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Peripartum pain management in opioid dependent women

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Abstract

Increased pain sensitivity and the development of opioid tolerance complicate the treatment of pain experienced by opioid maintained pregnant women during delivery and the perinatal period. The aim of the present study was to investigate differences in pain management of opioid maintained compared to non-dependent pregnant women during delivery and the postpartum period. 40 deliveries of 37 opioid dependent women enrolled in a double-blind, double-dummy randomized controlled trial (RCT) examining the safety and efficacy of methadone (mean dose at the time of delivery = 63.89 mg) and buprenorphine (mean dose at the time of delivery = 14.05 mg) during pregnancy were analyzed and participants were matched to a non-dependent comparison group of 80 pregnant women. Differences in pain management (opioid and non-opioid analgesic medication) during delivery and perinatal period were analyzed. Following cesarean delivery opioid maintained women received significantly less opioid analgesics (day of delivery $p = 0.038$; day 1: $p = 0.02$), NSAIDs were administered more frequently to opioid dependent patients than to the comparison group during cesarean section and on the third day postpartum. Significantly higher nicotine consumption in the group of opioid dependent women had a strong influence on the retrieved results, and might be considered as an independent factor of altered pain experience. Differences in pain treatment became evident when comparing opioid maintained women to healthy controls. These differences might be based on psychosocial consequences of opioid addiction along with the lack of an interdisciplinary consensus on pain treatment protocols for opioid dependent patients.

Keywords

pain; opioid dependence; pregnancy; NSAIDs; methadone; buprenorphine

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Introduction

Opioid dependence during pregnancy is a major public health problem with up to 30.000 pregnant women in Europe using opioids each year (EMCDDA, 2010). Exact numbers are difficult to obtain, as drug use remains often underreported (Ostrea et al., 1992; Frank et al., 1988; Lester et al., 2001); however in a large US-study using meconium-analysis for cocaine and opioids in over 8000 newborns, 2.3% were tested opioid-positive (Lester et al., 2001).

The standard therapy of opioid dependent women during pregnancy consists of pharmacological treatment with synthetic opioids and psychosocial support in order to stabilize the patient and avoid relapse to illicit substance abuse (Winklbaur et al., 2008). There is strong scientific evidence that the treatment with methadone improves maternal health and life circumstances as well as fetal/neonatal morbidity and mortality (Burns et al., 2007; Jones et al., 2010; Kaltenbach et al., 1998; Kandall et al., 1999; McCarthy et al., 2008). The implementation of buprenorphine for the treatment of opioid addiction has broadened the therapeutic possibilities as this therapeutic agent has been shown to exert efficacy and safety comparable to methadone, with scientific data even indicating that the partial μ -receptor agonist is favourable with regard to the prevalence of the neonatal abstinence syndrome (NAS) of the newborn, which seems to be attenuated (Fischer et al., 2006; Johnson et al., 2003; Jones et al., 2005; Jones et al., 2010; Lejeune et al., 2006; Unger et al., 2010a).

Patients who consume opioids over longer periods, prescribed or illicitly, experience altered pain sensitivity in terms of opioid-tolerance and chronic hyperalgesia (Compton et al., 2001; Mao, 2002; Mao et al., 1995; Mayer et al., 1995). Increased pain sensitivity to experimental pain stimuli such as cold pressor pain has been observed in opioid dependent individuals (Compton et al., 2001; Doherty et al., 2001). Moreover, opioid dependent patients in methadone maintenance therapy seem to be more sensitive to pain than those opioid dependent patients maintained on buprenorphine (Compton et al., 2001). This experimental data is reflected by clinical investigations examining differences in pain management between opioid-dependent and non-opioid dependent pregnant women thus revealing higher pain scores and higher requirement of analgesics in the opioid dependent group in the postpartum period (Meyer et al., 2010; Meyer et al., 2007). The analysis of the influence of the applied maintenance drug on postpartum pain revealed adequate pain control both in buprenorphine and methadone maintained women with standard treatment options, with drug-specific differences in the time course of the reduction of NSAIDs in the immediate postpartum period (Jones et al., 2006; 2009). The pain-altering effect of nicotine consumption additionally contributes to the difficulties around pain management, as over 90% of opioid dependent women are highly addicted to nicotine (Creekmore et al., 2004; Hooten et al., 2009; Marco et al., 2005; Winklbaur et al., 2009; Woodside, 2000).

