet ikke aktuelt for informanten

1. Skjema

A. Informantens prosjektnummer ☐☐☐

B. Termin dato (ddmmåå) ☐☐☐☐☐☐

C. Dato utfylt (ddmmåå) ☐☐☐☐☐☐

4 Bakgrunnsopplysninger om kvinnen

A. Bostedsfylke

B Alder i hele år ved termin ☐☐

C. Antall år grunnskole/videregående skole ved fødsel ☐☐

D. Antall år med høyere utdanning ved fødsel ☐☐

E. Kroniske fysiske og psykiske sykdommer ved påvist graviditet (angi hvilke, angi alltid hvis pos på HIV eller hepatitt)

F. Antall år med opiatavhengighet før oppstart LAR ☐☐

G. Antall år med sprøytebruk før oppstart LAR ☐☐

H. Antall måneder med institusjonsbehandling før LAR ☐☐☐

I. Faste medikamenter (ikke LAR-medikament) ved påvist graviditet (angi alle preparater og dosering)

3. Graviditeter

A. Antall tidligere fødsler ☐☐

- årstall 1.fødsel ☐☐☐☐

- årstall 2.fødsel ☐☐☐☐

- årstall 3.fødsel ☐☐☐☐

- årstall 4.fødsel ☐☐☐☐

- årstall 5.fødsel ☐☐☐☐

B. Når ble denne graviditeten påvist (angi svangerskapsuke)
(positiv gravitest eller lignende) ☐☐

C. Var denne graviditeten planlagt
(0=nei, 1=ja) ☐

D. Når fikk lege/sosialsenter/andre med oppfølgingsansvar vite
om graviditeten (angi svangerskapsuke) ☐☐

4. Partner(ved fødsel)

A. Fast partner
(0=nei, 1=ja) ☐

B. Var fast partner ved fødsel barnefar
(0=nei, 1=ja) ☐

C. Partner i LAR (legemiddelassistert rehabilitering)
(1= partner i LAR, 2= partner ikke i LAR) ☐

D. Partners misbruk ved fødsel
(1= partner rusfri, aldri rusproblemer, 2= partner rusfri, tidligere rusproblemer,
spesifiser, 3= partner i aktivt misbruk, spesifiser)
evt.spesifisering ☐

5. LAR = legemiddelassistert rehabilitering ved påvist graviditet

A. Medikament (1= metadon, 2= Subutex, 3= Suboxone,
4= annet, angi hva, 5=ikke LAR) ☐

B. Antall måneder i LAR ved påvist graviditet ☐☐☐

C. Dosering i mg ved påvist graviditet ☐☐☐

D. Siste serumkonsentrasjon av metadon/buprenorfin før graviditet ☐☐☐☐

E. Angi hvor mange måneder før påvist graviditet serum ble tatt? ☐☐☐

F. Hvis påbegynt LAR i graviditet, i hvilken svangerskapsuke? ☐☐

G. Hvis forskrivning av "uoffisiell" vedlikeholdsmedikament (med vanedannende medikament) ved påvist graviditet, angi type, dosering og varighet av behandlingen.

6. Bruk av rusmidler siste måned *før påvist graviditet* -

A. Angi antall sigaretter pr dag ☐☐

B. Brukes annen type nikotin (0=nei, 1=ja) ☐
   Hvis ja, spesifiser type(snus, plaster, tyggegummi etc) *og mengde.....*

C. Antall urinprøver avlevert denne måneden ☐

D. Selvrapportert og påvist bruk av medikamenter/rusmidler i denne perioden
   (be om samtykke til å innhente urinprøveresultater)

	Brukt medikamentet/ rusmiddelet 0=nei, 1=ja	*Antall urinprøver positive på medikamentet/ rusmiddelet i perioden*
Opiater (annet enn LAR-medikament)	☐	☐☐
Benzodiazepiner	☐	☐☐
Cannabis	☐	☐☐
Amfetamin	☐	☐☐
Alkohol	☐	☐☐
Metadon/buprenorfin	☐	☐☐

