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Neonatal outcomes following in utero exposure to methadone or buprenorphine: A National Cohort Study of opioid-agonist treatment of Pregnant Women in Norway from 1996 to 2009☆

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ABSTRACT

Background: In Norway, most opioid-dependent women are in opioid maintenance treatment (OMT) with either methadone or buprenorphine throughout pregnancy. The inclusion criteria for both medications are the same and both medications are provided by the same health professionals in any part of the country. International studies comparing methadone and buprenorphine in pregnancy have shown differing neonatal outcomes for the two medications.
Method: This study compared the neonatal outcomes following prenatal exposure to either methadone or buprenorphine in a national clinical cohort of 139 women/neonates from 1996 to 2009.
Results: After adjusting for relevant covariates, buprenorphine-exposed newborns had larger head circumferences and tended to be heavier and longer than methadone-exposed newborns. The incidence of neonatal abstinence syndrome (NAS) and length of treatment of NAS did not differ between methadone- and buprenorphine-exposed newborns. There was little use of illegal drugs and benzodiazepines during the pregnancies. However, the use of any drugs or benzodiazepines during pregnancy was associated with longer lasting NAS-treatment of the neonates.
Conclusions: The clinical relevance of these findings is that both methadone and buprenorphine are acceptable medications for the use in pregnancy, in line with previous studies. If starting OMT in pregnancy, buprenorphine should be considered as the drug of choice, due to more favorable neonatal growth parameters. Early confirmation of the pregnancy and systematic follow-up throughout the pregnancy are of importance to encourage the women in OMT to abstain from the use of tobacco, alcohol, illegal drugs or misuse of prescribed drugs.

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1. Introduction

Opioid maintenance treatment (OMT) involves long-term prescription of opioid-agonist medication, as well as the provision of a variety of psychosocial supportive measures. Methadone is a full μ-opioid agonist and has been prescribed to opioid-dependent pregnant women for many years (Kandall et al., 1977; Newman et al., 1975). Methadone maintenance treatment (MMT), given in a multidisciplinary setting, has become the international standard of care for opioid-dependent pregnant women (Fischer et al., 1998a; Jansson et al., 2007; Jones et al., 2008; Kaltenbach et al., 1998; WHO, 2009; Winklbaur et al., 2008). MMT in pregnancy is associated with better prenatal care, higher birth weights, longer gestational ages and fewer complications for the infants than if the woman were using heroin during her pregnancy (Doberczak et al., 1987; Finnegan et al., 1977; Hulse et al., 1997).

In contrast, buprenorphine is a partial μ-opioid agonist and κ-antagonist and has been prescribed to pregnant women since the nineties (Fischer et al., 1998b, 2000; Johnson et al., 2001; Kahila et al., 2007). Generally, studies of buprenorphine maintenance treatment (BMT) in pregnancy have shown similar maternal, birth and neonatal outcomes as MMT (Johnson et al., 2003; Jones et al., 2008).

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Both medications have been associated with a neonatal abstinence syndrome (NAS) following prenatal exposure, e.g. (Fischer et al., 2006; Johnson et al., 2003; Jones et al., 2005; Lejeune et al., 2006). NAS is observed in 40–90% of neonates prenatally exposed to methadone or buprenorphine, and is characterized by symptoms of hyperirritability of the central-nervous, the gastrointestinal, the respiratory and the autonomic nervous systems (Finnegan et al., 1975; Fischer et al., 1998b). In a recent review of the relationship between the maternal dose of methadone and NAS in 67 studies, Cleary concludes that the severity of NAS does not appear to differ whether the woman is on low or high dose of methadone at delivery (Cleary et al., 2010). The use of illicit drugs in addition to MMT is associated with a greater likelihood of needing NAS-treatment (Jansson et al., 2012) and a longer duration of treatment for NAS (Seligman et al., 2008) than for the use of methadone alone.

Prospective clinical studies comparing MMT and BMT during pregnancy have shown differing neonatal outcomes in neonates prenatally exposed to either medication. A French multicenter study did not report any significant differences in either NAS parameters or neonatal growth (Lejeune et al., 2006). In contrast, a Swedish study found that BMT during pregnancy was significantly related to a lower incidence of NAS and higher average birth weights (Kakko et al., 2008) than MMT. Another French multicenter study found similar NAS results as did Kakko in 2008 (Lacroix et al., 2011). In all three studies, MMT was provided from specialized clinics and BMT was provided mainly by general practitioners. Results of randomized clinical trials (RTCs) indicate that BMT yields a milder abstinence syndrome for the neonate than does MMT (Fischer et al., 2006; Jones et al., 2005, 2010). The MOTHER study (Jones et al., 2010), an international multi-center RCT, found no significant difference in the incidence of NAS, but in the prenatally buprenorphine-exposed condition, the duration of NAS-treatment was shorter.