The described biological alterations as well as psychosocial consequences of opioid addiction contribute to the fact that anaesthetic service for opioid dependent patients is often referred to as challenging (Alford et al., 2006; Doherty et al., 2001; Kuczkowski, 2003; Ludlow et al., 2007). Based on these considerations and due to the lack of standardized treatment recommendations the objective of this study was to investigate differences in pain treatment in opioid dependent and non-opioid dependent pregnant women during delivery and in the immediate postpartum period. It was hypothesized that pregnant women maintained on either methadone or buprenorphine would require greater doses of opioid and non-opioid analgesics in the peripartum period compared to a non-opioid dependent comparison group.

Methods

Participants

40 pregnancies of 37 opioid dependent women who had participated in the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study, a multisite, double-blind, double-dummy, randomised controlled trial comparing the efficacy and safety of methadone and buprenorphine during pregnancy were matched to a comparison group (Jones et al., 2010). Three participants who were included in the present analysis had a second child as part of the study, but were excluded from the main MOTHER trial. Each of these participants was randomized to the respective opposite medication they had received during the first pregnancy, without revealing the blinded study medication from the first pregnancy. All opioid dependent women included in the present study were treated at the addiction clinic of the Medical University of Vienna which was one of 7 contributing sites (37 participants completed the study at the Vienna site, 94 at the other study sites) (Unger et al., 2010b). This retrospective investigation used data collected as part of the MOTHER trial, focusing on concomitant analgesic medication administered during and after delivery.

Comparison group

80 non-opioid dependent pregnant women who delivered at the University Clinic of Gynaecology of the Medical University of Vienna in the same time period were included as a comparison group in the present study. Each patient of the cohort-group was matched to two control patients following specific matching criteria: same age (within 5 years), mode of delivery (caesarean section/vaginal) and single fetus pregnancy, one control patient delivering immediately before the opioid dependent patient and one delivering immediately after. The buildup of the comparison group was performed according to a database containing essential delivery-related data on each patient (age, delivery mode, presence of psychiatric or physical disorders of mother or child, etc.).

Design

After enrolment to the MOTHER study, patients were randomised to one of two treatment groups (buprenorphine / methadone). Levels of the double-blind, double-dummy medication were adjusted as required with a maximum level of 32 mg buprenorphine/140 mg methadone, respectively, following a flexible dosing scheme. Randomization procedures were conducted at the Center for Substance Abuse Research (CESAR) at the University of Maryland, USA. From randomization until the time of delivery, participants were eligible to receive monetary vouchers based on drug negative urine results for opiates (excluding methadone and buprenorphine), cocaine, amphetamines and benzodiazepines. All women were admitted to the Medical University hospital of Vienna, Department of Gynecology for birth at onset of labor, or at the latest on the scheduled day of birth (Jones et al., 2010). All concomitant medication administered during the course of delivery and for the first three days after was recorded.

Pain management

The whole treatment team was blinded to the type of opioid agonist medication the women of the study group were maintained on. The peri- and postpartum pain treatment was performed following the usual anaesthetic treatment regime of the Medical University of Vienna as described below:

Vaginal birth—Peridural anaesthesia (=PDA) was performed between 3 to 8 cm of cervical dilatation only, upon the request of the parturient using an initial bupivacain bolus (0.125%), followed by an infusion of 10 ml bupivacain/h (0.1%). At the discretion of the

anaesthesiologist additional fentanyl was administered in the epidural space as needed. Furthermore there is the possibility of the intravenous application of 5–10 mg of an opioid-analgesic, usually nalbuphine, as well as the infusion of NSAIDs (e.g. acetaminophen) intravenously.