7. Oppfølging under svangerskap

A. Svangerskapskontroll ☐
   (1= fulgt opp alle avtaler, 2=fulgt opp de fleste avtaler
   3= uteblitt fra mange avtaler, 4= ikke møtt til noen avtaler)

B. Hvem har ansvar for LAR-forskrivning ☐
   (1= LAR-lege, 2= fastlege, 3= annen lege; angi hva slags lege)

C. Har du fulgt opp avtaler med forskrivende lege? ☐
   (skåring som 7A -svangerskapskontroll)

D. Angi andre personer og instanser med regelmessig oppfølging under sv.skapet ☐
   (1= sosialkontor, 2 = rus-poliklinikk, 3= spesial-team for gravide(rus, psyk.sos), ☐
   4= andre*; angi*. Kan skåre flere)

   ☐

8. Total bruk av rusmidler i graviditeten – selvrapportert

NB! Punkt A fylles ut med antall – eks 00 hvis ingen sigaretter/dag

1.trimester= sv.skapsuke 1 tom 13 2.trimester= sv.skapsuke 14 tom 26 3.trimester= sv.skapsuke 27 tom 40	Første trimester (1=ikke brukt, 2=brukt 2-3 ggr pr mnd, 3= brukt 1-3 ggr pr uke, 4=brukt daglig eller nesten daglig)	Andre trimester (kod som 1.trimester)	Siste trimester (kod som 1.trimester) *Fylles ut etter fødsel*	Hele graviditeten (1=ikke brukt, 2= brukt) *Fylles ut etter fødsel*
A. Nikotin (sigaretter/dag)	☐☐	☐☐	☐☐	☐
B. Opiater (andre enn metadon/buprenorfin)	☐	☐	☐	☐
C. Benzodiazepepiner	☐	☐	☐	☐
D. Cannabis	☐	☐	☐	☐
E. Amfetamin	☐	☐	☐	☐
F. Sprøyter	☐	☐	☐	☐
G. Andre rusmidler/medikamenter, *spesifiser………..*	☐	☐	☐	☐

9. Bruk av alkohol i svangerskapet

A. Hvor ofte drakk du alkoholunder graviditeten?

- Siste 3 måneder før siste menstruasjon (1=aldri, 2=sjeldnere enn 1 gang/mnd, 3=ca 1-3 ggr/mnd, 4=ca 1 gang/uke, 5= ca 2-3 ggr pr uke, 6= ca 4-5 ggr/uke, 7=6-7 ggr/uke) ☐

- I dette svangerskapet, 0-12.svangerskapsuke, scores som over ☐

- I dette svangerskapet, 13-24.svangerskapsuke, scores som over ☐

- I dette svangerskapet, etter 25.svangerskapsuke, scores som over ☐

B. Hvilken type alkohol drikker du vanligvis? (1=lettøl, 2=øl, 3= rød/hvitvin, 4=rusbrus, 5=hetvin, 6=brennevin) – score evt flere ☐

☐

☐

C. Dersom du har endret ditt alkoholbruk før eller under dette svangerskapet, når skjedde endringen? (det kan settes flere kryss)

- Siste 3 mndr før siste menstruasjon (1= endring til mindre mengder, 2=endring til større mengder)

