PREGNANT WOMEN IN OPIOID MAINTENANCE TREATMENT (OMT): MATERNAL AND NEONATAL OUTCOMES

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ABSTRACT

Background

The Norwegian Health Care system significantly differs from international settings such as the U.S., where the majority of research on pregnant opioid dependent women is conducted. Hence results from international research may not be generalized to the Norwegian setting. Therefore, to be able to offer the best possible care, it is of great importance to investigate how pregnant women in opioid maintenance treatment (OMT) in Norway are faring in regards to continued substance use and psychiatric problems both during pregnancy and sometime after the children are born. Secondly, the partners of pregnant opioid dependent women may contribute to the woman’s drug use relapses as well as to improved treatment outcomes and how the woman will cope as a mother. However, they are rarely included in studies on pregnant opioid dependent women. Moreover, there is a lack of studies offering a compete overview of use of prescription drug use prior to, and during pregnancy among OMT women. Lastly, maternal and neonatal outcomes after exposure to buprenorphine + naloxone has not been compared to other medicinal treatments for opioid dependence such as buprenorphine, methadone and methadone assisted withdrawal. Despite the lack of research on this, buprenorphine + naloxone is prescribed to pregnant opioid dependent women several places in the U.S.

Study aims

The aims of the present thesis were to investigate substance abuse and psychiatric problems in a national cohort of pregnant OMT women and their partners. Moreover, to investigate use of prescription drugs among women in OMT prior to, and during pregnancy. Furthermore, to investigate maternal and neonatal outcomes from use of buprenorphine + naloxone versus methadone, buprenorphine and methadone-assisted withdrawal.
**Materials and methods**

Different study designs were utilized for this thesis. Paper I and II were based on a cohort design; 38 pregnant OMT women and their partners (n= 23) were included. Paper III was based on a national cohort design, using the Norwegian birth registry and the Norwegian prescription database: 138 women and 159 pregnancies were included. Paper IV, a clinical mini-review, was based on published articles including both randomized controlled trials (RCTs) and retrospective studies.

**Results**

Use of illegal drugs among the women and their partners were low both during third trimester of pregnancy and one year after birth. One woman reported using illegal substances at each time interval. Two partners reported using illegal substances prior to the interview during third trimester. One year after one partner reported such use. Among the women, problem drinking increased from 0-15 % from third trimester to one year after birth. In contrast, problem drinking was significantly reduced (p < .01) among the partners, from 30-16 % from the third trimester to one year after birth. A majority of the women (81 %) and the partners (57 %) had experienced emotional and/or physical and/or sexual abuse earlier in life. Furthermore, most women (92 %) and their partners (91 %) had experienced psychological problems earlier in life. There was a significant reduction (p <.01) of depressive symptoms in the women from pregnancy to six months after the children were born and a tendency towards an increase at two years after birth. Among the partners, there was significant reduction (p < .05) in psychiatric problems from third trimester to one year after the children were born. Most pregnant OMT women (81 %) were dispensed prescription drugs during pregnancy. The most common prescription drugs were antiinfectives (48 %) and drugs acting on the central nervous system (45 %). Benzodiazepines were used by 26.4 % of women during pregnancy, whereas only 5 % of women used antidepressants during pregnancy. Malformations were significantly more common (p< .05) among neonates whose mother received co-medication with drugs with abuse potential during pregnancy. There were no significant differences in maternal outcomes in women that used buprenorphine + naloxone compared to buprenorphine, methadone and methadone-assisted...
withdrawal. Birth length was significantly shorter (p < .001) in the buprenorphine + naloxone group compared to neonates in the buprenorphine group.

**Conclusion**

Most pregnant OMT women in Norway and their partners were able to abstain from using illegal drugs both during pregnancy and after the children are born. Psychiatric problems among the OMT women and their partners appears to be reduced from pregnancy to after the children were born. This may influence both treatment outcome and parenting abilities in a positive way. Pregnant OMT women used more prescription drugs than pregnant women in the general population. Co-medication with drugs with abuse potential may increase the risk of malformations in neonates and should be addressed further. Although there were no significant difference in maternal outcomes and few on neonatal outcomes when comparing buprenorphine + naloxone to buprenorphine, methadone and methadone assisted withdrawal, the results should be considered preliminary due to a very small sample in the buprenorphine + naloxone group.
Bakgrunn

Helsevesenet og behandlingstilbudene i Norge er svært forskjellig fra for eksempel USA, hvor mye av forskningen på gravide kvinner i LAR er gjort; resultatene fra internasjonale studier kan muligens ikke overføres til norske forhold. For å kunne tilby best mulig behandling til gravide i LAR i Norge og deres familier er det viktig å undersøke bruk av rusmidler og psykisk helse både under svangerskap og etter at barnet er født. Partnere kan i stor grad påvirke behandlingsutfall hos opiatavhengige kvinner; de kan bidra til både tilbakefall og økt sjanse for et godt utfall og påvirke hvordan en kvinne klarer seg som mor. Likevel er de sjelden inkludert i studier om gravide opiatavhengige kvinner. Også forskrevne legemidler kan misbrukes, og noen kan være skadelige for fosteret. På den andre siden er det mulig at noen gravide kvinner i LAR ikke mottar de legemidlene de trenger fordi noen leger er for forsiktige og mangler kunnskap om LAR og ko-medisinering. Svangerskapsutfall og utfall hos nyfødte etter eksponering til buprenorfin + naloxone gjennom svangerskapet har ikke tidligere blitt sammenlignet med utfall etter eksponering til andre medikamentelle behandlinger for opiatavhengighet: buprenorfin, metadon eller metadonassistert nedtrapping. Likevel benyttes dette medikamentet til behandling av opiatavhengighet hos gravide kvinner flere steder i USA.

Forskningsspørsmål

Målene i denne studien var å undersøke rusmisbruk og psykiske plager i en nasjonal kohort gravide LAR kvinner og deres partnere; tidligere i livet, i svangerskapet og etter at barna var født. Neste mål var å undersøke bruk av reseptbelagte legemidler blant kvinner i OMT før og under svangerskapet. Siste mål var å studere svangerskapsutfall og utfall hos nyfødte etter eksponering fra buprenorfin + nalokson sammenlignet med metadon, buprenorfin og metadon-assistert nedtrapping.

Materiale og metode

Flere forskningsdesign ble brukt i denne studien; artikkel I og II er basert på et naturalistisk, longitudinelt, prospektivt kohort design. Studien inkluderte 38 gravide kvinner i LAR og deres...
partnere (n=23). Artikkelen III er basert på en nasjonal kohort: fra det norske fødselsregisteret og reseptregisteret ble 138 kvinner i LAR og 159 svangerskap inkludert. Artikkelen IV er et mini-review basert på 7 tidligere publiserte artikler; både retrospektive og randomiserte kontrollerte studier (RCT).

Resultater

Bruk av illegale rusmidler de siste 30 dagene før begge intervjuene var lav hos kvinnene; en kvinne rapporterte bruk ved hvert intervju. Problematisk bruk av alkohol økte fra 0-15 % fra intervju i tredje trimester til intervju ett år etter at barna var født. To partnere rapporterte bruk av illegale rusmidler ved intervju i tredje trimester, og ett år etter at barnet var født. Signifikant færre (p<.01) menn rapporterte problematisk bruk av alkohol ved andre (20 %) sammenlignet med første (38 %) intervju. Et flertall av kvinnene (81 %) og partnerne deres (57 %) hadde opplevd følelsesmessig og/eller fysisk, og/eller seksuelt misbruk tidligere i livet. De fleste kvinnene (92 %) og partnerne (91 %) hadde også vært plaget av en eller flere former for psykiske problemer tidligere i livet. Det var en signifikant reduksjon (p <.01) i symptomer på depresjon blant kvinnene fra svangerskap til seks måneder etter at barna var født. Fra seks måneder til to år etter var det derimot en tendens til økning i depressive symptomer. Blant partnerne var det en signifikant reduksjon i rapporterte psykiske problemer fra intervju i tredje trimester til intervju ett år etter at barna var født. De fleste gravide kvinner i LAR (81 %) fikk utlevert forskrevne legemidler utover LAR medikamenter på apotek under svangerskapet. De vanligste formene for forskrevne legemidler var antiinfektiva (48 %) og legemidler som virker på sentralnervesystemet (45 %). Benzodiazepiner ble brukt av 26.4 % i løpet av svangerskapet. Kun 5 % av kvinnene brukte antidepressiva gjennom svangerskapet. Det var signifikant flere misdannelser (p <.05) hos nyfødte hvis mor var ko-medisinert med legemidler med misbrukspotensial mens hun var gravid. Det var ingen signifikante forskjeller i svangerskapsutfall for kvinner som hadde brukt buprenorfin + naloxone sammenlignet kvinner som hadde brukt buprenorfin, metadon eller metadon-assistert nedtrapping. Barn i buprenorfin + naloxon gruppen var signifikant kortere (p < .001) sammenlignet med buprenorfingrunnen.
Diskusjon og konklusjon

LIST OF PAPERS


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<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ATC</td>
<td>Anatomic Therapeutic Chemical Classification System</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>DDD</td>
<td>Defined Daily Dose</td>
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<td>HSCL-25</td>
<td>Hopkins Symptom Checklist 25</td>
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<td>EuropASI</td>
<td>European Addiction Severity Index</td>
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<td>GP</td>
<td>General Practitioner</td>
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<td>GSI</td>
<td>Global Symptom Index</td>
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<td>IQR</td>
<td>Interquartile Range</td>
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<tr>
<td>LAR</td>
<td>Legemiddelassistert rehabilitering</td>
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<td>MBRN</td>
<td>Medical Birth Registry of Norway</td>
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<td>MCMI III</td>
<td>Millon Clinical Multiaxical Inventory III (MCMI III)</td>
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<td>NAS</td>
<td>Neonatal Abstinence Syndrome</td>
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<td>NorPD</td>
<td>Norwegian Prescription Database</td>
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<td>OMT</td>
<td>Opioid Maintenance Treatment</td>
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<td>PD</td>
<td>Personality Disorder</td>
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<td>RCT</td>
<td>Randomized controlled trial</td>
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<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitors</td>
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<td>TCA</td>
<td>Tricyclic Antidepressants</td>
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1.0 INTRODUCTION

1.1 Opioid dependence and OMT

There are approximately 1.4 million individuals with problem opioid use in Europe [1]. In Norway, the number of problematic opioid users is estimated to about 6900 – 12300. [2]. Individuals with opioid dependence are at an increased risk of morbidity and mortality [3-5]. Furthermore, they often experience problems with family and social networks, employment/financial legal and psychiatric problems [6-10].

Today several pharmacological treatment options exist for opioid dependence. Methadone was introduced as a treatment for opioid dependence in the 1960s in the United States [11] and in Norway as a national treatment program for opioid dependent individuals in 1998 [12]. Methadone is considered the gold standard for treatment of opioid dependence, but use of buprenorphine and buprenorphine + naloxone is becoming more common [12]. Whereas heroin is a short-acting opioid, buprenorphine and methadone are long-acting opioids with a less rewarding affect than heroin [13]. Methadone is a full opioid agonist, buprenorphine is a partial agonist, and exerts weaker opioid effect on the opioid receptors than methadone [14]. The combination drug buprenorphine + naloxone includes the opioid antagonist naloxone. When taken sublingually, the effect from buprenorphine will dominate and no clinically significant effect is exerted from naloxone. When injected however, the opioid antagonism cause withdrawal effect [15].

1.2 Opioid dependence and pregnancy

Opioid dependence in pregnant women is a major public health issue internationally and is associated with high costs to society and at the personal level, for the women and their children [16-23]. Approximately one third of heroin users are women [2]; the majority of an age when they may have children [24]. Women with opioid dependence often come from families where one or both parents have had substance abuse problems [9, 25], and a majority have experienced emotional,
physical and/or sexual abuse at an early age [9, 26-30]. They have typically experienced low level of cohesion and higher levels of conflicts in their families compared to women from similar socio-economic backgrounds without substance abuse and/or psychiatric problems [17, 31].

Heroin dependent women are at great risk of experiencing medical complications [32, 33]. Many get infections through use of needles used by others, as well as sexually transmitted diseases because of frequent unprotected sex [17, 34, 35]. Pregnant opioid dependent women are often poorly nourished and have vitamin deficiencies [17]. Abscesses, bacterial endocarditis, hepatitis and HIV is not uncommon [17]. Many do not get appropriate obstetric care and avoid seeking health care during pregnancy [36]. This may be due to the chaotic life circumstances of heroin dependent individuals. Previous negative experiences with the health care system, where interactions with health care personnel are characterized by stigmatization and blame [37] and worry about losing custody of their children if treatment providers know about their substance abuse, may hinder women from seeking help. The life context that comes with heroin dependence may seriously affect birth outcomes, and with a constant search for the next fix of heroin, women are often not well equipped to taking care of a baby [38].

Opioid Maintenance treatment (OMT) is considered the best treatment option for pregnant opioid dependent women [12, 39, 40]. Treatment providers that work with pregnant women in OMT should have special training in substance abuse (illness course and its treatment) and OMT during pregnancy and collaborate with specialist health care services [12, 41]. Compared to no treatment and medication assisted withdrawal/tapering, OMT has proved superior in regard to both maternal and neonatal outcomes [39, 42]. Pregnant opioid dependent women that enter OMT at an early stage of pregnancy, and stay in treatment, present earlier to antenatal care and the outcomes are better for their neonates [43]. Once stabilized on OMT, women are also better equipped to benefit from
psychosocial treatment and receive help to deal with other problems associated with substance abuse [40].

The prevalence of psychiatric problems among pregnant women in OMT is high [28, 33, 44-46]. This may compromise treatment outcomes [47] and a greater proportion of women with psychiatric problems test positive for illegal drugs while in OMT [48]. The increased risk of relapses may compromise their potential to be a dependable parent for their children. Additional psychiatric problems may contribute to longer hospital stay after birth [48, 49]. Furthermore, depression and other psychiatric problems may compromise early mother infant bonding and increase the risk of negative parenting behavior [50-53]. Pregnant women in OMT should be evaluated for depression and other psychological problems and offered appropriate treatment if needed.

A large proportion of existing research on pregnancy and OMT is conducted in the U.S. where homelessness and poverty among opioid dependent individuals may be confounding factors [54]. In Norway, all inhabitants are covered by a tax-funded National Insurance System, and all have equal access to free health care and education. Although many pregnant opioid dependent women in Norway also have a low socioeconomic status [55, 56], they are not homeless or experience the same degree of poverty [57] as many opioid dependent individuals in the U.S. Consequently, it may be that pregnant women in OMT in Norway may not experience the same extent of problems as reported in the international literature.

According to Norwegian law on substance abuse during pregnancy, women that continue to abuse illegal substances while pregnant may be admitted to inpatient treatment without her consent for parts of, or during the entire pregnancy [58]. The rationale is that this will reduce the chances of malformations and other negative birth outcomes that continued substance use may contribute to [58]. Many think these regulations are drastic and are skeptic to taking away a woman’s right to
make decisions in her own life. During the stay at the treatment facility the women are offered help to deal with both substance abuse and related problems. The women also receive help and guidance regarding taking care of a baby [58]. Because of major differences in health care systems and laws on substance abuse and pregnancy, it is important to study this population also in a Norwegian setting.