Opioid withdrawal in pregnancy is associated with increased risks of abortion, preterm birth and use of illegal drugs (Luty et al., 2003; McCarthy, 2012). Transferring a methadone maintained pregnant woman to buprenorphine also puts the fetus at risk through withdrawal (Jones et al., 2006; McCarthy, 2012). OMT is important in pregnancy, despite the possible effects of methadone or buprenorphine, to stabilize the woman and improve the neonatal outcomes compared to the untreated condition or opioid withdrawal in pregnancy.

The aim of the present study was to compare the neonatal outcomes following prenatal exposure to either methadone or buprenorphine. The design was a national clinical cohort study in which pregnant women were prescribed either methadone or buprenorphine. We wanted to ensure that the women in MMT and BMT were comparable: firstly, MMT and BMT were given according to the same national inclusion criteria; secondly, both medications were provided by the same health professionals in any part of the country; thirdly, only the first child of the women in OMT was included in the study; and lastly, we wanted to control for relevant covariates. We hypothesized that buprenorphine-exposed newborns would have higher birth weights, larger head circumferences, lower incidence of NAS needing medication, and shorter length of treatment for NAS than methadone-exposed neonates.

2. Methods

This study included a national cohort of pregnant women in opioid maintenance treatment (OMT) in Norway from 1996 to 2009.

Table 1
Overview of the number of children in Norway prenatally exposed to methadone or buprenorphine 1996–2009. $n = 139$.

	Methadone	Buprenorphine	Total
Before 1.1.2004, retrospective (first part)	38	13	51
After 1.1.2004	52	36	88
Prospective (second part)	24	12	36
Retrospective (third part)	28	24	52
TOTAL	90	49	139

Note: Only a single child, the first born of mothers in OMT during the period 1996–2009, was included in the study.

2.1. Norwegian OMT

From its beginning in 1991 through the conclusion of this study in 2009, the Norwegian OMT program had strict inclusion criteria, with a high threshold for qualification, and rigorous levels of control, including regular urinary drug screening. The inclusion criteria were: age above 25 years, at least five years of opioid dependence, and that the patient had previously tried non-medication drug abstinence-oriented treatment. OMT patients must be accepted by regional centers throughout Norway. Follow-up was coordinated by a multidisciplinary team for each patient, including specialized health care services for substance use patients, general practitioners providing general medical follow-up and MMT/BMT after initial stabilization, and social services agencies providing the psychosocial follow-up.

Buprenorphine was introduced in 2000 and, since that time, both methadone and buprenorphine have been prescribed according to the same national inclusion criteria and a treatment guideline for use of MMT in pregnancy (Welle-Strand and Waal, 2001). Since 2005, buprenorphine has been the first line drug for OMT-patients. The lowest efficient dose of methadone was recommended throughout pregnancy, with split-dosing of the medication if necessary towards the end of pregnancy. If the split-dosing was insufficient to alleviate abstinence, a dose increase was recommended. In the case of BMT, buprenorphine without naloxone was recommended for pregnant women because there was no need to expose the fetus to naloxone.

2.2. Participants

We recruited the participants for the study through the regional centers for OMT and, for the second part of the study, also through OMT users' organizations. Our study included 139 women who gave birth to 161 children. We chose to include only the first child the women delivered during her OMT in our analyses, in order to avoid dependence in the data created by the inclusion of siblings. Thus, our analyses included a total of 139 children (Table 1). Ninety of the children (65%) were exposed to methadone and 49 of the children (35%) were exposed to buprenorphine prenatally.

The study was conducted in three parts. The first part took place from 1996 to 2003 ($n = 51$), the second part took place from 2005 to 2007 ($n = 36$), and the third part lasted from 2004 to 2009 ($n = 52$). A crude estimate, based on data from the Norwegian Medical Birth Registry and the Norwegian Centre for Addiction Research (Seraf), is that 210 women in Norway had their first child while in OMT from 1996 to 2009. Hence, our study sample comprises approximately 65% of the estimated number of children born to women in OMT during the study period. The children were born at 18 different hospitals.

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