□

□

- I svangerskapsuke 0-6, scoring som over

□

- I svangerskapsuke 7-12, scoring som over

□

- I svangerskapsuke 13-24, scoring som over

□

- Etter svangerskapsuke 25, scoring som over

□

10. Medisinske komplikasjoner under svangerskapet

A. Oppsto medisinske komplikasjoner under svangerskapet? (0=nei, 1=ja)

□

Hvis ja spesifiser………

B. 1.komplikasjon - angi type, varighet og grad

C.2.komplikasjon - angi type, varighet og grad

11. Innleggelser under svangerskapet – Innleggelser på fødeavdeling, til avrusning, skjerming institusjon etc

A. Var pasienten innlagt under svangerskapet?
   (0=nei, 1=ja)

□

B. Totalt antall døgn innlagt under svangerskapet

□□□

(fyll ut for hver innleggelse)
C. Type institusjon, varighet og årsak

D. Type institusjon, varighet og årsak

E. Type institusjon, varighet og årsak

v

F. Innleggelse(r) etter § 6-2a (0=nei, 1= ja)

beskriv antall innleggelser etter § 6-2a, hvilken
institusjon, varighet og årsak

12. Nedtrapping av LAR-medikament

A. Forsøkt nedtrapping under graviditet (0=nei, 1=ja)?

B. I hvilken svangerskapsuke ble nedtrappingen startet?

C. I hvilken svangerskapsuke ble nedtrappingen
avsluttet?

D. Angi laveste medikamentdosering i mg

E. Kommenter hvordan evt nedtrapping forløp

F. Har pasienten byttet LAR-medikament under
graviditet (0=nei, 1=ja)

G. Hvis ja på forrige sp.mål, spesifiser i hvilken
svangerskapsuke og beskriv forløp

13. Delt dosering av LAR-medikament – kun for gr.1

A. Forsøkt deling av medikamentdose? (0=nei, 1=ja)

B. Hvordan ble medikamentdoseringen delt? (f.eks 2/3
om morgenen og 1/3 om kvelden)

C. Fra hvilken svangerskapsuke ble
medikamentdoseringen delt?

D. Hva var pasientens erfaring med delt medikamentdosering?

14. Abstinens under svangerskapet

A. Var pasienten abstinent under graviditeten? (0=nei, 1=ja)

☐

B. I hvilke(n) perioder av svangerskapet var dette?

C. Grad av abstinenser (1=milde, ingen tanker om rus, 2=moderate, noe tanker om rus, 3=sterke, alvorlige tanker om rus, 4=sterke, inntak av rusmidler)

☐

D. Utfyllende kommentarer

15. Bruk av rusmidler siste måned før fødsel

A. Angi antall sigaretter pr dag

☐☐

B. Ble annen type nikotin brukt? (0=nei, 1=ja)
   Hvis ja, spesifiser type(snus, plaster, tyggegummi etc).....*og mengde*

☐

C. Antall urinprøver avlevert denne måneden
   Kod NN hvis ikke aktuelt

☐☐

D. Selvrapportert og påvist bruk av medikamenter/rusmidler i denne perioden
   (jmfr innhentet samtykke til urinprøveresultater)

	Brukt medikamentet/ rusmiddelet 0=nei, 1=ja	*Antall urinprøver positive på medikamentet/ rusmiddelet i perioden*
Opiater (annet enn LAR-medikament)	☐	☐☐
Benzodiazepiner	☐	☐☐
Cannabis	☐	☐☐
Amfetamin	☐	☐☐
Alkohol	☐	☐☐
Metadon/buprenorfin	☐	☐☐