Caesarean section—Caesarean sections were performed under spinal anaesthesia using 0,5% bupivacain with or without supplementary fentanyl. In addition to the spinal anaesthetics patients received intravenous analgesics: NSAIDs (diclofenac, metamizol), benzodiazepines (diazepam) and opioid analgesics (tramadol, piritramid).

Postpartum pain management

In the postpartum period the first three days after delivery were analysed with respect to the administered opioid and non-opioid analgesics. The most commonly used analgesics were the NSAIDs acetaminophen and diclofenac, either orally or intravenously applied. In case of oral application the dosage was calculated on the basis of the oral bioavailability (diclofenac: 30–80%; acetaminophen 67–89%) to gain comparability to intravenously applied drugs. The standard dosages for the NSAIDs were 75 mg for diclofenac and 1000 mg for acetaminophen. Opioids were applied as tramadol drops whereas one tramadol drop equates to 2.5 mg tramadol hydrochloride. Apart from the analgesics for the treatment of acute pain the maintenance therapy was retained unchanged in the cohort group. The performance of objective pain ratings such as the visual analogue scale (VAS) is not part of the clinical routine at the Department of Gynecology of the Medical University of Vienna. The independent, self-contained decision of the patient about the necessity of pain medication is respected under consideration of the World Health Organization analgesic scheme and maximum dosages for each applied drug (WHO, 1990). The maximum frequency of the administration of the most frequently applied NSAIDs acetaminophen and ibuprofen is 2–3 times per day. Standard dosages for acetaminophen are either 1000 mg intravenously or 500 mg per os; this results in a maximum dosage of 3000 mg acetaminophen intravenously and 1500 mg orally. For ibuprofen standard dosages are 75 mg i.v. and per os resulting in a maximum dosage of 225 mg per day. For tramadol drops maximum frequency is three times per day and maximum dosage is 90 mg of tramadol hydrochloride.

Statistics

Statistical analysis was performed using SPSS 15.0 for Windows. Continuous data were displayed using mean, standard deviation and range (minimum, maximum), for proportions of categorical data relative frequencies were used. Comparisons of means between two groups (maintenance therapy vs. comparison group and vaginal delivery vs. Caesarean section) were performed parametrically using the *t*-test for independent samples or *Chi*²-tests. As it became evident that a significant difference in the incidence of smoking exists between the two investigated groups, smoking status and pain medication were included in a binary logistic model to specifically examine the influence on significant results in a second step. All comparisons were two-tailed with the level of significance set on $p < 0.05$.

Results

The first matching-step using the described database resulted in the screening for eligibility in 80 comparison patients. However in six primarily included comparison patients the analysis of all available data led to the exclusion, due to either unavailability of relevant information or the presence of birth complications necessitating the exclusion of the patient. These six patients were substituted by the next patient corresponding to all matching criteria

and delivering immediately before or after the index patient, respectively. Thus a total of 86 patients were screened to generate the analyzed comparison group.

Demographics are presented in Table 1 and 2. The demographic data of the opioid maintenance therapy (OMT) group (n = 40) and the non-dependent comparison group (n = 80) showed no significant differences except for a significantly higher prevalence of smokers in the group of OMT patients. Furthermore, the analysis of the incidence of delivery-related lesions in terms of perianal laceration, retrieved no significant difference between the two groups (OMT group: 11/21 (52.4%), comparison group (27/42 (64.3%); $p=0.363$).

The maintenance medication of the OMT patients is presented in Table 3. The subanalysis evaluating differences between the two possible treatment arms (methadone/buprenorphine) within the cohort of OMT patients retrieved no significant differences in terms of pain management during delivery and the first three days postpartum (results not displayed). Frequencies are displayed in mean and standard deviations.

Vaginal delivery

During delivery OMT patients required PDA more often than women of the comparison group (OMT group 8/21 (38.1%); comparison group 6/42 (14.3%); $p = 0.048$. When including smoking status into the model significance was diminished to a trend ($p = 0.08$). In the first three days there were no differences regarding pain management between the two groups (Tab 4 and 6). The cumulative mean dosages of the applied analgesics were as follows: diclofenac: OMT group: 46.25 ± 22.53 (25–100 mg); comparison group 59.5 ± 49.9 (25–150 mg); acetaminophen: OMT group: 748.25 ± 420.17 (385–1000 mg); comparison group: 673.5 ± 447.76 (385–2000 mg). Only one patient of the comparison group received opioid analgesics in the form of tramadol drops on postpartum days 1 and 3 at a dosage of 63 mg.