1.3 The role of the partners of pregnant OMT women

Many of the partners of pregnant OMT women have a similar history of serious substance abuse problems [59]. Physical violence towards women is six times more common in relationships where the man has substance abuse problems [60, 61], which is often the case for the partners of OMT women [62-65]. Female drug dependent women in abusive relationships have an increased risk of psychological problems and compromised treatment outcomes [66, 67]. The partners of pregnant OMT women may have a great influence regarding whether or not the woman will be able to stay substance free or relapse to substance abuse [68]. If the partners continue to abuse drugs it is difficult for the women to stay drug free [69]. Although partners play an important role regarding whether or not the women will stay drug free, they have typically not been included in studies of pregnant OMT women; not over time and never in a national cohort of pregnant OMT women. Substance abuse and psychiatric problems among pregnant OMT women and their partners may have an impact on how they are coping as caregivers and on whether they will keep custody over their children. Including the partners in treatment programs may reduce prevalence of interpersonal violence and drug use among opioid dependent women [70] and increase the level of support women receive from their partner [71].

1.4 Prescription drug use among pregnant OMT women

Although considered to be the best treatment option for pregnant opioid dependent women [33, 39, 49, 72, 73], OMT is not without risks, and adverse pregnancy and neonatal outcomes may occur [43,
Furthermore, due to the high prevalence of psychiatric and somatic problems among pregnant OMT women [4, 49], use of prescription drugs in pregnant OMT women may be high. The knowledge regarding the benefits from use of different prescription drugs among OMT women during pregnancy versus the potentially adverse effects on the fetus, is limited and incomplete. Pregnant OMT women are a vulnerable patient group, and knowledge on prescription drug use in this patient group is limited and incomplete. Many general practitioners (GPs) may have limited knowledge on pregnancy and co-medication among pregnant OMT women. Therefore, some women may not receive the medication they need. On the other hand, some pregnant OMT women may also receive co-medication that can be harmful for the fetus. Both under and over medication endangers the treatment stability of pregnant OMT women and increases the risk of relapse. It is therefore important to also study use of prescription drugs among pregnant OMT women.

1.5 Maternal and neonatal outcomes from exposure to different OMT drugs

Methadone has been prescribed to pregnant opioid dependent women since the late 1960s [76]. Although some women may have good outcomes with methadone assisted withdrawal for opioid dependence [77], most women that receive methadone-assisted withdrawal show worse maternal outcomes compared to other medicinal treatment options for opioid dependence [39]. More recently, use of buprenorphine to treat opioid dependence in pregnant women has increased [78-85]. Research suggests that maternal outcomes from use of buprenorphine and methadone during pregnancy are similar [74, 75, 86, 87], but buprenorphine may be superior to methadone on some neonatal outcomes: shorter duration of NAS and shorter length of infant stay at hospital [88-91]. Existing research on the safety of buprenorphine during pregnancy has focused on buprenorphine alone, Subutex® [37, 92-94] and there is a lack of research on the safety for the mother and child from use of buprenorphine + naloxone (Subuxone®) during pregnancy [95]. Despite a lack of research on its safety during pregnancy, buprenorphine + naloxone is prescribed to pregnant women many places in the U.S. and elsewhere.
1.6 Knowledge gaps

International studies have described substance abuse and psychiatric problems among pregnant women in OMT. However, few of these studies have included the OMT women’s partners. Furthermore, there exist great differences in health care systems and other factors, such as laws regarding substance abuse during pregnancy in Norway and the countries where the majority of this research is conducted. Accordingly, the findings from international research, may not apply in a Norwegian setting. Therefore, it was decided to study substance abuse and psychiatric problems among pregnant OMT women and their partners in a Norwegian context. Moreover, it was decided to include the women’s partners because the partners of pregnant OMT women may contribute to how the women are doing in regards to continued substance use and how they are coping as caregivers for their children.

There is limited knowledge regarding the benefits from use of different prescription drugs during pregnancy among OMT women versus the potentially adverse effects on the fetus. It was therefore decided to match information from the Norwegian prescription database and the Norwegian birth registry to get a more complete picture of prescription drug use among pregnant OMT women.

The Norwegian guidelines for pregnant women in OMT address different medicinal treatment options for opioid dependence. The guidelines suggest that buprenorphine + naloxone should not be used by pregnant women because there is a lack of research investigating fetal and neonatal outcomes from exposure to naloxone [40]. However, despite the lack of research on the safety of naloxone, buprenorphine + naloxone is used to treat opioid dependent pregnant women several places in the U.S. and elsewhere. On this background, it was decided to compare maternal and neonatal outcomes from exposure to buprenorphine + naloxone to other medicinal treatments for opioid dependence, including methadone-assisted withdrawal.
2.0 OBJECTIVES

The objectives were:

To describe substance abuse and psychological problems among pregnant OMT women and their partners, to describe prescription drug use among pregnant OMT women, and to evaluate outcomes from exposure to buprenorphine + naloxone during pregnancy compared to other treatments frequently provided to pregnant opioid dependent women.

The specific aims were:

I. To investigate substance abuse and related problems in a national cohort of pregnant OMT women and their partners prior to, during and after pregnancy (Paper I).

II. To investigate psychiatric problems among a national cohort of pregnant OMT women and their partners prior to, during and after pregnancy (Paper II).

III. To investigate all prescription drug use among women in OMT three months prior to, and during pregnancy. A main focus will be placed on prescription drugs with abuse potential (Paper III).

IV. To evaluate neonatal and maternal outcomes from exposure to buprenorphine + naloxone during pregnancy compared to buprenorphine alone or methadone (Paper IV).

This thesis includes both published (appendix) and unpublished results.
3.0 MATERIAL AND METHODS

3.1 Design

This thesis is based on two different designs. Table 1 shows the study designs used to address each of the aims.

Table 1. Design used to address aim I-IV

<table>
<thead>
<tr>
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<tr>
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<td>Small clinical review</td>
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3.2 Sources of data

Three different data sources were used to address aims I-IV. A national OMT cohort study from Norway was used to address aim I and II. The Norwegian birth registry and the Norwegian prescription database were used to address aim III. To address aim IV, data from seven previously published studies were used [39, 74, 86, 87, 96-98]. The sources used to address aim I-IV are presented in table 2.

Table 2. Sources used to address aim I-IV.

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<th>Aim II</th>
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<td>Data from already published papers</td>
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3.2.1 The national OMT cohort

The national OMT cohort includes 161 children born to 139 women from 1996 to 2009 [99]. The study has three parts; the first part is retrospective (n=51) and was undertaken in the period
between 1996-2003 [100]. The second part is prospective (n=37) and was undertaken from 2005 to 2007 [101]. Finally, the third study is retrospective (n=52) and was undertaken from 2004 to 2009. Aim I and II in this thesis were addressed using prospective data from the second part of the study. All regional centers and treatment facilities in Norway were asked to recruit women in OMT that were to give birth during January 2005 to February 2007. A research team of 3 persons; a psychologist, a medical doctor and a masters student contacted all OMT centers, and gave several lectures on risk factors related to substance abuse during pregnancy, at treatment facilities working with this patient group [102]. OMT centers, other drug treatment facilities, child mental health and child protection services received written information about the study [102]. Health care personnel in these settings working with pregnant OMT women were asked to forward information about the study to pregnant OMT women and ask for permission on behalf of the research team if they could contact the women about the study. Reminders were sent on a regular basis to treatment facilities [102]. Before being contacted by the research team, the pregnant women in OMT signed an informed consent form agreeing to participate in the study [102]. If the women had male partners, they were asked to inform their partner about the study and ask if he would consider participating. The partners that agreed to take part, signed informed consent before being contacted by the research team.

3.2.2 The Medical Birth Registry of Norway (MBRN)

The MBRN was established in 1967. All births in Norway are registered in MBRN. The registry is based on compulsory notification of all births and late abortions from 12 weeks of gestation. The aim of the registry is epidemiological surveillance of perinatal health problems and birth defects and surveillance of health services provided to: pregnant women, during child birth and in the neonatal period [103]. The notification form sent to MBRN includes name and personal identity numbers for the parents as well as for the child. Information about the maternal health prior to and during pregnancy and length of pregnancy and information about complications during pregnancy and birth
is recorded. Such complications include whether the baby is born alive and information about
diagnoses and congenital abnormalities. If the mother consents, information about occupation and
smoking habits are also registered [103]. Any additional information is included until mother and
baby are discharged from the hospital.

3.2.3 The Norwegian Prescription Database (NorPD)

From January 1st 2004 it was mandatory for all pharmacies in Norway to send electronically
information on all dispensed drugs to the NorPD. NorPD covers the entire Norwegian population
[104] and is run by the Institute of Public Health [104, 105]. Information regarding prescription drugs
at the individual level exists for all individuals that are dispensed prescription drugs at pharmacies.
Data on prescription drug use among individuals currently in inpatient treatment is only registered at
institutional level. For all prescriptions, age and sex are registered for both patient and prescriber.
Demographic information such as where the patient lives (municipality), specialization of the
prescribing medical doctor and information to identify which pharmacy the drugs were dispensed at
are also registered [106].

Dispensing date and detailed drug information is included; including Anatomic Therapeutic Chemical
(ATC) classification code and defined daily dose (DDD) dispensed. DDD is defined as “the assumed
per day mean dose for a drug used for the drugs main indication for adults” [106]. To evaluate
consumption of prescription drugs over time, both nationally and internationally, DDD may be used
as a method to simplify and improve the comparison process [107]. All prescription drugs in Norway
are classified according to the ATC classification system with 5 different levels. At level one the drugs
are divided into 14 main drug groups, at level two the groups are divided into pharmacological
/therapeutical sub-groups. At level three and four according to therapeutic/chemical/pharmacologic
subgroups, and at level five there is the unique chemical substance code for the drug [106]. The
evaluation of international use of a prescription drug is the basis for deciding on a drugs DDD [106].
Information recorded in NorPD does not include information on prescription drugs dispensed to
individuals at hospitals or other institutions; including receiving OMT drugs at OMT centers instead of pharmacies. This information is only registered at institutional level and not included in this thesis.

3.2.4 Papers included in the small clinical review

The articles in the clinical review were chosen on the background that they included a common subset of outcome measures and provided data that could be easily re-analyzed [39, 74, 86, 87, 96-98]. The maternal outcomes were: maternal weight gain, number of prenatal obstetrical visits, drug screening results, use of analgesia, cesarean section, medical complications at delivery and non-normal presentation of the fetus. The neonatal outcomes were: treated for neonatal abstinence syndrome (NAS), how many days treated for NAS, total mount of morphine used to treat NAS, birth parameters, days at the hospital, gestational age, preterm birth and Apgar scores. Furthermore, the articles represented both retrospective studies and RCTs, which increase the generalizability of the findings. No new data were gathered but the authors of some of the studies provided standard deviations that were not available in their articles. The articles included were published during 2005-2012.

3.3 Study population

Aim I and II: Substance abuse and psychiatric problems

To our knowledge, all pregnant OMT women in Norway in 2005 and 2006 and their partners were invited to participate in the study [102]. Of the 47 OMT women located during pregnancy, 41 women consented to participate. Of the 6 that declined, 3 did not respond to the request about participation and 3 women said they did not want to participate in the study because their partners were skeptical to take part, and they were concerned that child protection services might be involved as a result of study participation [102]. Of the 41 that gave their informed consent, one woman withdrew from the study before the study started and two women had a miscarriage. When the study started 38 women were included. This is likely to equate to a response rate of 81% of all pregnant OMT women in Norway during the study period. Methadone was used by 26, and buprenorphine by 12 women. Only
two women started OMT after conception; the majority of the women were enrolled in the OMT program prior to conception. [101]. On average the women had been in OMT for 2.7 years and their opioid dependent partners for 2.5 years.

Of the 38 women, 24 had male partners. All but one of the partners signed an informed consent and agreed to participate in the study. Most of the partners had a similar substance abuse background, with several years of heroin and polydrug abuse, as the women. However, seven men reported they had never used heroin and six of these seven reported they had never used illegal drugs.

**Aim III: Prescription drug use**

To address aim III, data from the MBRN and the NorPD were used. As regulated by Norwegian law for health registries linkage between MBRN and NorPD was generated through anonymous files for research purposes [108, 109]. Data regarding prescription drug use in all pregnant OMT women in Norway that were dispensed OMT drugs at a pharmacy during pregnancy, were collected for women that conceived from March 30th 2004, and pregnancies that ended no later than December 31st 2010. All singleton pregnancies during the study period were included (349,020 pregnancies). Pregnancy and neonatal complications are more common in twin pregnancies. Hence, twin pregnancies were excluded. After excluding pregnancies where the woman’s identity was unknown or she was living outside of Norway when she was giving birth, the number of pregnancies were 345,703.

To be defined as a pregnant OMT woman, women had to be a) pregnant and b) dispensed one of the following OMT drugs at a pharmacy at least once during pregnancy: methadone mixture (ATC system code N07BC02), buprenorphine sublingual tablets (Subutex/ATC code N07BC01) or buprenorphine + naloxone combined sublingual tablets (Suboxone / ATC code N07BC51). After all exclusions, the study included 138 women with a total of 159 pregnancies. The mean age of the pregnant OMT women were 32 years.
Aim IV: Maternal and neonatal outcomes after exposure to different OMT drugs

Seven previously published studies from 2005 to 2012 [39, 74, 86, 87, 96-98] were used to address aim IV. The outcome measures in the chosen papers were similar and could easily subject to re-analysis. Debelak and colleagues conducted a retrospective chart review; 10 women that received buprenorphine + naloxone during pregnancy were included in the study [97]. Another retrospective chart review was included 101 women that were prescribed methadone and 68 that were prescribed buprenorphine during pregnancy [96]. Fischer and colleagues conducted a RCT; at delivery there were six women in the methadone and eight in the buprenorphine condition [87]. Another RCT was conducted by Metz and colleagues: data on women that underwent structured standard pharmacotherapy protocol, 51 women exposed to methadone and 26 exposed to buprenorphine were included [98]. In a third RCT, 11 women on methadone and nine on buprenorphine completed the study [86]. In a fourth RCT 73 women on methadone and 58 women on buprenorphine completed the study [74]. Finally, a retrospective record review where 52 women received methadone and 28 women 7-day methadone assisted withdrawal was included [39]. See table 3 for an overview of the studies included.
Table 3. Overview of studies used to address aim IV

<table>
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</thead>
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<td>7-day methadone</td>
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<td>N=52</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

Data collected in the following country

| U.S.             | X | X | X | X | X | X | X |
| Austria          |   | X | X | X |   |   |   |
| Canada ‡         |   |   |   |   | X |   |   |

‡ Data from the Canada site was not included in the Jones (2010) paper because although participants were screened, they were not randomized.

3.4 Study instruments

Different study instruments were used to address aims I-IV. Table 4 shows an overview of which instruments were used at different time intervals to answer aim I-III.