16. LAR ved fødsel – gr. 1

A. Medikament (1=metadon, 2= Subutex, 3=Suboxone, 4=annet; angi hvilket)

☐

B. Dosering ved fødsel (i mg)

☐☐☐

C. Siste serumkonsentrasjon av medikament før fødsel (serumkonsentrasjon i nmol/l)

☐☐☐☐

D. Svangerskapsuke for siste serumkonsentrasjon

☐☐

17. Fødselen (primært fra fødselsjournal)

A. Hvilket sykehus ble barnet født på?

B. Måned og år barn født

☐☐☐☐

C. Antall svangerskapsuker ved fødsel (1 desimal)

☐☐☐☐

D. Fødsel (1= spontan, 2=indusert)

☐

E. Operativ (0=nei, 1=ja)

☐

angi type……

F. Hva slags smertelindring ble brukt?

18. Barnet ved fødsel (primært fra barnejournal)

A. Apgar score 1 minutt

☐

B. Apgar score 5 minutter

☐

C. Kjønn (1= gutt, 2= jente)

☐

D. Lengde (i cm, 1 desimal)

☐☐☐☐

E. Vekt (i hele gram)

☐☐☐☐

F. Hodeomkrets (i cm, 1 desimal)

☐☐☐

G. Metadonkonsentrasjon i navlestrengsblod

⬚⬚⬚⬚

H. Metadonkonsentrasjon i serum

⬚⬚⬚⬚

19. Barselperiode

A. Antall døgn innlagt på barselavdeling/sykehotell (mor)

⬚⬚⬚

B. Antall døgn innlagt barneavdeling (barn)

⬚⬚⬚

C. Mor utskrevet til (1=hjem, 2= institusjon, angi type institusjon)

⬚

D. Barnet utskrevet til (1=hjem med mor, 2=til institusjon med mor, 3=til institusjon alene (angi type institusjon), 4= annet, *angi til hva*

⬚

20. Abstinensproblematikk barn
(primært fra epikrise)

A. Hadde babyen neonatalt abstinenssyndrom (NAS)
(0=nei, 1=ja)

⬚

B. Brukte sykehuset Finnegans scoringsskjema til måling av NAS
   (0=nei, 1=ja)

⬚

hvis nei på 20 B, angi type scoringssystem som ble anvendt

C. Angi høyeste Finneganscore, alternativt annet score

⬚⬚

D. Hvilket levedøgn hadde babyen høyest abstinensscore?

⬚⬚

E. Behov for medikamentell behandling for NAS
   (0=nei, 1=ja)

⬚

- hvis ja på E, hvilket levedøgn startet den medikamentelle behandlingen

⬚⬚

- hvilket levedøgn ble den medikamentelle behandlingen avsluttet?

⬚⬚

- totalt antall døgn med medikamentell behandling for NAS

⬚⬚⬚

F. Hvilket/hvilke medikamente(r) ble i behandlingen av NAS ?
(1=morfinsulfat, 2=opiumsdråper, 3=Paragoric dråper, 4=annet)

⬚

hvis 4, angi hvilket preparat…..

G. Beskriv evt.ikke-medikamentell tiltak i forhold til NAS……….
  (*type tiltak og varighet av disse*)

21. Amming

A. Ammet mor?
  (0=nei, 1=ja)

B. Hva slags råd fikk mor i forhold til å amme
  (1=mor ble rådet til å amme, 2=mor ble frarådet å amme, 3= mor fikk ikke spesielle råd)

  Hvis mor ble frarådet å amme, angi hvorfor?

C. Ønsket mor å amme?
  (0=nei, 1=ja)

  hvis nei, angi hvorfor…..

D. Hvor mange uker ammet mor?

E. Evt kommentarer til amming

Ytterligere kommentarer/presiseringer rundt graviditet/fødsel

Appendix II
QUESTIONNAIRE FOR PREGNANCY AND BIRTH IN OMT

X= Do not know/do not want to answer, N = not a relevant question

1. Questionnaire information

    A.   The participant's project number   ☐☐☐

    B. Expected date of delivery (ddmmyy)   ☐☐☐☐☐☐

    C.   Date of completion of questionnaire (ddmmyy)   ☐☐☐☐☐☐

2. Background information about the woman

    A.   County of residence

    B.   Age (whole number) at expected date for birth   ☐☐

    C.   Number of years primary and secondary school (at delivery)   ☐☐

    D.   Number of years education after secondary school   ☐☐

    E.   Any chronic somatic and/or psychiatric disorders when the pregnancy was confirmed (write down the conditions, always ask about HIV and hepatitis)