Caesarean section

The peripartum parameters analyzed were the analgesics directly applied into the spinal space and the intravenously applied analgesic drugs. There were no differences regarding spinal anaesthesia. The first-step analysis of the analgesics applied intravenously during caesarean section though showed a significantly higher frequency of NSAID use in the OMT group, namely of diclofenac (OMT group: 8/19 (42.1%); comparison group: 4/38 (10.5%); $p = 0.006$) and of metamizol (OMT group: 3/19 (15.8%), comparison group 0/38; $p = 0.012$). Other intravenously applied drugs, namely acetaminophen (OMT group: 13/19 (68.4%); comparison group: 24/38 (63.2%)), metamizol (OMT group: 3/19 (15.8%); comparison group: 0/38), midazolam (OMT group: 3/19 (15.8%); comparison group: 9/38 (23.7%)) and piritramid (OMT group: 6/19 (31.6%), comparison group: 7/38 (18.4%)) showed no significant difference both in the frequency of application and in the dosage.

In regard to the use of NSAIDs in the postpartum period there were no differences on the first two postpartum days, but a higher proportion of opioid dependent patients received the NSAID on postpartum day 3 (OMT group: 10/19 (52.6%), comparison group: 9/38 (23.7%); $p = 0.029$) However, when including smoking status into the model significant differences in the frequency of NSAID application were forfeited ($p > 0.05$) (Tab. 5). The cumulative mean dosages for the NSAIDs over the first 3 postpartum days were as follows: diclofenac: OMT group: 106.59 ± 44.76 (25–225 mg); comparison group: 107.03 ± 47.89 (25–300 mg); acetaminophen: OMT group: 1114.45 ± 657.58 (385–3000 mg), comparison group: 1060.43 ± 552.96 .

The postpartum anaesthetic management differed between the two groups with regard to the frequency of opioid use. The administration of opioid analgesics varied strongly between the groups, with the comparison group receiving opioids significantly more often in the immediate postpartum period (Tab. 6). Opioids were applied in the form of tramadol drops (tramadol hydrochloride), the mean dosage for the opioid maintained patients was 50 ± 0 and 71.23 ± 21.05 (50–108 mg) for the comparison group. As can be seen in Tab. 4 and 5 maximum dosages for all applied drugs fell below maximum dosages.

Discussion

In the present study the comparison of pain treatment between opioid maintained women and non-dependent women revealed discrepancies in peripartum pain management, reflected by differences in the frequency of peridural anaesthesia (PDA) and differences in the frequency of application of opioid analgesics and NSAIDs in the postpartum period following cesarean section. Following cesarean section opioid maintained women received significantly less opioid analgesics (day 0: $p = 0,038$; day 1: $p = 0,020$); however, on day 3 a trend toward a significant difference in the frequency of NSAID application was revealed ($p = 0.089$).

The uniqueness of the present investigation was to evaluate pain management in a double-blind double-dummy study, ensuring a maximum of comparability between the participants and a minimum of illicit drug consumption in the group of opioid dependent women which would have potentially biased the results. Except for the study design the presented sample of opioid dependent pregnant women was comparable to participants of prior studies in this field with regard to medication doses and clinical characteristics (Birnbach, 2003; Cassidy and Cyna, 2004; Jones et al., 2009; Ludlow et al., 2007). The results illustrate several significant differences between opioid dependent women and non-dependent controls. Consistent with previous data, in the present study the OMT group required peridural anaesthesia significantly more often for vaginal deliveries. The feeling of inadequate analgesia and the desire to increase the dosage or frequency of pain medication received were the most commonly reported problems in the postoperative analgesia voiced by opioid-dependent patients of prior studies (Cassidy and Cyna, 2004).