Table 4. Instruments used to address aim I-III women (W) and partners (P) at different time intervals

<table>
<thead>
<tr>
<th>Instruments used</th>
<th>3 months prior to pregnancy</th>
<th>1st trimester</th>
<th>2nd trimester</th>
<th>3rd trimester</th>
<th>6 months</th>
<th>1 year after birth</th>
<th>2 years after birth</th>
<th>Aims</th>
</tr>
</thead>
<tbody>
<tr>
<td>EuropASI</td>
<td>W</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td>I</td>
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<td></td>
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<td>II</td>
</tr>
<tr>
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<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>III</td>
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<td>HSCL-25</td>
<td>W</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
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</tr>
<tr>
<td></td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<td>MCMII III</td>
<td>W</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>DDD</td>
<td>W</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

14
The European Addiction Severity Index (EuropASI)

EuropASI was used for aim I and II. EuropASI is a semi-structured interview used both for clinical and research purposes [110]. The most extensive part of the interview assesses drug and alcohol use. Respondents are first asked how old they were when he/she started using different drugs. To count as age of onset, the respondents had to report using the substance in question for at least three days per week, or have periods with binge drinking or heavy drug use for at least two days at the time per week at a level where normal daily activities such as work, school and family life is compromised. Furthermore, the respondents are asked how many years they have used different drugs, how many days during the last month they have used different substances, and how the substances were used; orally, injected or inhaled [111]. The respondents are also asked about injecting drug use and overdoses.

Areas often affected by drug and alcohol use are also evaluated; family and social relationships, employment, medical, legal and psychiatric problems. Questions regarding psychiatric problems include whether the respondents have been seriously depressed, experienced anxiety, hallucinations, problems concentrating and remembering, problems controlling violent behavior, attempts to suicide and more. Psychiatric problems that are directly related to substance abuse or abstinence should not be recorded [111].

There is a baseline and a follow-up version of the EuropASI interview. In both versions, the patient is asked how many of the last 30 days they have experienced problems in the different problem areas. This can be used to measure change in experienced problems in the different areas: substance use, medical and psychiatric, legal, employment/financial, family and social relations.

These interviews took place in late pregnancy and most women thought it most convenient to be interviewed in their own home. One member of the research team would travel to the
woman’s/couples home. The study participants were then contacted and asked to participate in a structured follow-up interview by telephone one year after the baby was born.

**Hopkins Symptom Checklist 25 (HSCL-25)**

HSCL-25, which is a shorter version of HSCL-90, was used to address aim II [112, 113]. HSCL-25 is a short self-administered instrument that measures symptoms of psychological distress: anxiety and depression. Some studies also report anxiety and depression combined, Global Symptom Index (GSI), also called “nervousness” [9]. The respondents answer how bothered they have been about each of the 25 items during the last week on a 5 point scale ranging from 0 (not at all), 1 (a little bothered), 2 (moderately bothered), 3 (quite bothered) and 4 (very bothered). The instrument is short and easy to administer and usually takes five minutes or less to complete. Respondents that received a score of 1.0 or more were classified as a “case” [9].

The study participants were asked to complete the HSCL-25 in the presence of the interviewer during third trimester of pregnancy. At six months after birth they were asked to complete and send HSCL-25 by post. The women were also asked to complete and send HSCL-25 by post two years after birth.

**Millon Clinical Multiaxical Inventory III (MCMI III)**

MCMI III is a self-report questionnaire which measures personality traits and personality disorders (PDs). The instrument contains 175 true/false items which measure 14 personality profiles and 10 clinical symptoms, for example dysthymia and anxiety [114]. The items form the basis for 24 clinical scales and three “modifier scales”. MCMI III and its earlier versions have been used among clinical populations both in Norway [9, 115-117], and internationally [118-120]. The MCMI scores are reported as base rate (BR) scores: transformed raw scores adjusted for gender differences. A BR score of 35 represents the average in the general population. In a clinical population the average BR score is 60. If an individual has a BR scores of 85 or above, he or she is considered to be a clinical case. Only the personality scales are presented in the present thesis. The personality scales are not
included in the articles as we received feedback from journals that we needed to limit the results we presented in each article. However, as PDs may complicate treatment outcomes and parenting abilities, it is important that these scales are presented in this thesis [121].

The women and their partners completed MCMI III in the presence of an interviewer during third trimester of pregnancy.

**Defined Daily Dose (DDD)**

In addition to describing prevalence of prescription drug use, it is also important to describe the amount of use. In the present study, defined daily dose was used to report the amount of opioids, benzodiazepines and z-hypnotics the pregnant women were dispensed 3 months prior to and during all trimesters of pregnancy. See table 5 for an overview of DDD for different benzodiazepines, z-hypnotics and opioid analgesics.
### Table 5. Defined Daily Dose (DDD) of benzodiazepines, z-hypnotics and opioid analgesics

<table>
<thead>
<tr>
<th>ATC code</th>
<th>DDD (oral administration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td></td>
</tr>
<tr>
<td><strong>Antiepileptics</strong></td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>N03AE01</td>
</tr>
<tr>
<td><strong>Anxiolytics</strong></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>N05BA01</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>N05BA02</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>N05BA04</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>N05BA06</td>
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<tr>
<td>Bromazepam</td>
<td>N05BA08</td>
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<tr>
<td>Clobazam</td>
<td>N05BA09</td>
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<tr>
<td>Alprazolam</td>
<td>N05BA12</td>
</tr>
<tr>
<td><strong>Hypnotics</strong></td>
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<tr>
<td>Nitrazepam</td>
<td>N05CD02</td>
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<td>Flunitrazepam</td>
<td>N05CD03</td>
</tr>
<tr>
<td>Estazolam</td>
<td>N05CD04</td>
</tr>
<tr>
<td>Triazolam</td>
<td>N05CD05</td>
</tr>
<tr>
<td>Midazolam</td>
<td>N05CD08</td>
</tr>
<tr>
<td><strong>Z-hypnotics</strong></td>
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</tr>
<tr>
<td>Zopiclone</td>
<td>N05CF01</td>
</tr>
<tr>
<td>Zolpidem</td>
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<tr>
<td>Zaleplon</td>
<td>N05C</td>
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<tr>
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<td>Morphine</td>
<td>N02AA01</td>
</tr>
<tr>
<td>Hydromorphone</td>
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</tr>
<tr>
<td>Oxycodone</td>
<td>N02AA05</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>N02AA08</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>N02AE01</td>
</tr>
<tr>
<td>Codeine</td>
<td>N02AA59</td>
</tr>
</tbody>
</table>

\(^a\) parenteral, sublingual, transdermal administration only
\(^b\) All codeine products are fixed combinations with acetaminophen. For the product that contain 400 mg paracetamol, one DDD will represent 1600 mg paracetamol and 120 mg codeine. For product that contain 500 mg paracetamol, one DDD will represent 1500 mg paracetamol and 90 mg codeine.
### 3.5 Data analysis

**Table 6. Summary of the statistical packages and methods used to address aim I - IV.**

<table>
<thead>
<tr>
<th>Aims</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
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</thead>
<tbody>
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<td></td>
<td>SPSS 18.0</td>
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<tr>
<td></td>
<td>Logistic regression analysis</td>
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</tr>
</tbody>
</table>

**Aim I and II: Substance abuse and psychiatric problems**

Descriptive statistics on all problem areas in EuropASI are presented: substance use, legal, family/relatives, employment, psychiatric, somatic/medical. Descriptive statistics regarding experienced emotional, physical and sexual abuse previous in life and during the past 30 days prior to the interview is presented. Crosstab analyses with Fischer’s exact test were used to examine if there were significant changes in substance use and psychiatric problems from the interview during third trimester of pregnancy to the EuropASI interview one year after birth. The same procedure was conducted to investigate if there were changes in all the problem areas: somatic/medical, family/relatives, employment, and legal. Paired t-test were used to examine changes in anxiety and depression among the women and their male partners from last month of pregnancy to six months after birth; for the women also from six months to two years after birth.

**Aim III: Prescription drug use**

Descriptive statistics: period prevalence, means, median, interquartile range (IQR) and confidence intervals (CI), regarding prescription drug use prior to and during pregnancy in pregnant OMT women
are presented. CIs for proportions were calculated using a corrected version of the score [122].

Period prevalence was measured in 3 month intervals: 3 months prior to conception and every trimester. Women that were dispensed a drug at least once during a 3-month time interval was registered as using that drug during that time period. The effect of co-medication with opioid analgesics, benzodiazepines or z-hypnotics on maternal and neonatal outcomes were examined using bivariate analysis as appropriate: chi square test or t-test.

**Aim IV: Maternal and neonatal outcomes after exposure to different OMT drugs**

Summary statistics were collected for the articles used to address aim IV [39, 74, 86, 87, 96-98]: means and standard deviations for continuous variables and frequencies for binary variables. Firth’s penalized maximum likelihood approach was utilized to conduct tests of significance for the logistic regression analyses [123] because some of the studies that did yield data had very small or zero frequencies. One-way analysis of variance was used to analyze the continuous outcome data [124]. Three single degrees of freedom were created for each outcome measure to address the three questions posed in the present study.

**3.6 Ethics**

**Aim I and II: Substance abuse and psychiatric problems**

The protocol was approved by the Regional Ethics Committee.

**Aim III: Prescription drug use**

The Norwegian Prescription Database and the Medical Birth Register of Norway was linked by using a pseudonymous personal identification number, according to regulations in Norwegian law for health registers. The research files did not contain any personal identification, and keys for matching were kept separately from the research team by a third party (Statistics Norway). Informed consent was not required for this study.
Aim IV: Maternal and neonatal outcomes after exposure to different OMT drugs

Additional approval from official bodies was not necessary since already published papers were used to address aim IV [39, 74, 86, 87, 96-98].
4.1 Aim I: Substance abuse and related problems

Both the women, and the partners that had a substance abuse background, had used heroin for on average eight years. Women reported an average of 10 years and their partners 13 years with polydrug abuse.

Only one woman reported using illegal substances during the last 30 days prior to the interview being conducted in the final month of pregnancy: heroin and amphetamine. Another woman reported using cannabis during the last 30 days prior to the interview being conducted one year after the children were born. Two of the partners used illegal substances during the 30 days prior to the interview conducted in the third trimester of pregnancy; other opiates than heroin or OMT medications, and cannabis. One of these men also reported using cannabis prior to the interview conducted one year after the birth.

No women reported problem drinking in the last 30 days prior to the interview conducted in the last month of pregnancy. However, five reported problem drinking prior to the interview at the interview conducted one year after the birth. The partners reported significantly less (p < .01) problem drinking at the interview conducted one year after birth (20 %) than at the interview during the third trimester of pregnancy (38 %).

Somatic/medical problems were significantly (p < .05) reduced among the women from third trimester to one year after (41-34 %). No prostitution or criminal activity was reported at any time interval. More women reported problems with families and relatives (8-20 %) and more partners reported problems with others (4-16 %) one year after the child was born. Reported problems with unemployment were relatively stable for both the women (3 %) and their partners (13-10 %).
4.2 Aim II: Psychiatric problems

A majority of the women (81%) and the partners (57%) had experienced emotional and/or physical and/or sexual abuse earlier in life. Two of the women reported emotional abuse, one of these also reported physical abuse, 30 days prior to the interview conducted during the last month of pregnancy. One of these women was single. The other had an opioid dependent partner; he was the only partner who reported any form of abuse, physical abuse, during the same time interval.

A majority of women (92%) and their partners (91%) reported that they had experienced one or more forms of psychiatric problems earlier in life. More partners with substance abuse history reported psychological problems (94%) compared to partners without such a background (71%). The most common psychological problems among the women both during pregnancy and one year after the child was born, were problems concentrating, understanding and remembering (41% and 32%), followed by serious anxiety (15% and 14%) and depression: (8% and 0%). Serious thoughts of suicide were reported by two women and two partners during pregnancy. One year after the child was born however, there no reports of thoughts of suicide among the women or their partners.

There were no reports of hallucinations or problems controlling violent behavior among the women or their partners at any of the time intervals. There were no differences in report of psychiatric problems among women with and without partners. More women without daily care of children born prior to joining the study reported psychiatric problems (75%), compared to women that had daily care of their previously born children (20%). There was a significant decrease (p < .05) in psychiatric problems among the partners from interview in third trimester (42%) to one year after the children were born (30%).

The GSI showed that 36%, 12% and 19% nervousness cases among the women during the last seven days prior to the interviews during third trimester, six months and two years after birth respectively. Among the partners, there were 4% and 8% nervousness cases prior to the interview
during third trimester and 6 months after the children were born respectively. Among the women there was a significant reduction \( (p < .01) \) in depressive symptoms from last month of pregnancy to six months after giving birth, and the number of depressive “cases” were reduced from 36-10 \%. From six months to two years after birth there was a tendency towards an increase in depressive symptoms among the women; both on average \( (0.54 – 0.77) \) and “cases” \( (10-26 \%) \). There was a reduction in both average anxiety symptoms score \( (0.44 – 0.33) \) and percentages of “cases” \( (9-4 \%) \) among the partners from third trimester to six months after, whereas depressive cases increased from 4-8 \%.

According to MCMI-III, fourteen (41 \%) women and eight (33 \%) partners had one or more personality disorders (PDs). The most common PDs among women were depressive (21 \%), histrionic (12 \%) and masochistic (12 \%). Among the partners depressive (21 \%) and antisocial (13 \%) PD were most common (table 7).
**Table 7.** Prevalence of personality disorders among the OMT women and their partners, measured in the last month of pregnancy, MCMI III.

<table>
<thead>
<tr>
<th>Personality disorders</th>
<th>OMT Women (n=34)</th>
<th>Partners (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Schizoid</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Avoidant</td>
<td>2 (6)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Depressive</td>
<td>7 (21)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Dependent</td>
<td>3 (9)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Histrionic</td>
<td>4 (12)</td>
<td>-</td>
</tr>
<tr>
<td>Narcissistic</td>
<td>2 (6)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Antisocial</td>
<td>3 (9)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Sadistic</td>
<td>1 (3)</td>
<td>-</td>
</tr>
<tr>
<td>Compulsive</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Negativistic</td>
<td>1 (3)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Masochistic</td>
<td>4 (12)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Schizotypal</td>
<td>-</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Borderline</td>
<td>2 (6)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Paranoid</td>
<td>-</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

4.3 Aim III: Prescription drug use

During pregnancy, 51 % of women were dispensed methadone, 49 % buprenorphine and 10 % buprenorphine + naloxone. All the women that used buprenorphine + naloxone switched to buprenorphine alone during pregnancy.

Excluding OMT drugs, 81 % of women were dispensed prescription drugs during pregnancy and 69 % during the 3 months prior to pregnancy. The proportion of women that were dispensed drugs was higher both prior to pregnancy, and during all trimesters, than among pregnant women in the general population [108]. In particular, use of antiinfectives (48 %) and drugs acting on the central nervous system (45 %) were higher among pregnant women in OMT (Table 8).
Table 8. Number, prevalence (%) and confidence interval (CI) of pregnancies in Opioid Maintenance Treatment in Norway (2004-2010) where the women were dispensed prescription drugs 3 months prior to and during pregnancy (n=159) compared to prescription drugs dispensed to pregnant women in the general population in 2004-2006 (n=106 329).