    F.   Number of years of opioid dependency prior to OMT   ☐☐

    G.   Number of years of injecting drug use prior to OMT   ☐☐

    H.   Number of months in-patient addiction treatment prior to OMT   ☐☐☐

    I.   Any regular medications when the pregnancy was confirmed? (write down all medications and their dosing schedule)

3. Pregnancies

    A.   Number of previous deliveries   ☐☐

         -   Year of 1.birth   ☐☐☐☐

         -   Year of 2.birth   ☐☐☐☐

- Year of 3.birth ☐☐☐☐

- Year of 4.birth ☐☐☐☐

- Year of 5.birth ☐☐☐☐

B.   When was the current pregnancy confirmed (week of gestation) ☐☐
(pregnancy test positive or similar confirmation)

C.   Was this a planned pregnancy? ☐
(0=no, 1=yes)

D.   When did your doctor or other professionals get to know about ☐☐
the current pregnancy (week of gestation)?

4. Partner (at delivery)

A.   Regular partner? ☐
(0=no, 1=yes)

B.   Was the regular partner the biological father? ☐
(0=no, 1=yes)

C.   Was the regular partner in OMT (Opioid maintenance treatment)? ☐
(1= partner in OMT, 2= partner not in OMT)

D.   Partner's use of drugs at delivery ☐
(1= partner no drug use, never have had drug use disorders,
2= partner no drug use, previous drug use disorders, please specify,
3= partner actively using drugs, please specify)

5. OMT = opioid maintenance treatment when pregnancy was confirmed

A.   Medication (1= methadone, 2= Subutex, 3= Suboxone, ☐
4= other, please specify, 5=no OMT)

B.   Number of months in OMT when pregnancy was confirmed ☐☐☐

C.   Dose of OMT-medication when pregnancy was confirmed (mg) ☐☐☐

D.   Last blood concentration of methadone/buprenorphine before pregnancy ☐☐☐☐
(nmol/l)

E.   How many months before the confirmation of pregnancy ☐☐☐
was the blood concentration test taken?

F.   If OMT was started in this pregnancy, in which week of gestation? ☐☐

G. Any other prescriptions of addictive drugs prior to the pregnancy? (please state all prescribed addictive drugs, including type of medication, dosing and for how long the prescription had lasted)

6. Use of any legal and illegal drugs *last month before the pregnancy was confirmed* -

A. Number of cigarettes/day

B. Use of any other type of nicotine (0=no, 1=yes)
If yes, specify type and quantity…..

C. Number of urine samples delivered this month

D. Self-reported and confirmed use of medications/drugs during this month
(remember written consent form for results of urine tests etc)

	Used the medication/ the drug this period (0=no, 1=yes)	*Number of urine tests positive for the medication/ the drug during the period*
Opiates (other than the OMT-medication)		
Benzodiazepines		
Cannabis		
Amphetamines		
Alcohol		
Methadone/buprenorphine		

7. Follow-up during the pregnancy

A. Pregnancy check-ups
(1= attended all appointments, 2=attended most appointments 3= attended some appointments, 4= not attended any appointments)

B. Who prescribes the OMT-medication?
(1= OMT-doctor, 2= GP, 3= other doctor; please specify)

C. Have you attended the appointments with the prescribing doctor?
(Score as 7A – pregnancy check-ups)

D. Other persons or offices with regular follow-up during the pregnancy
(1= social welfare, 2 = out-patient addiction unit, 3= special team for pregnant women 4= others; please specify. Several scores can be made)

8. *Total use of legal/illegal drugs in pregnancy – self report*
NB! A: Score a number – example 00 if no cigarettes/day

1.trimester= 1 to 13 week of gestation 2.trimester= 14 to 26 week of gestation 3.trimester= 27 to 40 week of gestation	First trimester (1=no use, 2=used 2-3 times/ month, 3= used 1-3 times/week, 4= used every day or almost)	Second trimester (score as 1.trimester)	Last trimester (score as 1.trimester) *Score after delivery*	All pregnancy (1=not used, 2= used) *Score after delivery*
A. Nicotine (cigarettes/day)	☐☐	☐☐	☐☐	☐
B. Opiates (other than methadone/buprenorphine)	☐	☐	☐	☐
C. Benzodiazepepines	☐	☐	☐	☐
D. Cannabis	☐	☐	☐	☐
E. Amphetamines	☐	☐	☐	☐
F. Injecting	☐	☐	☐	☐
G. Other drugs/medications, please specify..	☐	☐	☐	☐