Further results consistent with previous data refer to the postpartum pain management following vaginal delivery, no differences in analgesia were found between the opioid dependent and non-dependent patients. Similarly Meyer et al. describe no differences in the postpartum pain treatment of groups, of whom altogether 40% received opiate drugs as analgesia in the postpartum phase regardless of whether opioid dependent or non-dependent (Meyer et al., 2007). One of the strengths of this study was the close match between study and comparison group. Demographic data of the comparison group did not differ significantly from the study population except for one aspect – nicotine consumption was much higher in the OMT group. The statistical analysis revealed that this significant difference in smoking status had a strong influence on results concerning peripartum pain management. A part of primary significant results fell under the significance level when including the smoking status into the model. The connection between nicotine consumption and pain is well established, nicotine blunts pain perception; however, there is no consensus on the exact mechanism involved (Anderson et al., 2004; Creekmore et al., 2004; Hooten et al., 2009; Marco et al., 2005; Woodside, 2000). A form of cross-tolerance between morphine and nicotine has been observed, as the abrupt discontinuation of nicotine consumption due to hospitalization leads to higher requirements of pain medication in smokers (Zarrindast et al., 1999). Smokers who are deprived of nicotine show an increased pain perception as do former smokers, so that permanent neurophysiological changes induced by nicotine consumption are probable. Along with the neurophysiological changes induced by the

administration of opioids, the influence of nicotine on the intensity of pain must be taken into consideration in light of the high prevalence of nicotine dependence in this patient group (Winklbaier et al., 2009). Therefore the consideration of the smoking status in the context of pain treatment in opioid dependent should be emphasized, as the present data point toward a potential role as independent factor for altered pain experience in concordance with previous clinical studies.

Interestingly, the significant higher prevalence of smokers was not reflected by differences in the birth weight, possibly due to the specialization of the University Department of Gynecology in high-risk pregnancies. This fact is reflected by a higher incidence of cesarean sections of 49.82% at the Department of Gynecology of the Medical University of Vienna at the time patients were included in the present study compared to an incidence of 28.0% in the general population (Husslein et al, 2008; Austrian Ministry of Health, 2011).

In contrast to the present study, several previous retrospective investigations in this field could refer to pain scores collected as a part of the routine clinical management, revealing significant higher pain intensities in opioid-dependent compared to non-opioid dependent women. These results and those of other studies elucidating pathophysiological mechanisms of opioid dependence, allow for the assumption that opioid dependent women generally have a higher postoperative perception of pain (Compton et al., 2001; Mao et al., 1995; Mao et al., 2002; Mayer et al., 1995; Mehta and Langford, 2006). Therefore the question arises why in our study the amount of opioids dispensed to the opioid-dependent women was far below the amount of the comparison group. This could have several reasons. As already mentioned in the introduction, some of the common misconceptions published by Alford et al. might explain this: The fear of treating physicians concerning cognitive, respiratory and psychomotor side effects, the fear of inducing relapse to illicit substance abuse, the fear of patients reporting pain as a means to manipulate doctors, making it a “drug-seeking” behavior (Alford et al., 2006).

The analyzed data showed that medical staff might have not wanted to dispense opioids to opioid dependents instead trying to cover the higher need for analgesics with NSAIDs. Evidence for this lies in the more frequent distribution of NSAIDs to the study population for caesarean sections and the higher use of NSAIDs on the third post-section day.

In the present study maximum dosages for opioid and non-opioid analgesics were reached neither after cesarean section nor after vaginal delivery, possibly reflecting the fact that pain intensities were of medium strengths. This suggestion plays in concert with previous clinical studies including the performance of pain scores which showed median pain scores in the immediate post partum period of approximately 2.7 (Meyer et al., 2007) and 4.43 (Jones et al., 2009) after vaginal delivery and 5.0 after cesarean section (Meyer et al., 2007) in opioid dependent women despite significant higher scores compared to non-opioid dependent controls.