<table>
<thead>
<tr>
<th>Drug groups (ATC group)</th>
<th>3 months before to pregnancy</th>
<th>Entire pregnancy (40 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. trimester</td>
<td>2. trimester</td>
</tr>
<tr>
<td></td>
<td>N  %  CI [95]</td>
<td>N  %  CI [95]</td>
</tr>
<tr>
<td>Genitourinary system and sex hormones (G)</td>
<td>15 9 [6-15]</td>
<td>6 4 [2-8]</td>
</tr>
<tr>
<td>Antineoplastic and immunomodulating agents (L)</td>
<td>2 1 [0-5]</td>
<td>1 0 [0-4]</td>
</tr>
<tr>
<td>Musculoskeletal system (M)</td>
<td>18 11 [7-18]</td>
<td>9 6 [3-11]</td>
</tr>
<tr>
<td>Antiparasitic products, insecticides and repellents (P)</td>
<td>4 3 [1-7]</td>
<td>2 1 [0-5]</td>
</tr>
<tr>
<td>Sensory organs and various (S+V)</td>
<td>7 4 [2-9]</td>
<td>4 3 [1-7]</td>
</tr>
<tr>
<td>Total</td>
<td>110 69 [61-76]</td>
<td>96 60 [52-68]</td>
</tr>
</tbody>
</table>

\(^a\) ATC = Anatomical Therapeutic Chemical
\(^i\) Data (prevalence %) on use of prescription drugs among pregnant women (n=106 329) in the general Norwegian population (2004-2006) from Engeland and colleagues [108].
Benzodiazepines (anti-epileptics, anxiolytics or hypnotics) were used by 26.4 % (95 % CI 20-34) of the women during the entire pregnancy. Anxiolytics were the benzodiazepine group used most often during pregnancy (21 %). All groups of benzodiazepines were reduced from prior to pregnancy to the last trimester of pregnancy. During pregnancy 15 % of women were dispensed opioid analgesics. Use was reduced from 11 % during the three months prior to pregnancy to 3 % during the last trimester.

Women that were dispensed opioids, benzodiazepines and z-hypnotics often received these prescriptions from another GP than the GP prescribing OMT drugs. This applied for 17 of 30 women that received opioid analgesics, six of eight that received benzodiazepine antiepileptics, 20 of 42 that were dispensed benzodiazepine anxiolytics, seven of eight that received benzodiazepine hypnotics and in 11 of 16 that were dispensed z-hypnotics.

The women that received hypnotics received high doses during pregnancy: median 145 DDD. The doses of strong opioids were also relatively high; median 85 DDD, as were the doses for z-hypnotics; median 80 DDD.

Only 5 % of the women were dispensed antidepressants during pregnancy. Use of non-selective monoamine reuptake inhibitors and selective serotonin reuptake inhibitors were the same (2 %) during pregnancy. Use of other antidepressants was 1 % during pregnancy.

Significantly more (p < .05) neonates were born with malformations if their mother was co-medicated with drugs with abuse potential.
4.4 Aim IV: Maternal and neonatal outcomes from exposure to different OMT drugs

There were no significant differences in any of the maternal outcomes measured; number of prenatal obstetrical visits, maternal weight gain, medical complications at delivery, cesarean section, use of analgesia at delivery, drug screening results and non-normal presentation of the fetus, between the group of women exposed to buprenorphine + naloxone compared to women exposed to buprenorphine alone, methadone, or 7-day methadone-assisted withdrawal. The neonates in the buprenorphine + naloxone group had significantly higher (p < .05) head circumference compared to neonates in the methadone-assisted withdrawal group. Neonates in the buprenorphine + naloxone group were significantly shorter (p < .001) than neonates in the buprenorphine group. The Apgar scores at 5 minutes were significantly lower (p < .05) in the buprenorphine + naloxone group compared to the buprenorphine group. No significant differences in neonatal outcomes from exposure to buprenorphine + naloxone compared to buprenorphine, methadone or methadone assisted withdrawal were observed in regards to whether the neonates needed to be treated for NAS, amount of morphine needed to treat NAS, days of infant hospital stay, birth weight, pre-term birth or gestational age at delivery.

4.5 Brief summary of main findings

Use of illegal substances during pregnancy was low and further reduced one year after the children were born among both the women (3-0 %) and their partners (8-5 %). More women (0-15 %) and fewer partners (30-16 %) reported drinking alcohol one year after the children were born.

There was a significant reduction in depressive symptoms from pregnancy to six months after among the women (p<.01), but a tendency for increase in depressive symptoms from six months to two years after birth. There was a significant decrease (p< .05) in psychiatric problems among the partners from pregnancy to one year after the children were born.
Pregnant women in OMT used more prescription drugs than pregnant women in the general population. Antiinfectives and drugs acting on the central nervous system were the most commonly used drug groups. Use of benzodiazepines was high, but was reduced from prior to pregnancy to the third trimester of pregnancy. Use of antidepressants was low and malformations were significantly more common among children born to pregnant women that were co-medicated with drugs with abuse potential.

There were no significant differences in maternal outcomes from use of buprenorphine + naloxone during pregnancy compared to buprenorphine, methadone and methadone assisted withdrawal. Neonates in the buprenorphine + naloxone group were significantly shorter at birth, compared to the buprenorphine alone group.
5.0 DISCUSSION

5.1 Methodological considerations

5.1.1 Type 2 error

Research on small patient groups is challenging. Norway only has 5 million inhabitants and the number of pregnant women in OMT every year is limited. Some challenges with small sample sizes are that existing differences are not detected because the sample size is too small to show these differences. These concerns apply for all the studies included in this thesis. The national OMT cohort comprises of only 38 women and their 23 partners, the registry study consists of 159 pregnancies in 138 women in OMT, and all the studies included in the clinical mini review are small or relatively small. In paper IV, the buprenorphine + naloxone sample was very small, and it may be that existing differences may not have been detected are due to lack in power. In the U.S., pregnancy and opioid dependence is more common and recruitment for larger studies is more likely. However, to achieve a large sample size in a Norwegian setting would take many years. To estimate whether co-medication with drugs with abuse potential increase the risk of important neonatal outcomes we would need: A statistical power of at least 0.8 at an alpha level of 0.05 is needed to detect a 10 % increase in NAS, 200 g lower birth weight and a doubling in proportion of preterm birth, in a cohort size of 700 women, where about 1/3 receive co-medication.

5.1.2 Selection bias

Selection bias has been described as systematic errors that result from selective losses of individuals prior to the data analysis, or from the way individuals are selected into the study [125].

All pregnant women known to be in OMT in Norway were invited to participate in the national OMT cohort study. The majority of women (81 %) agreed to participate. The recruitment was entrusted to treatment providers in contact with OMT patients in Norway. Due to confidentiality reasons, we do not know whether or not the women that chose vs. chose not to participate differ significantly.
The women and the partners that did not participate in the six months, one and two year follow up may be different from those that wanted to continue to contribute to the study.

Selection bias may also have occurred when addressing aim III. The prescription database contains information on all prescription drugs dispensed to all individuals outside institutions. However, OMT dispensed at OMT centers or other treatment facilities, is not registered in the prescription database at an individual level but at an institution level. It has become increasingly common that OMT patients receive prescriptions for buprenorphine or methadone by a GP and are dispensed the medications at a pharmacy. In 2004, about 60% of OMT patients received their medication at pharmacies, whereas in 2010, close to 100% of OMT patients in Norway were dispensed OMT drugs at a pharmacy [126]. The pregnant opioid dependent women that receive buprenorphine or methadone at OMT centers may differ in significant ways from women that are prescribed OMT drugs from their GP. To receive OMT outside specialist treatment centers, patients need to show compliance with the treatment plan and adequate cooperation [12, 40]. If patients continue to use illegal substances while they receive OMT from GPs in the primary health care service, their treatment plan will be moved to the specialist health care services [12]. This may indicate that the women that receive OMT outside institutions are healthier and/or are more stable than women that daily receive OMT at OMT centers.

The selection of studies used to answer aim IV may have affected the results. The studies were chosen because we wanted to include studies with different study designs and studies that reported the same maternal and neonatal outcomes. However, the exclusion criteria in each study differed, loss of individuals prior to the data analysis in the studies varied, and the way individuals were selected differed [39, 74, 86, 87, 96-98].
5.1.3 Information bias

Information bias has been defined as systematic error that occurs when the information collected from or about study subjects is erroneous or misclassified [127]. Study subjects in the National OMT cohort study may have had recall biases. The women know that many children that are exposed to OMT in utero are born with NAS and may be especially aware of other potential risk factors such as continued substance abuse, use of prescription drugs and psychiatric problems. This may have affected answers at the EuropASI interview one year after the children were born. Mothers whose children were born with NAS may remember all potential risk factors better than mothers whose babies were not born with NAS. This recall discrepancy is called maternal recall bias [127].

The data collection procedure at the different time intervals differed. The EuropASI and HSCL-25 that were completed during third trimester were face to face interviews and self-completing questionnaire with the interviewer present, respectively. At the follow-up data collection points, the EuropASI was conducted as a telephone interview and HSCL-25 was sent via mail. The changes in data collection procedure may have affected how women and their partners responded to the interview questions and/or the way the questionnaire was completed. Furthermore, social desirability responding is more common when interviews are conducted in person [128].

Data used to address aim III was collected from MBRN and NorPD. Data on dispensed drugs were registered at pharmacies so it can be assumed that information bias was low. However, the ATC and DDDs were used to describe prevalence and amount of different prescription drugs used. NorPD was established in 2004, and during the first year 6 % of the prescriptions drugs dispensed had invalid personal identification numbers. This proportion had been reduced to 2 % per year by 2007 [105]. Prescriptions with invalid personal identification may have contributed to a slightly lower prevalence figure than the accurate number of women in OMT that receive prescription drugs. For the same
reason, it may be that the amount of opioids, benzodiazepines and z-hypnotics presented in this study is slightly lower than what is accurate.

5.1.4 Confounding

Confounding has been defined as “the confusion, or mixing, of effects” [127]. This definition suggests that effects of one or more variables are mixed with the effects of exposure, which leads to a bias [127].

The present study investigated if there were differences in neonatal outcomes in children born to women that were dispensed drugs with abuse potential during pregnancy compared to women that did not receive such co-medication. Because our research data file did not include necessary information on confounding variables to conduct multivariate analyses, only bivariate analyses were performed. Therefore, we do not know whether the significantly higher prevalence of malformations in neonates whose mothers had received co-medication with abuse potential was due to the co-medication or confounding variables such as smoking, continued substance abuse or poor nutrition etc. Confounding by indication is a problem that arise because those that take a drug differ from those who do not take this drug [127]. The women who received such co-medication may have worse health and thus have higher risk of adverse pregnancy and neonatal outcomes.

We lack background information about potential confounding factors regarding the women in some of the studies used to answer aim IV. Therefore, we do not know how comparable the women in the retrospective studies are to the women in the RCT studies. Confounding by indication may also be an issue: opioid dependent women that use buprenorphine + naloxone may differ from women that use buprenorphine or methadone. The retrospective study on buprenorphine + naloxone during pregnancy does not offer information about disease history of the women however, and we can only speculate how comparable they are to the women using methadone or buprenorphine.
5.1.5 Instruments used

The validity and reliability of EuropASI are reported as satisfactory by some [129], whereas others are more critical to the instrument [130]. However, most of the critique raised towards the instrument is related to the composite scores, which were not used in the present study. One of the problems raised is related to lack of sensitivity in weighing the scores [131]. For example, for substance abuse the composite score is not sensitive to low use of substances such as heroin. Even with reports on low use of heroin, any use of such a substance is a problem. Low use of heroin should be weighed differently than low use of some other substances [131].

The present study used problems in the last 30 days instead of composite scores to measure change in substance abuse and related areas. It may be that the relatively short timeframe is not representative of the usual situation for the respondents [9]; for example it is unlikely that the interview conducted during the last month of the pregnancy was not representative in some aspects, especially for the women that may have experienced more physical problems because they were carrying a baby.

The validity of the terms severe depression and anxiety may be questioned. Even though the EuropASI manual offers description of symptoms of severe depression and anxiety, these are not very specific. Whether or not the respondents will describe their symptoms as severe depends on their personality and also on how the interviewer phrases his or her questions[111]. Furthermore, the symptoms should be present also when the person is not under the influence of alcohol or drugs [111].

HSCL-25 is considered to be a reliable and valid measure of symptoms of anxiety and depression [132]. If items for depression and/or anxiety were missing at any of the time intervals for any of the respondents, data on depression and/or anxiety were excluded for that respondent at that time.
interval. This decision was reached on the background that we had no control over what their answer might have been and it was considered inappropriate to calculate a score where items were missing. HSCL-25 has been criticized for not separating well enough between anxiety and depression [9]. On the other hand, it has been argued that these symptoms often occur concomitantly [133] and some studies report GSI, anxiety and depression combined, as an expression of “general nervousness” [9]. Despite criticism towards HSCL-25, the instrument may give a more accurate picture of symptoms of depression and anxiety than EuropASI [9], which only asks one question regarding anxiety and depression respectively. There also exist a 4-point SCL scale, where a common cut-off is 1.75 [134]. In the present study, however, we chose to use the 5-point HSCL-25 version, and a cut-off for psychiatric case on 1.0. This version was chosen to more easily compare findings with a previous study on opioid dependent individuals in Norway, which used a 5-point HSCL-scale and [9].

It may be questioned whether self-completion forms such as MCMI III are as suitable to measure personality disorders as personal structured interviews. Because of the different approach, self-completion instruments and interviews are likely to map different dimensions of the same personality disorder or even different PDs [135, 136]. However, such differences appear also between different personal structured interviews, such as SCID and MMPI [136]. The decision to use MCMI III to evaluate PDs was reached on the background of practical considerations, such as lack of resources to conduct time consuming clinical interviews.

There exist some limitations with measuring prescription drug use during a month with DDDs. Firstly, looking at opioids as one group may be problematic, since one DDD of weak opioids, such as codeine, would then count similarly as one DDD of a stronger opioid, such as morphine. To avoid this problem, DDDs were grouped into strong and weak opioids in the present study. Secondly, it is not uncommon for prescribers to prescribe opioid analgesics to be used “as agreed with GP” or “as needed”. Therefore, amount used per day may vary considerably according to level of pain on
different days [137]. Accordingly, DDDs may not give a correct picture of amount of opioids consumed by pregnant women in OMT.

5.1.6 Classifications and labeling

If the respondents answered yes to ANY psychiatric problems or having used ANY illegal or legal substances in the past 30 days prior to the EuropASI interviews, it was classified as having reported psychiatric problems with legal or illegal substances. For psychiatric problems, this classification led to high prevalence of psychiatric problems according to EuropASI. On the HSCL-25 (range from 0-4) a score above 1 was the cut-off point for a possible “case” with depression and/or anxiety problems [9].

5.1.7 External validity

External validity or generalization is the assumption that the results of the study also apply outside that population [138].

Although a national cohort of pregnant OMT women were used to answer aim I and II, these results may be more easily generalized to Nordic countries and countries with similar health care systems. The Norwegian health care system differs greatly from many countries. Furthermore, the strict laws in Norway regarding substance abuse during pregnancy greatly differ from most other countries [58]. In a Norwegian setting however, the results should be considered representative for pregnant OMT women and their partners.

Regarding use of prescription drugs prior to and during pregnancy (Aim III), OMT women in other countries probably experience similar health problems as OMT women in Norway. Therefore, antiinfectives and drugs acting on the central nervous system may also be the most used prescription drug groups among pregnant OMT women in other countries.
The majority of the studies included to address aim IV were from the U.S. We know that extreme poverty and homelessness is common among substance dependent pregnant women in the U.S. [139]. These factors are additional stressors that may have a negative influence on maternal and neonatal outcomes. Furthermore, several of the studies were retrospective and we lack background information about the women in these studies. Therefore, we do not know if the women included differ significantly from pregnant OMT women in general.

5.1.8 Strengths

The data in the national OMT cohort is unique. It is the first national cohort that includes the partners of pregnant OMT women and follow their families over time.

To our knowledge, no previous study has described all prescription drug use in a six year national cohort (2004-2010) of pregnant OMT women. The unique personal identity number assigned to all individuals in Norway, and the population based registries on birth, prescriptions and more, provide high quality linkages between registries in Norway. These data sources offer opportunities to answer important questions about prescription drug use among pregnant women in OMT and maternal and neonatal outcomes after exposure to different prescription drugs during pregnancy. Studying dispensed, rather than prescribed prescription drugs has an advantage since some individuals may not comply to treatment and fail to go to the pharmacy to hand in the prescription [140]. Consequently, the prescribed drug may not be dispensed. Following all patients to control that they actually ingest the prescription drugs is not an option. Therefore, studying prescription drugs that are dispensed is probably the closest we can get to accurately describe use of prescription drugs in a patient population [137].

As far as we know, no previous studies have compared maternal and neonatal outcomes after exposure to buprenorphine + naloxone vs. buprenorphine vs. methadone assisted
5.2 Discussion of results

5.2.1 Aim I: Substance abuse

The study showed that substance abuse was low both during interview in the third trimester and one year after birth both among the women and their partners.

The women had a long history of heroin and poly-drug use prior to joining OMT. However, illegal substance use remained low from the last month of pregnancy to one year after child birth among the women in OMT. This applied also for problems that are often related to substance abuse; legal, psychiatric, financial as well as problems with social relations. Medical /somatic problems were significantly reduced among the women from third trimester to one year after birth.

Low use of illegal substances is positive for the women's parenting and care giving abilities. A majority of the children were still living with their mothers when they were two and a half years old, only three children lived in foster homes [102]. One child was placed directly in foster care after being born, but moved back to the parents after one year. One child was placed in permanent foster care one month after being born, and two children were placed in foster care when they were aged between one and two and a half years old [102]. This percentage is low compared to a study of women with substance abuse problems in Finland, where 38 % of children were in “out of home care” when up until they were two years old [18].

On the other hand, there was an increase in problem drinking among the women from pregnancy to one year after. No women reported drinking the 30 days prior to the interview during pregnancy, whereas 15 % reported problem drinking one year later. This may suggest that women are having a
difficult time, and the increased alcohol consumption needs to be addressed. Parental alcohol abuse may have severe consequences for the children [141, 142]. Furthermore, individuals that are opioid dependent and have additional alcohol problems may have more severe dependence problems in general and are at increased risk of poor treatment outcomes [143, 144]. Moreover, the prevalence of psychiatric problems among opioid dependent women with co-occurring alcohol problems is also significantly higher compared to women with only opioid dependence [143]. Relapses to drug abuse after birth is common [91], and these findings underscore the importance of following pregnant OMT women and their families closely for a longer time period after birth. The Norwegian guidelines for pregnant women in OMT suggest that these families should be offered close follow-up until the child starts school [40]. This may contribute to better treatment outcome for the parents and improved developing outcomes for the child in a secure care giving situation [40].

The majority of the partners of the national cohort of pregnant OMT women in Norway had a similar substance abuse background as the women. However, seven of the partners had never used heroin and six of the seven had never used illegal drugs. The other two thirds had on average eight years of heroin and 13 years of poly-drug abuse behind them. Studies show that if the partner relapses to substance use again this is likely to subsequently increase the chance of a relapse in the woman [71, 145]. However, in the present study, use of illegal substances was low both during 3 trimester and one year after child birth among the partners.

Becoming a parent is an important life event that may contribute to additional motivation to stay drug free. The parents may be less likely to experience a relapse and may be motivated to make an extra effort to deal with their own problems, because they know this would also benefit their children. From an economic perspective it is beneficial that the OMT women and their partners stay in treatment for a longer period since relapse to illicit substance use, entry into new treatment and
increased dependence on unemployment and disability pensions are expensive. What the best solution for the child, the parents and society is, has to be carefully evaluated in every case [9].

5.2.2 Aim II: Psychiatric problems

The prevalence of psychiatric problems among the women and their partners was low both during third trimester of pregnancy and one year after the children were born. The prevalence of personality disorders however, was substantial among the women and their partners alike.

The majority of the women and their partners had experienced one or more forms of abuse earlier in life: emotional and/or physical and/or sexual. Lifetime emotional and physical abuse were higher in the present study than what was reported in previous Norwegian and international literature [26, 65, 139, 146]. Reported lifetime sexual abuse among the women was higher than in some U.S studies [65, 139] whereas both sexual abuse and emotional abuse were lower than in other studies from the U.S, both in a lifetime perspective and during pregnancy [26, 147]. Previous studies have shown that substance dependent women are at greater risk of experiencing intimate partner violence [148, 149] and a study from the U.S. reported that 38 % of men in methadone maintenance were violent towards their intimate partner during the last six months [150]. In comparison, the prevalence of physical abuse reported among the women during last 30 days prior to interview in third trimester was very low. These findings may indicate that when both people in the relationship have been in treatment for a while, as was the case for the majority of the women and their partners in paper II, these problems may be greatly reduced or no longer experienced at all. It is therefore important to include the partners of pregnant OMT women in treatment and research, since they may have a great impact on treatment retention and how the woman will cope as a parent [59, 66, 67, 71].

Except for problems concentrating, understanding and remembering, reported psychiatric problems was low among pregnant OMT women and their partners during pregnancy compared to international literature [44, 48, 49]; and was further reduced after the children were born. One
possible explanation to why there was a low prevalence of psychiatric problems among the women and their partners, compared to previous studies, is that they had been in OMT on average about two and a half years prior to joining the study. In most previous studies women start OMT only when they discover they are pregnant, [39, 86, 151]. At that point they are probably less stable than what is the case in the present study [152]. There were fewer nervousness cases among the women in paper II during third trimester (35 %), six months (12 %) and two years (19 %) after birth, compared to nervous “cases” among opioid dependent individuals (55 %) at intake to methadone treatment in a Norwegian study [9],

About two out of every fifth OMT woman and one third of the men had one or more PDs. Previous studies have shown that victims of childhood abuse are at increased risk for developing PDs in addition to being more prone to depression, anxiety, drug and alcohol dependence [119, 153]. Drug dependent individuals with co-occurring PDs are at increased risk of negative treatment outcomes [116, 121, 145, 154].

Compared to previous international and Norwegian studies on opioid dependent individuals, the prevalence of PDs in this cohort of OMT women and their partners is low. In a Canadian study, 77 % of OMT patients had one or more PDs [120] and a Norwegian study reported PDs in three of four individuals [9]. Antisocial and borderline PD are often the most common PDs in substance dependent populations [9]. This was not the case in the present study. Depressive, histrionic and masochistic PDs were most common among the women. Among the partners, depressive PD was most common, followed by antisocial. PDs are also related to lower functioning in interpersonal domains, including negative parenting behavior which may severely affect the parent-child interaction [155, 156]. Thorough psychiatric evaluations should be conducted in pregnant OMT women, also checking for PDs. Pregnant OMT women with co-occurring PDs and/or psychiatric problems should be followed
closely and offered additional help to increase their chances to cope well in their parenting role [156].

5.2.3 Aim III: Prescription drug use

In paper I, 8% of the OMT women reported using benzodiazepines during the past 30 days prior to the interview undertaken in the third trimester. In paper III use of benzodiazepines was lower (4%) even though this was over three months: the entire third trimester. Although different data collection procedures were used, there is probably some overlap between the women included in paper III for the time period 2005-2006, and the women included paper I. However, some of the women in paper I probably received methadone or buprenorphine at OMT centers or other treatment facilities for parts of, or the entire pregnancy. Information on prescription drug use among women that receive methadone or buprenorphine at OMT centers or other treatment facilities for the entire pregnancy is not included in NorPD at an individual level, and therefore not included in paper III. Therefore, it may be that the reports on use of benzodiazepines in paper I is higher because reported use also include benzodiazepines acquired at the illegal market, something which is not captured in paper III.

A high proportion of pregnant OMT women experience depression [48, 157, 158] and psychiatric problems are associated with negative pregnancy outcomes [159]. In paper II, 8% of the women reported serious depression during the 30 days prior to the EuropASI interview and 36% were classified as “cases” on depressive symptoms during the last week according to SCL-25, conducted during third trimester. However, in paper III only 5% of the OMT women were prescribed antidepressants during pregnancy in Norway. In comparison, 24% of pregnant opioid dependent women in an study including data from the U.S., Austria and Canada received SSRI during pregnancy [44], and in a Norwegian study of OMT patients in general, 23% of the women received at least one prescription of antidepressants during one year [160]. Among all women in the general population, 7.9% were dispensed an antidepressant drug at least once during 12 months [126]. The increase in
depression among OMT women in paper II, from six months to two years after the baby was born, is cause for concern. The women represent a vulnerable, high-risk group, given their history of substance abuse and psychiatric problems.

If treatment providers fail to address depression in pregnant OMT women and do not provide appropriate treatment, this poses a major risk to the health of both the woman and the neonate [16]. Among the risks are: lower fetal growth and dysfunctional bonding between mother and child [161]. Pregnant OMT women should be carefully evaluated for depression and offered appropriate medication if the potential benefits of treating depression with pharmacological alternatives outweigh the risk of not doing so [40, 162]. Compared to the OMT patients in general in Norway, where only one in five that receive antidepressants received Tricyclic antidepressants (TCAs) [160], it is worth noting that TCA is as common as SSRI among pregnant women in OMT [160]. This may indicate that they receive antidepressants to treat pain [163].

Concerns have been raised regarding how stigma and fear of drug-seeking behavior, may result in over caution in prescribers [16]. This was probably not the case in the present study however, since the proportion of women who received strong and weak opioid analgesics was the same. In comparison, among pregnant women in the general population that are dispensed opioid analgesics, 99% receive weak opioids [164]. Opioid dependence may be associated with increased sensitivity to pain, and tolerance to opioids, including opioid analgesics. [165-167] On this background, pain management in pregnant OMT women is challenging. In Norway the national guideline for pregnant OMT women offers suggestions to what pain medications should be used during birth. However, the guideline does not address how to treat pain earlier in pregnancy [40].

Use of antiinfectives were about twice as high among pregnant women OMT women as in the general population of pregnant women [108, 168]. Prior life circumstances with injection drug use,
poor nutrition, poor personal hygiene, prostitution, co-morbidity and stress, which is associated with high prevalence of infections, may contribute to higher use of antiinfectives in OMT women [9, 169].

5.2.4. Aim IV: Maternal and neonatal outcomes from exposure to different OMT drugs

Findings in Paper IV suggest that there are no significant adverse maternal outcomes from use of buprenorphine + naloxone compared to buprenorphine and methadone. Neonates exposed to buprenorphine + naloxone were significantly shorter at birth and had significantly lower Apgar scores at 5 minutes compared to the buprenorphine group. Only 10 women and neonates were included in the buprenorphine + naloxone group, and the findings on maternal and neonatal outcomes should therefore be considered preliminary. Since there is a lack of literature that compares buprenorphine + naloxone to other medicinal treatments for opioid dependence in pregnant women, we were unable to compare our results to results from other studies.

Only maternal and neonatal outcomes that could be measured objectively were included. For example, whether the women gave birth through cesarean section, complications at delivery and number of prenatal obstetrical visits. However, it may be questioned how objective the measurements of some of the outcomes really were. Anxiety and uncertainty among pregnant women and health care personnel without special competence on opioid dependence in pregnant women may have contributed to decisions to use cesarean section more often than in the general population. Furthermore, competence on scoring of NAS may be limited at some hospitals, which may lead to different practice for length of hospital stay and treatment of NAS [99].

There is an ongoing debate regarding which OMT medication is the better choice for pregnant opioid dependent women. In Norway buprenorphine is the number one recommendation for opioid dependent individuals in general and also for pregnant women [12, 40]. Buprenorphine appears to be superior to methadone for some neonatal outcomes: shorter duration of NAS and shorter hospital
stay to treat NAS [86, 88-90, 170-173]. However, sometimes a patient does not respond well to buprenorphine, or simply prefers methadone over buprenorphine [16, 74]. Therefore, both treatment options should be available. The safety of buprenorphine + naloxone has not been sufficiently studied yet, and should generally not be used to treat pregnant opioid dependent women before the woman has tried buprenorphine alone. More research should be conducted before use of buprenorphine + naloxone is recommended to pregnant opioid dependent women.
6.0 FUTURE RESEARCH

Ethical considerations has to be taken, when studying vulnerable groups such as pregnant women in OMT. Researchers and clinicians should to be careful not to make the women feel pressured into participating in research projects. However, not conducting research on this patient group would be equally problematic, since research is needed in order to offer the best possible knowledge-based treatment. Furthermore, we need to carefully consider how we can best contribute to this in a small country such as Norway, where conducting clinical research on pregnant women in OMT is challenging, because the number of pregnant OMT women is quite low. Clinical and epidemiological studies complement each other, and contribute to a more complete picture of pregnant women in OMT.

Limited knowledge exists on long term outcomes in the children exposed to OMT and co-medication and more research is needed on long term outcomes to investigate if children exposed to OMT and co-medication are more prone to diseases or early deaths, than children exposed to only OMT and children in the general population.

With a high prevalence of psychiatric and somatic problems [4, 49], co-medication with other prescription drugs is common among pregnant OMT women. Knowledge of potential risks from co-medication among pregnant OMT women is scarce, incomplete and lacks details of the potential effects on pregnancy and neonatal outcomes. Consequently, pregnant OMT women may not receive the medications they need for psychiatric symptoms and pain, because prescribing doctors lack knowledge on OMT and co-medication during pregnancy. Prescribing doctors may also be concerned about increased risk of adverse pregnancy and neonatal outcomes, as well as drug seeking behavior and overmedication [174]. Conversely, some women receive co-medication that may be harmful, such as benzodiazepines which may increase the risks of adverse outcomes, including prevalence of,
and prolonged treatment of NAS [175, 176]. Both over and under-medication endangers treatment stability and may cause a relapse to illegal substance use. Co-medication may contribute substantially to adverse pregnancy and neonatal outcomes [176]. At this point it can only be speculated whether this is due to the combination of prescription drugs themselves, or if the women that receive these prescription drugs have more health problems, and therefore higher probability of adverse pregnancy and neonatal outcomes. Therefore, large scale high quality studies are warranted to produce findings that may reduce the high societal and personal costs that accompany these outcomes [177].

OMT has become the main treatment intervention for heroin dependence, in Norway and many other countries; also for women of childbearing age. In recent years most patients in Norway are dispensed OMT drugs in pharmacies. Dispensed prescription drugs in Norway are recorded in the prescription registers which offers a new opportunity to study OMT patients. In Norway, several studies have already described co-medication among OMT patients in general [160, 178], and paper III in the present thesis looked specifically at co-medication among pregnant OMT women.

However, to study the important consequences of such treatment, there is a need for more data than what is available in Norway. An overall Nordic cohort may offer the size necessary to study these outcomes. Each Nordic country has national registers, which include prospectively collected information on the health of all inhabitants. Linking and investigating data in the prescription databases, birth registries, cause of death registries, patient registries and data on socio-economic status from the statistical central bureaus in the Nordic countries may produce findings on new and reliable knowledge on pregnant women in OMT and their children.
7.0 CONCLUSIONS

The thesis contribute to increased knowledge regarding substance abuse and psychiatric problems among pregnant women in OMT in Norway and their partners. The thesis contribute to a reduction in the knowledge gap regarding prescription drugs among pregnant OMT women, and awareness regarding maternal and neonatal outcomes from exposure to buprenorphine + naloxone compared to other medicinal treatment options for opioid dependence among pregnant women.

The main findings and implications of the present study can be summarized as:

✓ Use of illegal substances was low both during third trimester and one year after the birth among the women and their partners. The increase in problem drinking among the women one year after birth may indicate that some women may not be coping with motherhood.

✓ Psychiatric problems was low, relative to the OMT population, among the women and the partners alike both during the third trimester and one year after delivery.

✓ A high prevalence of PDs among both women and their partners, and the increase in depressive symptoms among women when the children were two years old, may compromise the child-parent relationship. It is therefore important that parents in OMT and their children are followed closely for several years after delivery.

✓ Pregnant OMT women use more prescription drugs than pregnant women in the general population. Particularly use of drugs acting on the central nervous system and antiinfectives were high.

✓ Benzodiazepines were the most commonly used prescription drug, but use was reduced from prior to pregnancy to third trimester.

✓ Preliminary findings suggest no significant adverse maternal or neonatal outcomes related to the use of buprenorphine + naloxone for the treatment of opioid dependence. However, GPs should exercise caution when using buprenorphine + naloxone to treat opioid dependent pregnant women due to limited research.


58. Lovdata, Lov 1999, nr 61, Sosialtjenesteloven § 6-2a. Tilbakeholdelse av gravide rusmisbrukere [Only in Norwegian: Social Services Act § 6-2a Retention of substance dependent pregnant women in institutions], Available at http://www.lovdata.no 2010, Norway


ERRATA

Paper I, Table III, p values for “illegal substances sum” and “legal substances sum” should be listed under the table instead of in own column. For women the increase in use of legal substances from 8-19% from pregnancy to one year after was not significant (p = .08) whereas the reduction from 38-20% among the partners was significant (p = .01)

Paper II, figure I. Last box for women should read “2 years after birth”, not 1 year after birth

Paper II. The reference “Hans, Bernstein, Henson” is listed twice in the reference list.
A Comparison of Buprenorphine+Naloxone to Buprenorphine and Methadone in the Treatment of Opioid Dependence during Pregnancy: Maternal and Neonatal Outcomes

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Abstract

Objectives: Given that buprenorphine+naloxone is prescribed for opioid-dependent pregnant women, it is important to examine the extent to which it differs from buprenorphine alone, methadone, or methadone-assisted withdrawal on neonatal and maternal outcomes.

Methods: All data presented are gathered from 7 previously published studies. Not all studies from which data were extracted had data for all outcomes.

Results: Differences in maternal and neonatal outcomes from exposure to buprenorphine+naloxone during pregnancy compared to buprenorphine alone, methadone, or methadone-assisted withdrawal were non-existent or small.

Conclusions: These preliminary findings suggest no significant adverse maternal or neonatal outcomes related to the use of buprenorphine+naloxone for the treatment of opioid dependence during pregnancy. However, further research should examine possible differences between buprenorphine+naloxone and buprenorphine alone or methadone in fetal physical development. Patient preference, individual risk:benefit ratio, and treatment context should be considered when prescribing any medication during pregnancy.

Key words: buprenorphine; methadone; opioid dependence; pregnancy; neonates
Background

Since the late 1960s methadone has been prescribed to pregnant women to treat opioid dependence (Blinick, 1968). Research conducted during the last decade indicates that maternal outcomes following use of buprenorphine during pregnancy are similar to maternal outcomes following use of methadone during pregnancy (Fischer et al., 2006; Jones et al., 2005; Jones et al., 2010; Kakko, Heilig, & Sarman, 2008; Lejeune, Simmat-Durand, Gourarier, & Aubisson, 2006; Siedentopf, Nagel, Eßer, Casteleyn, & Dudenhausen, 2004). However, buprenorphine seems to be superior to methadone in regard to some neonatal outcomes, including yielding a shorter duration of neonatal abstinence syndrome (NAS) and a shorter length of hospital stay (Binder & Vavrinkova, 2008; Colombini et al., 2008; Fischer et al., 2000; Johnson, Jones, & Fischer, 2003; Jones et al., 2005; Kakko et al., 2008; Schindler et al., 2003; Whitham et al., 2010).

To date, research on the use of buprenorphine during pregnancy has focused almost exclusively on buprenorphine alone rather than the most commonly prescribed form of buprenorphine in the U.S., buprenorphine+naloxone. Buprenorphine+naloxone has been the preferred form of prescribed buprenorphine due to its reduced abuse liability relative to buprenorphine alone (Fudala et al., 2003; Strain, Harrison, & Bigelow, 2011). This emphasis on buprenorphine alone is largely due to two reasons. First, pregnant women are advised to limit fetal exposure to exogenous compounds, thus prescribing buprenorphine alone avoids fetal exposure to naloxone. Second, data from animal studies suggest that prenatal exposure to naloxone may produce maternal and subsequently fetal hormonal changes (Brunton et al., 2005; Douglas, Meddle, Toschi, Bosch, & Neumann, 2005).

Little is known about buprenorphine+naloxone relative to either buprenorphine alone, methadone, or methadone-assisted withdrawal in the treatment of opioid dependence during pregnancy. Buprenorphine+naloxone is now being prescribed to opioid-dependent pregnant women. It is therefore important to examine whether neonatal and maternal treatment outcomes for pregnant women in treatment for opioid dependence with
buprenorphine+naloxone differ from these outcomes for pregnant women in treatment for opioid dependence with buprenorphine, methadone, or methadone-assisted withdrawal.

The three objectives of the present study are to compare neonatal and maternal outcomes from a group of opioid-dependent women who were prescribed buprenorphine+naloxone during their pregnancy to: (1) groups of opioid-dependent pregnant women who were prescribed buprenorphine alone; (2) groups of opioid-dependent pregnant women prescribed methadone; and (3) a group of opioid-dependent pregnant women who underwent a 7-day methadone-assisted withdrawal.

Methods

All data presented in this review come from previously published studies (Czerkes, Blacstone, & Pulvino, 2010; Debelak, Morrone, O'Grady, & Jones, 2012, in press; Fischer et al., 2006; Jones et al., 2005; Jones et al., 2010; Jones, O'Grady, Malfi, & Tuten, 2008; Metz et al., 2011), which represented a wide range of studies on use of buprenorphine and methadone during pregnancy. However, several authors of these papers provided additional data (e.g., standard deviations) that were not available in their published papers. The articles included were chosen because they represented a range of study methodologies; RCTs and retrospective studies, increasing generalizability of the findings. Moreover, all studies reported a common subset of outcome measures, and provided data that could be easily subject to re-analysis.

Studies

**Buprenorphine+naloxone: an initial study of maternal and neonatal safety**

_Debelak et al._ (2012) conducted a retrospective chart review in a community health setting that produced 10 women who had received buprenorphine+naloxone during the course of their pregnancies. Maternal outcomes reported in this study were: cesarean section, days of maternal hospital stay, maternal weight gain, non-normal presentation, analgesia during delivery, drug-screen at delivery, medical complications at delivery, number of prenatal obstetrical visits, fetal presentation at delivery and breastfeeding following delivery. Neonatal outcomes included were: treated for NAS, total amount of morphine for
NAS, days treated for NAS, days of infant hospital stay, head circumference, birth weight, infant length, pre-term birth, gestational age at delivery, Apgar scores at 1 and 5 minutes. They reported neonatal growth parameters within normal limits, with only 40% of the neonates treated for NAS. Mean number of days with NAS treatment was 6.9 (SD=10.1). Findings indicated that there were no obvious adverse maternal or neonatal outcomes related to the use of combination buprenorphine+naloxone product for treatment of opioid-dependence in pregnant women. Maternal outcomes were similar to what has been found for women using buprenorphine alone.

Comparing maternal and/or neonatal outcomes; methadone v. buprenorphine

Czerkes et al. (2010) conducted a retrospective chart review from 2004-2008 that examined differences in outcomes in neonates born to women who had been prescribed methadone (n=101) or buprenorphine (n=68) during pregnancy. Exclusion criteria’s were: delivery not performed at Maine Medical Center and preterm delivery (before 37 weeks of gestation). The following neonatal outcomes were measured: treated for NAS, length of stay, neonatal abstinence score, neonates requiring treatment, birth weight, Cord pH, 1 and 5 minute Apgar scores. The Finnegan scale was used to evaluate NAS scores. Neonates in the buprenorphine group had a lower mean NAS score than neonates in the methadone group. Number of neonates (48.8 % v. 73.3%, p<.001) treated for NAS and mean length of hospital stay (8.4 v. 15.7 days, p<.0001) of those neonates treated were also significantly lower in the buprenorphine group. Analyses also revealed no significant differences in maternal characteristics between the two groups.

Fischer et al. (2006) conducted a randomized, double-dummy, double-blind, flexible-dosing trial comparing buprenorphine to methadone in opioid-addicted pregnant women to evaluate safety and efficacy of the two medications in pregnant women. Inclusion criteria’s were: informed consent, willing to follow protocol and not use illegal drugs. Women with high risk pregnancies, additional severe psychiatric or somatic diseases were excluded. The maternal outcome reported, separately for buprenorphine and methadone conditions, was cesarean section. Neonatal outcomes reported were: treated for NAS, total amount of
Buprenorphine+naloxone v. Buprenorphine v. Methadone - 6

morphine for NAS, days treated for NAS, birth weight, pre-term birth, gestational age at
delivery, Apgar scores at 1 and 5 minutes. The Finnegan scale was used to assess NAS.
Eighteen women were randomly assigned to either buprenorphine or methadone. There
were 6 women in the methadone and 8 women in the buprenorphine condition at delivery.
Methadone dose ranges were 40-100 mg while buprenorphine dose ranges were 8-24 mg.
Retention was higher in the buprenorphine condition, whereas methadone was more
effective than buprenorphine in preventing use of additional opioids ($p<.05$).

Metz et al. (2011) examined maternal and neonatal outcome in pregnant opioid-
maintained women in a randomized clinical trial compared to a group of women undergoing
a structured standard pharmacotherapy protocol with either buprenorphine or methadone at
the Medical University of Vienna. The women included in the randomized controlled trial
portion were part of Jones et al. (2010). Therefore, only data from the women that underwent
structured standard pharmacotherapy protocol with either buprenorphine or methadone were
included in the present paper. Inclusion criteria were: 18 to 41 years of age, single fetus
pregnancy, and that they were not drop-outs from the clinical trial in the same study. Women
were excluded from the study if they had an abortion, miscarriage or decided to deliver at
another clinic. The maternal outcomes reported were cesarean section and urine toxicology
during the third trimester. The neonatal outcomes reported were: treated for NAS, total
amount of morphine for NAS, days treated for NAS, days of hospital stay, head
circumference, birth weight, infant length, gestational age at delivery, Apgar scores at 1 and
5 minutes. NAS was assessed using a modified version of the Finnegan scale. Opioid
maintenance medication was determined on an individualized basis and chosen according to
patient preference for buprenorphine or methadone as well as medical criteria. Maternal
outcomes were fairly similar in the buprenorphine and methadone groups, apart from more
positive urine toxicologies overall in the methadone than the buprenorphine group. Neonatal
outcomes were superior in the buprenorphine than in the methadone group in terms of
gestational age at delivery and the following physical characteristics: body length, body
weight, and head circumference. Fewer neonates in the buprenorphine group needed NAS
treatment and among neonates who did need treatment, total morphine dose was lower and days of morphine treatment were fewer compared to neonates in the methadone group.

Jones et al. (2005) conducted a randomized, double-blind, double-dummy, flexible-dosing parallel-group controlled trial that compared NAS in neonates born to women maintained on buprenorphine or methadone. Inclusion criteria’s were: age 21-40 years, estimated gestational age 16-30 weeks, currently meet DSM IV criteria for opioid dependence, asking for maintenance therapy, report using opioids > 4 days during the past 7 days, and positive urine sample at intake. Exclusion criteria’s were: positive urine sample for undocumented methadone at intake, Alcohol abuse or dependence according to DSM IV criteria, using benzodiazepines > 7 days per month or more than >1 per week. Women that receive co-medication for other axis I disorder or have a serious medical illness than may compromise study participation were also excluded. Thirty women who met all of the eligibility criteria were randomized to either the buprenorphine or methadone condition. At delivery, 11 women in the methadone and 9 in the buprenorphine group had completed the study. Maternal outcomes reported were: cesarean section, days of hospital stay, non-normal presentation, analgesia during delivery, drug screen at delivery and maternal medical complications. Neonatal outcomes included were: treated for NAS, total amount of morphine for NAS, NAS peak score, days of infant hospital stay, head circumference, birth weight, infant length, pre-term birth, gestational age at delivery, Apgar scores at 1 and 5 minutes. A modified 19-item Finnegan Scale was used to assess NAS. Morphine sulfate was the pharmacotherapy treatment for NAS. Two of ten (one woman gave birth to twins) neonates (20%) exposed to buprenorphine and 5 of 11 (45.5%) exposed to methadone were treated for NAS. The total amount of morphine solution to treat NAS was three times higher in the methadone condition than in the buprenorphine condition, although this difference was not significant (93.1 v. 23.6; \( p = .3 \)). Length of hospitalization was significantly shorter for buprenorphine- than for methadone-exposed neonates (\( p = .02 \)).

Jones et al. (2010) conducted a double-blind, double-dummy, flexible-dosing, randomized study comparing use of buprenorphine and methadone in 175 pregnant women
in comprehensive care at seven international sites. Of the 131 neonates born to the mothers followed to the end of their pregnancies, 73 were exposed in utero to methadone and 58 to buprenorphine. Exclusion criteria's were: medical or other condition that may compromise participation in the study, pending legal action that may contradict participation and disorders related to use of alcohol or benzodiazepines. The following maternal outcomes were reported: cesarean section, days of maternal hospital stay, maternal weight gain, non-normal presentation, analgesia during delivery, drug-screen at delivery, medical complications at delivery, number of prenatal obstetrical visits. Neonatal outcomes reported were: treated for NAS, total amount of morphine for NAS, days treated for NAS, days of infant hospital stay, head circumference, birth weight, infant length, pre-term birth, gestational age at delivery, Apgar scores at 1 and 5 minutes. NAS was assessed using a modified Finnegan Scale. Dose adjustments were based on medication adherence, urine toxicology results, participant request, and self-reported symptoms of craving or withdrawal. Hospitalized neonates were examined every 4 hours by trained staff, while NAS scores were obtained twice a day for neonates already released to their homes. The mean morphine sulfate dose required to treat the buprenorphine-exposed neonates were significantly lower (1.1 mg v. 10.4 mg, p<.01) than the dose for methadone-exposed neonates. Buprenorphine-exposed neonates also required a significantly shorter hospital stay (10 days v. 17.5 days, p<.01) and duration of treatment for NAS (4.1 days v. 9.9 days, p<.01).

Maternal and neonatal outcomes: methadone maintenance v. methadone taper

Jones et al. (2008) conducted a retrospective record review that compared neonatal and maternal outcomes in pregnant women in treatment for opioid dependence. The women received either continuous methadone maintenance (n=52) or seven-day (n=28) methadone assisted withdrawal. The women were not randomized to these treatment options. Methadone-assisted withdrawal inclusion criteria included: meeting and refusing methadone maintenance criteria, receiving a prescription for 3 or 7 days of methadone assisted withdrawal, were not receiving medication assisted taper for benzodiazepines or alcohol. Medical charts and complete information on delivery outcome had to be available at Johns
Hopkins Bayview Medical Center. The maternal outcomes reported were: positive drug screen at delivery. Neonatal outcomes were: treated for NAS, days of infant hospital stay, head circumference, birth weight, infant length, pre-term birth, gestational age at delivery, and Apgar score at 1 and 5 minutes. The proportion of women with positive urine toxicology tests for illegal drugs at delivery was more than twice as high (57%) among women in 7-day detoxification compared to women in methadone maintenance (23%). Women in methadone maintenance attended more obstetrical visits and remained in treatment longer than the women with 7-day methadone-assisted withdrawal.

Outcome Measures

**Neonatal outcomes.** Summary descriptive statistics (frequencies or means and standard deviations) for 10 neonatal outcomes were extracted from the above articles: Treated for NAS (yes v. no), Total amount of morphine used to treat NAS (mg), number of days treated for NAS, infant length of hospital stay, Pre-term (<37 weeks) birth, estimated gestational age at delivery (weeks), Apgar scores at 1 and 5 minutes, infant head circumference (cm), birth weight (gm), and length (cm).

**Maternal outcomes.** Summary descriptive statistics (frequencies or means and standard deviations) for 8 maternal outcomes were extracted from the above articles: whether the women gave birth through cesarean section (yes v. no), days of maternal hospital stay, maternal weight gain (kg), non-normal presentation of fetus at delivery (yes v. no), used analgesia during delivery (yes v. no), positive drug screening (for opioids [other than their study medication], cocaine, barbiturates, benzodiazepines) at delivery (yes v. no), medical complications at delivery (yes v. no), and number of prenatal obstetrical visits.

Statistical Analysis

Two different types of summary statistics were collected from articles that provided comparison data: frequencies for binary variables (e.g., Treated for NAS: yes v. no) and means and standard deviations for continuous variables (e.g., Total amount of morphine for NAS). Data were not available for all outcome variables in every article. However, because frequencies were available for the binary outcomes and means and standard deviations
were available for the continuous outcomes for the respective groups in each comparison article for which data were available, it was possible to utilize logistic regression to analyze the binary data using an events/trials approach. Because some of the cells for studies that did yield data had zero or very small frequencies, Firth’s penalized maximum likelihood approach was utilized to conduct tests of significance for the logistic regression analyses (Firth, 1993). Oneway analysis of variance was employed to analyze the continuous outcome data, making use of the summary statistics (Larson, 1992).

In order to address the three questions posed in this study, three single-degree-of-freedom, non-orthogonal planned contrasts were created for each outcome measure. The first planned contrast compared the buprenorphine+naloxone group to the available buprenorphine groups, pooled, which addressed the question of whether or not buprenorphine+naloxone produces superior neonatal and/or maternal outcomes relative to buprenorphine. The second planned contrast compared the buprenorphine+naloxone group to the available methadone groups, pooled, which addressed the question of whether or not buprenorphine+naloxone produces superior neonatal and/or maternal outcomes relative to methadone. The third planned contrast compares buprenorphine+naloxone to 7-day methadone-assisted withdrawal, which addressed the question of whether or not buprenorphine+naloxone produces superior neonatal and/or maternal birth outcomes relative to methadone-assisted withdrawal. The error term for all contrasts in the oneway ANOVAs was the within cells term (as in ‘standard’ oneway ANOVA).

Due to the relative complexity of the proposed contrasts, the last row of Table 1 illustrates the set of coefficients that would be used for the outcome variable total amount of morphine for NAS in order to compare the mean of the buprenorphine+naloxone group to the pooled means of the Fisher et al. (2006), Jones et al. (2005), and Jones et al. (2010) comparison samples. In this case, $x$ indicates data were missing for the respective comparison group, zero indicates data were available for that comparison sample, but weren’t included in the contrast – in this case because the data in question were for methadone – while the non-zero values indicates that the buprenorphine+naloxone mean is
being compared to the unweighted average of the means of the three comparison samples with buprenorphine data. Thus, this comparison is the ‘standard’ oneway ANOVA contrast among means, which would likewise use the unweighted average of the means for a planned contrast.

Results

In general, the samples were similar in maternal age (mean age range was 23.9-30.3 years). [Demographic data other than age were not consistently available in the studies in order to present a general summary.] Only two studies reported opioid-agonist medication dose at delivery: Metz et al. (2001) reported mean methadone dose of 74.2 and buprenorphine dose of 9.9, while Jones et al. (2010) reported means of 79.1 and 18.7, respectively.

Table 1 contains the frequencies (percentages) or means (standard deviations) of the outcome measures available in each study. Table 2 contains results for maternal and neonatal outcomes.

Maternal outcomes

There were no significant differences in maternal outcomes for women exposed to buprenorphine+naloxone compared to women exposed to buprenorphine, methadone, or methadone-assisted withdrawal.

Neonatal outcomes

Head circumference was significantly higher on average among neonates exposed in utero to buprenorphine+naloxone compared to neonates exposed to methadone-assisted withdrawal \([M_s=32.8 \ (SE=.60) \ v. \ 31.2 \ (SE=.36), \ F(1, \ 307)=5.24, \ p<.03]\), while neonates exposed in utero to buprenorphine+naloxone were shorter on average than neonates exposed to buprenorphine \([M_s = 46.3 \ (SE=1.08) \ v. \ 50.56 \ (SE=.51), \ F(1, \ 307) =12.74, \ p<.001]\), although both groups were within the normal range according to the WHO international standards of child growth (WHO, 2006). Mean Apgar scores at 5 minutes were significantly lower in the buprenorphine+naloxone group compared to the buprenorphine alone group \([M_s= 8.6 \ (SE=.29) \ v. \ 9.6 \ (SE=.12), \ F(1, \ 499)=4.88, \ p<.03]\).
Discussion

The present evaluation of buprenorphine+naloxone suggests that maternal and most neonatal outcomes from exposure to buprenorphine+naloxone are not dissimilar from those same outcomes found in women and their neonates exposed to buprenorphine and methadone.

Findings suggest that rates of cesarean section, non-normal presentation, analgesia during delivery, screening positive for illicit substances, and medical complications at delivery, together with length of maternal hospital stay, maternal weight gain, and number of prenatal visits for women using buprenorphine+naloxone during pregnancy do not differ significantly from women using either buprenorphine or methadone. These findings are not surprising, given previous research has indicated that maternal outcomes are comparable across buprenorphine and methadone treatment (Fischer et al., 2006; Jones et al., 2005; Jones et al., 2010; Kakko et al., 2008; Lejeune et al., 2006; Siedentopf et al., 2004).

There were three significant differences in neonatal outcomes when neonates exposed to buprenorphine+naloxone were compared to neonates exposed to buprenorphine alone, methadone, or 7-day methadone-assisted withdrawal. Head circumference in the buprenorphine+naloxone group was significantly greater than in the 7-day methadone-assisted withdrawal group. Neonates in the buprenorphine+naloxone group were significantly shorter at birth compared to the buprenorphine alone group. However, the birth parameters of the buprenorphine+naloxone group were within normal birth parameters (Debelak et al., 2012, in press). Apgar scores at 5 minutes were significantly lower in neonates in the buprenorphine+naloxone group compared to neonates exposed to buprenorphine alone; however, the mean Apgar scores for both groups are considered normal and not clinically concerning. There were no significant differences between the groups on any other neonatal outcome measures: treated for NAS, total amount of morphine used in treatment of NAS, days treated for NAS, days of infant hospital stay, preterm birth, gestational age at delivery, and Apgar scores at 1 minute. Although not significant, the differences in birth length between the neonates in the buprenorphine+naloxone group and
the neonates in the buprenorphine alone group may be related to differences (although not significant) between the groups in gestational age. Although these birth parameters are within the normal range, future studies should consider investigating these potential differences further.

**Limitations:** The strength of any inferences from the present findings must be tempered by the fact that the sample size for buprenorphine+naloxone was small. Moreover, use of summary descriptive statistics to conduct inferential analyses does not allow examination of the extent to which violation of the statistical assumptions might have impacted the findings. Data were only collected for neonates and mothers where pregnancy ended in live births. Therefore, we lack information about abortion frequency and miscarriage, which is potentially important information when comparing medications for opioid dependence in pregnant women. Finally, the various studies under review used various forms of the Finnegan scale to assess neonatal abstinence syndrome.

It is also true that some factors were uncontrolled in several studies included in the present article. For example, there is no available information on use of illicit substances, depression, exposure to sexual victimization, physical violence, or inadequate nutrition in Czerkes et al. (2010) and Debelak et al. (2012). Thus, analyses in the present study cannot control for such factors that may account for some degree of the differences between medications in neonatal outcomes (Kaltenbach, Berghella, & Finnegan, 1998). Assessment of the benefits and risks for opioid-dependent pregnant women associated with buprenorphine+naloxone, buprenorphine alone, methadone, and methadone-assisted withdrawal can best be undertaken when such factors are taken into consideration (Jones et al., 2012).

Pooling data from randomized controlled trials with data from retrospective chart reviews offers challenges. For example, information regarding factors such as exclusion of preterm births is not included in all the studies. There is a lack of background information on the women, such as information on what kind(s) of treatment in addition to their medication, when they started their medication and medication dose. Hence, it is uncertain how
comparable the women in these studies are to the women in the randomized controlled trials where information regarding inclusion and exclusion criteria was available. These same challenges are present in the conduct of meta analyses, which must attempt to aggregate data across research studies. Most meta-analyses have focused on the characteristics of the studies under evaluation – such as whether or not a study is a randomized controlled trial – with little attention to these same issues of patient, treatment, and outcome measure similarities. Rather than focus on such a narrow bandwidth in the choice of our studies, we determined to choose representatively among studies that would provide us with similarity of outcome information. As with most meta-analyses, such an effort at breadth was done at the cost of choosing studies whose patient populations and treatment characteristics were substantially different. However, the gain in our strategy of choosing a representative sample of studies across the spectrum of designs was on the potential generalizability of the findings, and allows for an examination of the extent to which there is enough signal in the medication differences to overcome the heterogeneity of study characteristics.

There are still unanswered questions about the maternal and neonatal safety of buprenorphine+naloxone. The neonatal outcomes (Debelak et al., 2012, in press) presented in the present study would benefit from confirmation from other and larger samples of women.

It is important to note that in most U.S. locales, buprenorphine+naloxone may be the only buprenorphine treatment available to pregnant women. In other nations, such as Norway for example, buprenorphine alone is the recommended opioid medication for pregnant women with opioid dependence (Bakstad, 2011). Pregnant women already in buprenorphine+naloxone treatment are encouraged to transfer to buprenorphine alone. This recommendation is based on the existing research on maternal and neonatal safety of buprenorphine alone and the lack of research investigating the safety of buprenorphine+naloxone during pregnancy.

Strengths: This is the first comparison of neonatal and maternal outcomes from exposure to buprenorphine+naloxone to the other available treatment options for opioid-
dependent pregnant women: buprenorphine, methadone, and methadone-assisted withdrawal.

Conclusions

Findings from the present study suggest no obvious significant adverse maternal outcomes related to the use of buprenorphine+naloxone for the treatment of opioid dependence in pregnancy. The birth parameters for the neonates in the buprenorphine+naloxone group were within the normal range. However, the potential for lower neonatal birth length, weight, and head circumference in this group merit further research on neonatal physical development, and suggests caution in the use of buprenorphine+naloxone. Larger samples are necessary to further examine the relative neonatal safety of buprenorphine+naloxone for the treatment of opioid-dependent pregnant women.

Clinical Implications: The advent of buprenorphine+naloxone has brought a new treatment option for opioid-dependent pregnant women and new challenges to clinicians regarding rational decision-making about which treatment option is the most appropriate for their opioid-dependent pregnant patients. Clinicians who choose to treat their opioid-dependent pregnant patients with buprenorphine+naloxone may need to closely monitor the neonates of their patients in terms of their fetal and neonatal outcomes, until further research has addressed this issue. The data on the safety of buprenorphine+naloxone is not sufficient for the medication to be recommended to pregnant women. Buprenorphine alone should be available for opioid-dependent pregnant women, because the maternal and neonatal safety of this medication has been investigated and the collective results suggest that, when taken as a part of a treatment program, it has an acceptable safety profile for both mother and child (Fischer et al., 2006; Jones et al., 2005; Jones et al., 2010; Metz et al., 2011). Patients' preference, side effects, and retention in treatment should be evaluated carefully.
Acknowledgements

We thank Dr. Metz for providing the means and standard deviations for Apgar scores at 1 and 5 minutes (Metz et al., 2011). We thank Dr. Czerkes for providing standard deviations separately for the methadone and buprenorphine group on gestational age, prenatal visits, length of stay, neonatal abstinence score, birth weight, 1 and 5 minute Apgar scores (Czerkes et al., 2010).
References

Bakstad, B., Welle-Strand, G. (2011). National guidelines for pregnant women in opioid maintenance treatment (OMT) and follow-up of their families until the children reach schoolage [In Norwegian only]. Oslo, Norway: Norwegian Directorate of Health.


assure the safety of the fetus? *Journal of Maternal-Fetal and Neonatal Medicine*(00), 1-3.


im Vergleich zu L-Methadon bei schwangeren Opiatabhängigen. Geburtsh Frauenheilk, 64(7), 711-718.


## Table 1. Neonatal and maternal outcomes in 7 published studies: Comparing Buprenorphine+naloxone (B+N) to Buprenorphine (B), Methadone (M), and Methadone-assisted withdrawal

<table>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated for NAS [Yes]</td>
<td>4 (40%)</td>
<td>74 (73.3%)</td>
<td>33 (48.5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total amount of morphine for NAS (mg): All neonates</td>
<td>1.4 (2.38)</td>
<td>1.4 (1.82)</td>
<td>1.3 (1.83)</td>
<td>13.1 (23.22)</td>
<td>.85 (1.16)†</td>
<td>19.2 (51.47)</td>
<td>1.7 (2.99)</td>
<td></td>
</tr>
<tr>
<td>Total amount of morphine for NAS (mg): Neonates treated for NAS</td>
<td>3.5 (2.64) [n=4]</td>
<td>2.7 (1.68) [n=3]</td>
<td>2.0 (2.00) [n=5]</td>
<td>21.6 (26.64) [n=31]</td>
<td>1.9 (.99) [n=5]</td>
<td>33.7 (64.82) [n=41]</td>
<td>3.5 (3.54) [n=27]</td>
<td></td>
</tr>
<tr>
<td>Days Treated for NAS: All neonates</td>
<td>5.2 (8.51)</td>
<td>2.7 (3.06)</td>
<td>3.0 (3.30)</td>
<td>13.0 (19.51)</td>
<td>3.81 (6.89)</td>
<td>12.3 (17.23)</td>
<td>4.6 (6.22)</td>
<td></td>
</tr>
<tr>
<td>Days Treated for NAS: Neonates treated for NAS</td>
<td>13.0 (9.06) [n=4]</td>
<td>5.3 (1.53) [n=3]</td>
<td>4.8 (2.87) [n=5]</td>
<td>21.3 (21.22) [n=31]</td>
<td>6.6 (8.07) [n=16]</td>
<td>21.7 (17.89) [n=41]</td>
<td>9.8 (5.33) [n=27]</td>
<td></td>
</tr>
<tr>
<td>Days of infant hospital stay: All neonates</td>
<td>10.1 (9.84)</td>
<td>15.7 (11.02)</td>
<td>8.4 (4.85)</td>
<td>29.4 (19.74)</td>
<td>13.9 (17.33)</td>
<td>8.3 (2.65)</td>
<td>8.3 (2.57)</td>
<td>18.3 (11.2)</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>32.8 (1.24)</td>
<td>32.9 (1.72)</td>
<td>33.6 (1.75)</td>
<td>34.5 (2.20) [n=7]</td>
<td>33.2 (1.98)</td>
<td>33.0 (2.12)</td>
<td>31.8 (2.11)</td>
<td>31.2 (1.71)</td>
</tr>
<tr>
<td>Birthweight (gm)</td>
<td>2816.1 (368.2)</td>
<td>2886.7 (570.51)</td>
<td>2922.9 (786.96)</td>
<td>3151.1 (541.64)</td>
<td>2973.9 (502.6)</td>
<td>3376.3 (455.7) [n=27]</td>
<td>2800.0 (546.07)</td>
<td>3096.9 (961.2)</td>
</tr>
<tr>
<td>Infant length (cm)</td>
<td>46.3 (2.15)</td>
<td>48.3 (3.30)</td>
<td>30.2 (2.26)</td>
<td>49.6 (2.73)</td>
<td>51.7 (3.20) [n=7]</td>
<td>47.8 (4.62)</td>
<td>49.8 (2.75)</td>
<td>48.2 (2.87)</td>
</tr>
<tr>
<td>Pre-term (&lt;37 weeks) birth [Yes]</td>
<td>2 (20%)</td>
<td>3 (50%)</td>
<td>2 (25%)</td>
<td>1 (9.1%)</td>
<td>14 (19%)</td>
<td>4 (7%)</td>
<td>10 (19.2%)</td>
<td>10 (35.7%)</td>
</tr>
<tr>
<td>Gestational age at delivery (weeks)</td>
<td>37.5 (3.49)</td>
<td>38.7 (1.36)</td>
<td>38.5 (4.71)</td>
<td>38.6 (1.93)</td>
<td>38.7 (2.05)</td>
<td>38.0 (2.29)</td>
<td>38.2 (2.3)</td>
<td>37.3 (2.3)</td>
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<tr>
<td>Apgar score at 1 minute</td>
<td>8.0 (2.49)</td>
<td>7.7 (1.36)</td>
<td>7.8 (1.11)</td>
<td>9.0 (0)</td>
<td>8.6 (6.93)</td>
<td>8.1 (1.57)</td>
<td>8.1 (1.55)</td>
<td>7.9 (1.8)</td>
</tr>
<tr>
<td>Apgar score at 5 minutes</td>
<td>8.6 (1.26)</td>
<td>8.7 (7.75)</td>
<td>8.8 (4.46)</td>
<td>10.0 (0)</td>
<td>9.4 (1.0)</td>
<td>8.9 (0.30)</td>
<td>8.7 (4.87)</td>
<td>8.9 (0.99)</td>
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<tr>
<td>MATERNAL:</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean section [Yes]</td>
<td>1 (11%)</td>
<td>0†</td>
<td>2 (25%)</td>
<td>17 (33%)</td>
<td>9 (35%)</td>
<td>1 (9.1%)</td>
<td>0</td>
<td>27 (37.0%)</td>
</tr>
<tr>
<td>Days of maternal hospital stay</td>
<td>4.1 (4.54)</td>
<td>2.2 (6.0)</td>
<td>2.2 (6.3)</td>
<td>6.6 (6.96)</td>
<td>6.6 (5.67)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal weight gain (kg)</td>
<td>7.8 (3.89)</td>
<td>8.7 (7.83)</td>
<td>8.8 (6.33)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Non-normal presentation [Yes]</td>
<td>2 (20%)</td>
<td>0</td>
<td>0</td>
<td>10 (14.1%)</td>
<td>3 (5.2%)</td>
<td></td>
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<tr>
<td>Anesthesia during delivery [Yes]</td>
<td>6 (60%)</td>
<td>7 (63.6%)</td>
<td>7 (77.8%)</td>
<td>60 (82.2%)</td>
<td>49 (64.5%)</td>
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<tr>
<td>Drug screen at delivery [Positive]</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11 (15.3%)</td>
<td>5 (8.8%)</td>
<td>12 (23.1)</td>
<td>16 (57.1%)</td>
<td></td>
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<tr>
<td>Medical complications at delivery [Yes]</td>
<td>0 [n=5]</td>
<td>0</td>
<td>0</td>
<td>37 (51%)</td>
<td>18 (31%)</td>
<td></td>
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<tr>
<td>Number of prenatal obstetrical visits</td>
<td>9.0 (6.38)</td>
<td>8.7 (3.57)</td>
<td>8.8 (3.05)</td>
<td></td>
<td></td>
<td></td>
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<td>Sample contrast</td>
<td>1</td>
<td>x</td>
<td>x</td>
<td>0</td>
<td>-¼</td>
<td>0</td>
<td>-¼</td>
<td>0</td>
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</tbody>
</table>
Notes

Values are frequencies (percentages) or means (standard deviations). Standard deviations for the Czerkes et al. (2010) means were not reported in their article. We thank Dr. Czerkes for his kindness in providing this information. The subsample means and standard deviations for Czerkes et al. reported their birth weights in kilograms. The means and their respective standard deviations reported in this table have been transformed to grams to allow for comparison among the groups. The subsample means (standard deviations) for total amount of morphine required to treat NAS, birth weight, estimated gestational age at delivery, 1- and 5-minute Apgar scores, and maternal weight gain for Fischer et al. (2006) were not reported in their article. We thank Drs. Fischer and Jagsch for their kindness in providing this information. We thank Dr. Metz for providing the means and standard deviations for Apgar scores at 1 and 5 minutes as for Metz et al (2011).

As noted in Table 2 of Jones et al. (2005), twin data from the set of buprenorphine-exposed neonates whose mother was part of the trial were removed from the analyses of: gestational age at delivery, birth weight, head circumference, and length, reducing the sample to n=7 in the buprenorphine group for these four variables. These same data were omitted from the respective analyses in the present study, given findings that suggest that these four variables are altered by twin status. The means (standard deviations) for the Jones et al. (2005) and Jones et al. (2010) studies do not agree with the values in Table 2 of their respective articles, because model-derived means (standard errors) are reported in Table 2 of the respective tables, while simple means and standard deviations are reported in the present table. The means (standard deviations) for the total amount of morphine drops for Jones et al. (2005) are based on the 2 and 5 neonates, respectively, who were treated for NAS. The sample contrast in the last row of the table illustrates the coefficients that would used for the outcome variable total amount of morphine for NAS in order to compare the mean of the buprenorphine+naloxone group to the pooled means of the Fisher et al. (2006), Jones et al. (2005), and Jones et al. (2010) buprenorphine comparison samples.

*There are two rows for the variable “total amount of morphine” because Fischer et al. (2006) reported their data only for the neonates treated for NAS in total amount of morphine in mg, Jones et al. (2005) reported their data only for neonates treated for NAS in “Total number of morphine drops administered”, while Jones et al. (2010) reported their data for all infants (including those neonates not treated with values of zero) in total amount of morphine in mg. The mean and standard deviation provided by Fischer (2006) were used to calculate the mean and standard deviation for total amount of morphine for the total sample of 6 and 8 neonates, respectively. The mean and standard deviation provided by Fischer (2006) were used to calculate the mean and standard deviation for total amount of morphine for the total sample of 11 and 9 neonates, respectively (see next footnote).

‡The total number of drops of medication in Jones et al. (2005) was transformed into mg based on the fact that the drops were “equivalent to morphine 0.02mg/drop”.

€Day of hospital stay is not included for Fischer et al. (2006) since there was an obligatory 10 day stay in inpatient treatment independent of symptoms of NAS.

§Vacuum extraction due to “prolonged delivery”.

*Both were planned cesarean sections.

*Article says anesthesia.
Table 2. Results for Tests of Significance for Planned Contrasts

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Planned Contrast</th>
<th>Test Statistic</th>
<th>( p )</th>
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<tbody>
<tr>
<td><strong>NEONATAL:</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Treated for NAS</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>( \chi^2(1) = .03 )</td>
<td>.86</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine+naloxone v. Methadone</td>
<td>( \chi^2(1) = 1.36 )</td>
<td>.24</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine+naloxone v. 7-day methadone-assisted withdrawal</td>
<td>( \chi^2(1) = .06 )</td>
<td>.81</td>
</tr>
<tr>
<td>Total amount of Morphine for NAS: All neonates*</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>( F(1, 168) = .00 )</td>
<td>.99</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine+naloxone v. Methadone</td>
<td>( F(1, 168) = .20 )</td>
<td>.66</td>
</tr>
<tr>
<td>Total amount of Morphine for NAS: Neonates treated for NAS*</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>( F(1, 80) = .00 )</td>
<td>.95</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine+naloxone v. Methadone</td>
<td>( F(1, 80) = .13 )</td>
<td>.72</td>
</tr>
<tr>
<td>Days treated for NAS: All neonates‡</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>( F(1, 150) = .09 )</td>
<td>.77</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine+naloxone v. Methadone</td>
<td>( F(1, 150) = .22 )</td>
<td>.64</td>
</tr>
<tr>
<td>Days treated for NAS: Neonates treated for NAS‡</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>( F(1, 119) = .52 )</td>
<td>.47</td>
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<td>Buprenorphine+naloxone v. Methadone</td>
<td>( F(1, 119) = .14 )</td>
<td>.71</td>
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<tr>
<td>Days of infant hospital stay</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>( F(1, 476) = .02 )</td>
<td>.90</td>
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<tr>
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<td>Buprenorphine+naloxone v. Methadone</td>
<td>( F(1, 476) = 3.46 )</td>
<td>.06</td>
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<tr>
<td></td>
<td>Buprenorphine+naloxone v. 7-day methadone-assisted withdrawal</td>
<td>( F(1, 476) = .07 )</td>
<td>.80</td>
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<tr>
<td>Head circumference</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>( F(1, 307) = 3.10 )</td>
<td>.08</td>
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<tr>
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<td>Buprenorphine+naloxone v. Methadone</td>
<td>( F(1, 307) = .13 )</td>
<td>.72</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine+naloxone v. 7-day methadone-assisted withdrawal</td>
<td>( F(1, 307) = 5.24 )</td>
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<td>Birthweight</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>( F(1, 486) = 2.99 )</td>
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<tr>
<td></td>
<td>Buprenorphine+naloxone v. Methadone</td>
<td>( F(1, 486) = .03 )</td>
<td>.87</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine+naloxone v. 7-day methadone-assisted withdrawal</td>
<td>( F(1, 486) = .00 )</td>
<td>.97</td>
</tr>
<tr>
<td>Length</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>( F(1, 307) = 12.74 )</td>
<td>&lt;.001</td>
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<tr>
<td></td>
<td>Buprenorphine+naloxone v. Methadone</td>
<td>( F(1, 307) = 3.84 )</td>
<td>.051</td>
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<td>Buprenorphine+naloxone v. 7-day methadone-assisted withdrawal</td>
<td>( F(1, 307) = .90 )</td>
<td>.33</td>
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<tr>
<td>Pre-term birth</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>( \chi^2(1) = .89 )</td>
<td>.34</td>
</tr>
<tr>
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<td>Buprenorphine+naloxone v. Methadone</td>
<td>( \chi^2(1) = .01 )</td>
<td>.91</td>
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<tr>
<td>Outcome measure</td>
<td>Planned Contrast</td>
<td>Test Statistic</td>
<td>p</td>
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<tr>
<td>Gestational age at delivery</td>
<td>Buprenorphine+naloxone v. 7-day methadone-assisted withdrawal</td>
<td>$\chi^2(1)=.60$</td>
<td>.44</td>
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<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>$F(1, 486)=2.72$</td>
<td>.10</td>
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<td>Buprenorphine+naloxone v. Methadone</td>
<td>$F(1, 486)=.83$</td>
<td>.36</td>
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<td>Buprenorphine+naloxone v. 7-day methadone-assisted withdrawal</td>
<td>$F(1, 486)=.04$</td>
<td>.84</td>
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<tr>
<td>Apgar 1 minute</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>$F(1, 488)=.72$</td>
<td>.40</td>
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<td>Buprenorphine+naloxone v. Methadone</td>
<td>$F(1, 488)=.52$</td>
<td>.47</td>
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<td>Buprenorphine+naloxone v. 7-day methadone-assisted withdrawal</td>
<td>$F(1, 488)=.04$</td>
<td>.84</td>
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<tr>
<td>Apgar 5 minutes</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>$F(1, 499)=4.88$</td>
<td>.03</td>
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<td>Buprenorphine+naloxone v. Methadone</td>
<td>$F(1, 499)=3.61$</td>
<td>.06</td>
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<td>Buprenorphine+naloxone v. 7-day methadone-assisted withdrawal</td>
<td>$F(1, 499)=.09$</td>
<td>.77</td>
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<tr>
<td><strong>MATERNAL:</strong></td>
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<tr>
<td>Cesarean section</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>$\chi^2(1)=.24$</td>
<td>.62</td>
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<td>Buprenorphine+naloxone v. Methadone</td>
<td>$\chi^2(1)=.16$</td>
<td>.69</td>
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<tr>
<td>Days of maternal hospital stay</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>$F(1, 156)=.02$</td>
<td>.89</td>
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<td>Buprenorphine+naloxone v. Methadone</td>
<td>$F(1, 156)=.02$</td>
<td>.89</td>
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<tr>
<td>Maternal weight gain</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>$F(1, 138)=.18$</td>
<td>.68</td>
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<td>Buprenorphine+naloxone v. Methadone</td>
<td>$F(1, 138)=.14$</td>
<td>.70</td>
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<tr>
<td>Non-normal presentation</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>$\chi^2(1)=2.16$</td>
<td>.14</td>
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<td>Buprenorphine+naloxone v. Methadone</td>
<td>$\chi^2(1)=1.33$</td>
<td>.25</td>
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<td>Analgesia during delivery</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>$\chi^2(1)=1.87$</td>
<td>.17</td>
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<td>Buprenorphine+naloxone v. Methadone</td>
<td>$\chi^2(1)=.76$</td>
<td>.38</td>
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<tr>
<td>Drug screen at delivery</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>$\chi^2(1)=.02$</td>
<td>.90</td>
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<tr>
<td></td>
<td>Buprenorphine+naloxone v. Methadone</td>
<td>$\chi^2(1)=.39$</td>
<td>.53</td>
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<td>Buprenorphine+naloxone v. 7-day methadone-assisted withdrawal</td>
<td>$\chi^2(1)=3.8$</td>
<td>.051</td>
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<td>Medical complications at delivery</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>$\chi^2(1)=.09$</td>
<td>.77</td>
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<td></td>
<td>Buprenorphine+naloxone v. Methadone</td>
<td>$\chi^2(1)=.22$</td>
<td>.64</td>
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<tr>
<td>Number of prenatal obstetrical visits</td>
<td>Buprenorphine+naloxone v. Buprenorphine</td>
<td>$F(1, 138)=.03$</td>
<td>.87</td>
</tr>
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<td>Buprenorphine+naloxone v. Methadone</td>
<td>$F(1, 138)=.06$</td>
<td>.81</td>
</tr>
</tbody>
</table>

Notes. *, ‡ See Table 1 for an explanation for why there are two outcome measures for total amount of morphine for NAS and days treated for NAS.