9. *Use of alcohol during pregnancy*

A. *How often did you drink during the pregnancy?*

- Last 3 months before last menstrual period (1=never, 2=more seldom than 1 /month, 3= approx 1-3/month, 4=approx 1/week, 5= approx 2-3/week, 6= approx 4-5 /week, 7=6-7/week) ☐

- In this pregnancy, 0-12.week/gestation, score as above ☐

- In this pregnancy, 13-24. week/gestation, score as above ☐

- In this pregnancy, after 25. week/gestation, score as above ☐

B. *What kind of alcohol do you usually drink? (1=light beer, 2=beer, 3= red/white wine, 4=alcopops, 5=stronger wine, 6=liquor) – may score several* ☐ ☐ ☐

C. If you have changed your use of alcohol before or during the course of the present pregnancy, when did the change take place? (it is possible to score several changes)

- Last 3 months before the last menstrual period (1= change to less use, 2=change to more use) ☐

- In gestational week 0-6, scoring as above ☐

- In gestational week 7-12, scoring as above ☐

- In gestational week 13-24, scoring as above ☐

- After gestational week 25, scoring as above ☐

10. Medical complications during the pregnancy

A. Did any medical complications occur during the pregnancy? (0=no, 1=yes) ☐

If yes, specify………

B. 1.complication – specify type, duration and severity

C. 2.complication - specify type, duration and severity

11. In-patient treatment during pregnancy – In patient treatment in a maternity ward, detoxification ward, in patient drug treatment etc

A. During the pregnancy, was the patient treated as an in-patient? (0=no, 1=yes) ☐

B. Number of days in-patient treatment during the pregnancy ☐☐☐

(fill in for each episode of in-patient treatment)
C. Type of institution, duration of stay and reason for the in-patient treatment

D. Type of institution, duration of stay and reason for the in-patient treatment

E. Type of institution, duration and reason for the in-patient treatment

F. In-patient treatment according to§ 6-2a (compulsory treatment) (0=no, 1= yes)

☐

Describe the number of treatment episodes according to § 6-2a, which institution, duration and the reason for the use of § 6-2a

12. Tapering the OMT-medication

A. Did you attempt to taper the dose of OMT-medication during pregnancy (0=no, 1=yes)?

☐

B. In which pregnancy week was the tapering started?

☐☐

C. In which pregnancy week did you stop the tapering?

☐☐

D. What was the lowest dose of your OMT-medication during pregnancy (in mg)?

☐☐☐

E. Please comment how the tapering process was proceeding?

F. Did the patient change the OMT-medication during the pregnancy (0=no, 1=yes)

☐

G. If yes to the last question, specify in which pregnancy week and describe the process

13. Splitting the daily dose of the OMT-medication

A. Did you try to split the daily dose of the OMT-medication? (0=no, 1=yes)

☐

B. How was the OMT-medication dose split? (eg 2/3 in the morning and 1/3 in the evening)

C. From which pregnancy week did you split the
OMT-medication dose? □□

D. What was your experience with splitting the OMT-
medication dose?

14. Opioid withdrawal during pregnancy

A. Was the patient in opioid withdrawal during
pregnanacy? (0=no, 1=yes) □

B. If yes, during which period(s) of pregnancy was
this?

C. Degree of opioid dependence (1=mild, no thoughts
about using drugs, 2=moderate, no thoughts about
using drugs, 3=strong, serious thoughts about using
drugs, 4=strong, have used drugs) □

D. Additional comments

15. The use of drugs the last month before delivery
    A.   Number of cigarettes/day □□

    B.   Use of any other type of nicotine (0=no, 1=yes) □
    If yes, specify type and quantity…..

    C.   Number of urine samples delivered this month □

D. Self-reported and confirmed use of medications/drugs during this month
(remember written consent form for results of urine tests etc)