Limitations

Some of the limitations that deserve mentioning pertain to the design of this substudy. The retrospective nature allowed for no subjective self-report measures using pain severity scales and therefore the interpretation of the results had to rely on preclinical and clinical data previously investigating this research question. Thus the results of the present study might be seen as preliminary, which may be biased by existing local pain management strategies and therefore need corroboration in prospective studies. Furthermore, the double-blind, double-dummy design of the MOTHER study might have contributed to the caution with administering additional opioids to patients maintained on methadone or buprenorphine. Interestingly, no significant differences in pain management were found between the

buprenorphine and the methadone group. In most clinical studies on pain treatment of opioid dependent patients, methadone is used as maintenance treatment. Due to the high affinity of buprenorphine to the μ -receptor the pain management of patients maintained on buprenorphine has added difficulties (Roberts and Meyer-Witting, 2005). Some prior guidelines regarding the treatment of pain for patients in buprenorphine therapy have been published (Alford et al., 2006). The recommendation is to keep buprenorphine as maintenance medication and add short lasting opioids as analgesics, splitting the total dosage in half and administering buprenorphine every 6–8 hours, or pausing buprenorphine and titrating opioid analgesics so that no withdrawal symptoms occur and analgesia is sufficient. When the pain treatment is completed the maintenance treatment with buprenorphine is restarted. Furthermore although opioid maintained patients were derived from a randomized controlled trial, the present study was conceptualized as case-control study as the comparison group consisted of non-randomly selected women according to defined matching criteria.

Implications

Although some recommendations for the treatment of acute pain in opioid dependent patients have already been published, due to a lack of randomized controlled trials most of the evidence for this field has been collected in case reports, retrospective studies and expert opinions (Mehta and Langford, 2006). These emphasize the importance of continuing the opioid agonist maintenance therapy as a basis.

The opioid saving and pain stilling effects of NSAIDs should be employed more frequently as part of a multimodal treatment plan. NSAIDs are a valuable form of treatment for this patient population because their mechanism of action is entirely different to that of opioids (Ludlow et al., 2007).

Furthermore, opioid dependent patients have a high prevalence of other psychiatric diagnoses such as depression and anxiety disorder both of which are independent predictors for an intensified postoperative experience of pain which can complicate management (Carroll et al., 2004). In order to ensure adequate pain treatment psychiatric co-morbidities should not be left untreated and the patient should be treated according to the WHO scheme of pain treatment (WHO, 1990). Cassidy et al. present an algorithm for peripartum pain management of opioid dependent women. It emphasizes the indispensability of frequent controls pertaining to the analgesic needs beyond the routine protocol of pain treatment (Cassidy and Cyna, 2004; Jones et al., 2006).

A case series by Jones et al. illustrates the described treatment strategies on one methadone and one buprenorphine maintained woman after caesarean section using Patient-Controlled Analgesia (PCA) (Jones et al., 2006). The authors underline two main points: One, that methadone and buprenorphine can be administered during pregnancy, birth and the postpartum period without risk. Second, the adequate control of pain using opioids other than the ones used for maintenance and the combination of acetaminophen and NSAR. The dosage of opioids had to be adjusted individually, mostly opioid dependent women needed higher dosages than according to routine protocol (Jones et al., 2009).

In summary, these results suggest that there are significant differences in approaches to pain treatment of women in OMT compared to a non-dependent comparison group. Clinicians must be aware that this specific target population may require higher than average doses of analgesic drugs and opioid analgesic undertreatment should be avoided. The reasons for differences in pain management were beyond the scope of the present study but might be based on psychosocial consequences of opioid addiction, the fear of consequences of the application of opioid analgesics in an opioid dependent patient group and the treatment of

opioid dependent women in the framework of a double-blind study, along with the lack of an interdisciplinary consensus on pain treatment protocol for opioid dependent patients. Furthermore the fact that a significant impact of nicotine consumption on the retrieved results became evident in the statistical analysis underlines the relevance of nicotine consumption in the context of pain management and might be taken into account in future studies.

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Table 1Demographic data of the mothers^a

	Maintenance therapy (n= 40)	Comparison group (n = 80)	p
Vaginal delivery	n= 21	n=42	
Age	25 ± 5 (21–35) ^b	26.3 ± 4.9 (22–38)	0.408
Gestational age at delivery	39 ± 2.4 (37–41)	38.1±2.7 (31–41)	0.368
Primipara	9 (45%)	18 (43.9%)	0.935
Episiotomy	4 (19%)	6 (14.3%)	0.626
Smoker	20 (95.2%)	8 (20%)	< 0.001
Cesarean delivery	n = 19	n=38	
Age	25 ± 5.6 (21–36)	26.1±4.6 (21–37)	0.68
Gestational age at delivery	38 ± 2.1 (33–41)	38±2.1 (33–40)	0.349
Primipara	11 (57.6%)	18 (47.4%)	0.454
Smoker	19 (100%)	7 (18.4%)	< 0.001

^a n in the group of opioid-dependent women refers to number of deliveries.^b results are displayed as mean ± SD; minimum and maximum values in parentheses.

Table 2Birth outcomes^a

	Maintenance therapy (n=40)	Comparison group (n=80)	p
Vaginal delivery	n=21	n=42	
Birth weight	2893.4±482.4 (1595–3860) ^b	3055.6±684.7 (1742–4110)	0.11
Birth length	48.9±2.5 (48–51)	49.7±3.4 (48–56)	0.113
Head circumference	33.4±2.6 (31–35)	33.8±1.8 (31–37)	0.333
Apgar 5 minutes less than 7	0	0	
Cesarean section	n=19	n=38	
Birth weight	2876.9±488.5 (1440–3380)	3019.4±671.9 (1270–4880)	0.632
Birth length	48.8 (41–51)	49.5±3.3 (39–55)	0.955
Head circumference	33.3±2.62 (21–36)	33.8±1.8 (29–36)	0.375
Apgar 5 minutes less than 7	0	0	

^a n in the group of opioid-dependent women refers to number of deliveries.

^b results are displayed as mean ± SD; minimum and maximum values in parentheses.

Table 3Maintenance therapeutics in the opioid maintenance therapy (OMT) group at the time of delivery^a

	Methadone	Buprenorphine	p
Vaginal delivery (n=21)	8 (38.1%)	13 (61.9%)	0.275
	56.25±33.35 mg (20–100 mg) ^b	12.77±5.32 mg (6–22 mg)	
Cesarean section (n=19)	13 (68.4 %)	6 (31.6%)	0.108
	71.54±37.15 mg (20–130 mg)	15.33±7.86 mg (8–28 mg)	

^a n in the group of opioid-dependent women refers to number of deliveries.^b results are displayed as mean ± SD; minimum and maximum values in parentheses.

Table 4Use of NSAIDs for pain control in the first three days after vaginal delivery^a

	Maintenance Therapy (n=21)	Comparison group (n=42)	p
Day of delivery			
Acetaminophen	5 (23.8%)	12 (28.6%)	0.688
Dosage	854±474.31 mg (385–1500) ^b	583.4±305.04 mg (385–1000)	0.177
Diclofenac	5 (23.8%)	6 (14.3%)	0.348
Dosage	55±27.39 mg (25–100)	62.5±46.77 mg (25–150)	0.760
Total of participants receiving NSAIDs	9 (42.1%)	12 (57.1%)	0.407
Postpartal day 1			
Acetaminophen	5 (23.8%)	7 (16.7%)	0.496
Dosage	754±336.65 mg (385–1000)	725.7±590.49 mg (385–2000)	0.926
Diclofenac	2 (9.5%)	2 (4.8%)	0.465
Dosage	37.5±17.68 mg (25–50)	62.5±53.03 mg (25–100)	0.592
Total of participants receiving NSAIDs	6 (28.6%)	8 (19.1%)	0.558
Postpartal day 2			
Acetaminophen	2 (9.5%)	3 (7.1%)	0.742
Dosage	692.5±434.87 mg (385–1000)	385 mg	0.272
Diclofenac	0	1 (2.4%)	0.476
Dosage	0	50 mg	/
Total of participants receiving NSAIDs	2 (9.5%)	4 (9.5%)	1
Postpartal day 3			
Acetaminophen	2 (9.5%)	1 (2.4%)	0.209
Dosage	692.5±434.87 mg (385–1000)	1000 mg	0.667
Diclofenac	0	1 (2.4%)	0.476
Dosage	0	63 mg	/
Total of participants receiving NSAIDs	2 (9.5%)	1 (2.4%)	0.209

^a n in the group of opioid-dependent women refers to number of deliveries.^b results are displayed as mean ± SD; minimum and maximum values in parentheses.

Table 5Use of NSAIDs for pain control in the first three days after Cesarean section^a

	Maintenance Therapy (n=19)	Comparison group (n=38)	p
Day of delivery			
Acetaminophen	10 (52.6%)	19 (50%)	0.851
Dosage	1460±884.68 mg (600–3000) ^b	1093.16 mg±446.68 (385–2000)	0.146
Diclofenac	17 (89.5%)	34 (89.5%)	1.000
Dosage	110.29±46.82 mg (75–225)	116.18±48.02 mg (75–225)	0.679
Total of participants receiving NSAIDs	19 (100%)	35 (92.1%)	0.208
Postpartal day 1			
Acetaminophen	10 (52.6%)	24 (63.2%)	0.445
Dosage	1177±495.89 mg (385–2000)	1298.13±788.824 mg (1000–3385)	0.657
Diclofenac	14 (73.7%)	33 (86.8%)	0.218
Dosage	116.7±43.42 mg (25–150)	139.02±45.69 mg (75–225)	0.117
Total of participants receiving NSAIDs	17 (98.5%)	36 (94.7%)	0.436
Postpartal day 2			
Acetaminophen	3 (15.8%)	7 (18.4%)	0.805
Dosage	1128.33±815.11 mg (385–2000)	1132.14±665.61 mg (385–2000)	0.994
Diclofenac	10 (52.6%)	24 (63.2%)	0.445
Dosage	112.5±44.49 mg (25–150)	93.75±54.80 mg (75–225)	0.346
Total of participants receiving NSAIDs	12 (63.2%)	27 (71.1%)	0.546
Postpartal day 3			
Acetaminophen	2 (10.5%)	3 (7.9%)	0.741
Dosage	692.5±434.87 mg (385–2000)	718.3±310.74 mg (770–1000)	0.942
Diclofenac	8 (42.1%)	6 (15.8%)	0.03 ^c 0.998 ^d
Dosage	87.5±44.32 mg (25–150)	79.2±43.06 mg (25–150)	0.731
Total of participants receiving NSAIDs	10 (52.6%)	9 (23.7%)	0.029 ^c 0.997 ^d

^a n in the group of opioid-dependent women refers to number of deliveries.^b results are displayed as mean ± SD; minimum and maximum values in parentheses.^c result in the first-step analysis;^d result in the second-step analysis (inclusion of smoking status into a binary logistic model).

Table 6Administration of opioid analgesics in the first three days postpartum^a

	Maintenance Therapy (n=40)	Comparison group (n=80)	p
Vaginal Delivery	n=21	n=42	
Day of delivery	0	0	/
Postpartal day 1	0	1 (4.8%)	0.476
Dose	/	63 mg	/
Postpartal day 2	0	0	/
Postpartal day 3	0	1 (4.8%)	0.476
Dose	/	63 mg	/
Cesarean Section	n=19	n=38	
Day of delivery	3 (15.8%)	15 (39.5%)	0.024 ^b 0.038 ^c
Dose	50±0	76.4±17.65 (50–108) ^b	0.057
Postpartal day 1	1 (5.3%)	17 (44.7%)	0.003 ^c 0.020 ^d
Dose	50 mg	67.53±31.45 (50–166)	0.596
Postpartal day 2	0	8 (21.1%)	0.031 ^c > 0.05 ^d
Dose	/	79.50±19.54 (50–100)	/
Postpartal day 3	0	4 (10.5%)	0.142
Dose	/	61.5±15.59	/

^a n in the group of opioid-dependent women refers to number of deliveries.^b results are displayed as mean ± SD; minimum and maximum values in parentheses.^c result in the first-step analysis;^d result in the second-step analysis (inclusion of smoking status into a binary logistic model).