	Used the medication/ the drug this period (0=no, 1=yes)	*Number of urine tests positive for the medication/ the drug during the period*
Opiates (other than OMT-medication)	☐	☐☐
Benzodiazepines	☐	☐☐
Cannabis	☐	☐☐
Amphetamine	☐	☐☐
Alcohol	☐	☐☐
Methadone/buprenorphine	☐	☐☐

16. OMT at delivery

A. Medication (1=methadone, 2= Subutex, 3=Suboxone, 4= no OMT)   ☐

B. What was the dose of OMT-medication (mg) at delivery?   ☐☐☐

C. Last blood concentration of methadone/buprenorphine before pregnancy (nmol/l)   ☐☐☐☐

D. Gestational week for the last blood concentration   ☐☐

17. Delivery (primarily from hospital records)

A. At which hospital was the baby born?

B. Month and year of birth (mmyy)   ☐☐☐☐

C. Gestational week at delivery (1 decimal)   ☐☐☐

D. Delivery (1= spontaneous, 2=induced)   ☐

E. Operative (0=no, 1=yes)   ☐

Please specify type……

F. What kind of pain relief was used during delivery?

18. The neonate at delivery (primarily from hospital records)

A. Apgar score 1 minute ☐

B. Apgar score 5 minutes ☐

C. Sex (1= boy, 2= girl) ☐

D. Length (cm, 1 decimal) ☐☐☐☐

E. Birth weight (gram) ☐☐☐☐

F. Head circumference (cm, 1 decimal) ☐☐☐

G. Methadone concentration in blood from umbilical chord ☐☐☐☐

H. Methadone concentration in the child's blood ☐☐☐☐

19. Neonatal periode

A. Number of days as in-patient at the maternal ward/ hospital hotel (mother) ☐☐☐

B. Number of days as in-patient at pediatric ward (neonate) ☐☐☐

C. Mother discharged to (1=home, 2= institution, please specify) ☐

D. Neonate discharged to (1=home with mother, 2=to an institution with mother, 3=alone to an institution (please specify), 4= other, please specify) ☐

20. Neonatal Abstinence Syndrome (NAS) (primarily from hospital records)

A. Did the neonate develop NAS? (0=no, 1=yes) ☐

B. Did the hospital use the Finnegan's scale to assess NAS? (0=no, 1=yes) ☐

 If no to *20 B, please specify which NAS scoring system which was used*

C. Please specify the highest Finnegan score, alternatively other score ☐☐

D. On which day after delivery was the highest score recorded? ☐☐

E. Did the neonate receive pharmacological treatment of NAS? ☐
   (0=no, 1=yes)

      - if yes to E, which day after delivery was the pharmacological treatment started ☐☐

      - which day after delivery was the last day of pharmacological treatment? ☐☐

      - total number of days with pharmacological treatment for NAS ☐☐☐

F. Which medication(s) were used in the treatment of NAS? ☐
(1=morphine sulphate, 2=tincture of opium, 3=Paragoric , 4=other medication)

   if *4, please specify which medication*.....

G. Please specify none-pharmacological treatment of NAS……….
   (*type and duration of treatment)*

21. Breastfeeding

A. Did the mother breastfeed? ☐
   (0=no, 1=yes)

B. What kind of advice did the woman receive concerning breastfeeding? ☐
   (1=the mother was advised to breastfeed, 2=the mother was advised not to breastfeed,
3= the mother did not receive advice on breastfeeding)

   If the mother was advised not to breastfeed, please specify why

C. Did the mother want to breastfeed? ☐
   (0=no, 1=yes)

   If no, please specify why.....

D. How many weeks did the mother breastfeed? ☐☐

E. Any other comments concerning breastfeeding

Any other comments linked to the pregnancy/delivery: