HELDA
HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI

UNIVERSITY OF HELSINKI

https://helda.helsinki.fi

Buprenorphine-naloxone, buprenorphine, and methadone throughout pregnancy in maternal opioid use disorder

Kanervo, Minna M.

2023-03

Kanervo , M M , Tupola , S J , Nikkola , E M , Rantakari , K M & Kahila , H K 2023 , ' Buprenorphine-naloxone, buprenorphine, and methadone throughout pregnancy in maternal opioid use disorder ' , Acta Obstetricia et Gynecologica Scandinavica , vol. 102 , no. 3 , pp. 313-322 . https://doi.org/10.1111/aogs.14497

http://hdl.handle.net/10138/355743
https://doi.org/10.1111/aogs.14497

cc_by_nc_nd
publishedVersion

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

Received: 13 July 2022 | Revised: 14 November 2022 | Accepted: 2 December 2022

DOI: 10.1111/aogs.14497

ORIGINAL RESEARCH ARTICLE

Buprenorphine-naloxone, buprenorphine, and methadone throughout pregnancy in maternal opioid use disorder

Minna M. Kanervo[1,2] | Sarimari J. Tupola[1] | Eeva M. Nikkola[1] | Krista M. Rantakari[1] | Hanna K. Kahila[3]

[1]Children's Hospital, Pediatric Research Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

[2]Doctoral Program in Clinical Research, University of Helsinki, Helsinki, Finland

[3]Gynecology and Obstetrics, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

Correspondence
Minna M. Kanervo Children's Hospital, Helsinki University Hospital, P.O. Box 347, FI-00029 HUS, Helsinki, Finland.
Email: minna.kanervo@hus.fi

Funding information
Lastentautien Tutkimussäätiö; Päivikki ja Sakari Sohlbergin Säätiö

Abstract

Introduction: Current WHO guidelines recommend using methadone or buprenorphine as maintenance treatments for maternal opioid use disorder. However, buprenorphine-naloxone, with a lower abuse risk than buprenorphine monotherapy or methadone, offers a potentially beneficial alternative, but scientific evidence on its effects on pregnancies, fetuses, and newborns is scarce. This paper compares the outcomes of the pregnancies, deliveries, and newborns of women on buprenorphine-naloxone, buprenorphine, or methadone maintenance treatments. According to the hypothesis, as a maintenance treatment, buprenorphine-naloxone does not have more adverse effects than buprenorphine, whereas methadone is more complicated.

Material and methods: In this population-based study, 172 pregnant women on medical-assisted treatments were followed-up at Helsinki University Women's Hospital (Finland). Women receiving the same opioid maintenance treatment from conception to delivery and their newborns were included. Consequently, 67 mother–child dyads met the final inclusion criteria. They were divided into three groups based on their opioid pharmacotherapy. The outcomes were compared among the groups and, where applicable, with the Finnish population.

Results: The buprenorphine-naloxone and buprenorphine groups showed similar outcomes and did not significantly differ from each other in terms of maternal health during pregnancies, deliveries, or newborns. Illicit drug use during the pregnancy was common in all groups, but in the methadone group it was most common ($p = 0.001$). Most neonates (96%) were born full-term with good Apgar scores. They were of relatively small birth size, with those in the methadone group tending to be the smallest. Of the neonates 63% needed pharmacological treatment for neonatal opioid withdrawal syndrome. The need was lower in the buprenorphine-based groups than in the methadone group ($p = 0.029$).

Abbreviations: HCV, hepatitis C virus; MOUD, maternal opioid use disorder; NOWS, neonatal opioid withdrawal syndrome; OMT, opioid maintenance treatment.

Hanna K. Kahila and Krista M. Rantakari contributed equally as co-last authors.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2022 The Authors. *Acta Obstetricia et Gynecologica Scandinavica* published by John Wiley & Sons Ltd on behalf of Nordic Federation of Societies of Obstetrics and Gynecology (NFOG).

16000412, 2023, 3, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1111/aogs.14497 by Duodecim Medical Publications Ltd, Wiley Online Library on [07/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: Buprenorphine-naloxone seems to be as safe for pharmacotherapy for maternal opioid use disorder as buprenorphine monotherapy for both mother and newborn. Hence it could be a choice for oral opioid maintenance treatment during pregnancy, but larger studies are needed before changing the official recommendations. Women on methadone treatment carry multifactorial risks and require particularly cautious follow up. Furthermore, illicit drug use is common in all treatment groups and needs to be considered for all patients with opioid use disorder.

KEYWORDS
buprenorphine, buprenorphine-naloxone, maternal opioid use disorder, methadone, neonatal opioid withdrawal syndrome, opioid maintenance treatment, pregnancy

1 | INTRODUCTION

The worldwide opioid crisis affects pregnant women. Maternal opioid use disorder (MOUD) poses risks to the woman, to the fetus, and to the newborn. It is associated with several adverse effects on the central nervous system and other organs, increased risk for infections, poor nutrition, and antisocial lifestyle.[1–3] Furthermore, untreated MOUD has been linked with increased risk for preterm labor and low birthweight.[4] The child may develop neonatal opioid withdrawal syndrome (NOWS), as well as suffer from short- and long-term medical and social consequences.[5–7] Given these problems, every pregnant opioid-addicted woman should receive an opioid maintenance therapy that is as safe as possible, because it improves compliance to prenatal care and addiction treatment.

Current WHO guidelines recommend opioid maintenance treatment (OMT) for MOUD during pregnancy either with methadone or buprenorphine.[1] Methadone seems to be more effective for the mother than buprenorphine, but the interaction potential, the overdose risk, and the severity of NOWS limits its medical use.[2,8,9] Furthermore, the problem with both methadone and buprenorphine is their abuse potential. Combination product with buprenorphine and naloxone has been developed to prevent parenteral abuse of buprenorphine.[10,11] However, naloxone crosses the placenta in minimal quantities,[12] and scientific knowledge on its possible effects on pregnancies, fetuses, or children is scarce.[13] Naloxone has shown no teratogenicity, but some hormonal and behavioral changes in animal studies.[12] Hence, before renewing recommendations of its use during pregnancy, solid scientific evidence of the effects is needed.

The objective of this paper was to compare the outcomes of women and neonates on buprenorphine-naloxone, buprenorphine, or methadone maintenance treatment for MOUD. According to the hypothesis, the adverse effect profile would remain similar in the buprenorphine-naloxone and the buprenorphine monotherapy groups, whereas in the methadone group the outcomes would be more complicated.

Key message

Opioid maintenance therapy with buprenorphine-naloxone during pregnancy appears to be comparable to buprenorphine monotherapy for mothers and newborns. Women on methadone treatment carry multifactorial risks and require particularly cautious follow up. Larger trials are needed to confirm these results.

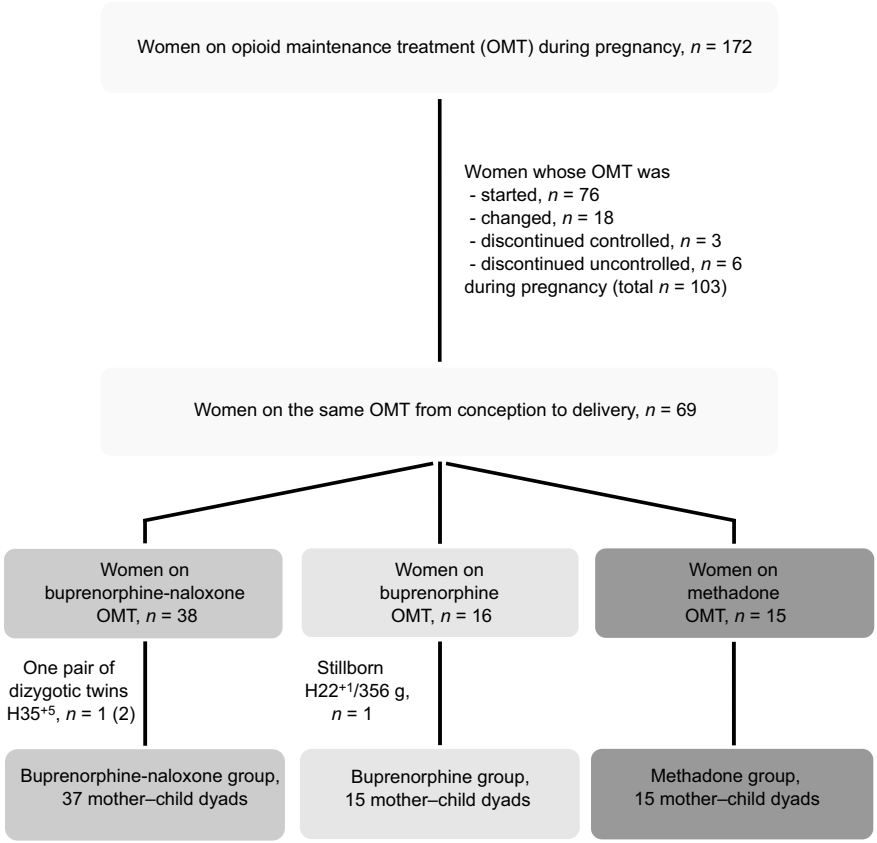
2 | MATERIAL AND METHODS

This population-based study investigates pregnancies, births, and newborn outcomes of women on buprenorphine-naloxone, buprenorphine, or methadone maintenance treatment in the Helsinki metropolitan area of 1.7 million inhabitants (Figure 1). The women were treated because of their opioid use disorder by addiction medicine physicians or psychiatrists who were responsible for the chosen OMT pharmacotherapy and its daily dose. The women were followed up by obstetricians throughout their pregnancies in the Women's Hospital maternity clinic, Helsinki University Hospital, Finland. The newborns were treated at the same hospital's neonatal unit.

The initial research population consisted of 172 pregnant women between January 1, 2011 and December 31, 2018. Patients receiving the same OMT throughout the pregnancy, from conception to delivery, and their newborns were included for the analysis. To ensure the study groups were as pure as possible, women whose OMT was started (n = 76), changed (n = 18), discontinued under control (n = 3), or uncontrolled (n = 6, ie 3.5% of all) during pregnancy were excluded. Five of these six dropouts were on buprenorphine and one was on methadone therapy. Sixty-nine women met the inclusion criteria. One pair of twins and one stillbirth were excluded. Consequently, the final analysis included 67 mother–child dyads. The women were divided into three groups based on their OMT: 37 dyads in the buprenorphine-naloxone group, 15 in the buprenorphine group, and 15 in the methadone group. We compared

16000412, 2023, 3, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1111/aogs.14487 by Duodecim Medical Publications Ltd, Wiley Online Library on [07/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

FIGURE 1 The study flow chart



the outcomes between the groups and, where applicable, with the Finnish population.

The clinical data covered information on women's background (eg age, ethnicity); health and medication; smoking, alcohol, and substance use; OMT; reported experiences of violence, suicide attempts, and intoxications during pregnancies; parity; delivery; and postpartum data. Smoking, alcohol, and substance use were determined by self-reports and voluntary urine tests. The neonatal data contained birth-related parameters and medical data.

2.1 | Statistical analyses

We performed statistical analyses with IBM SPSS version 25 for Windows. For ensuring patients' non-identifiability we anonymized the data. For categorical variables, outcomes between the groups were compared using Pearson's chi-squared tests, and when appropriate, Fisher's exact tests. Kruskal–Wallis tests, in turn, were applied for comparisons between the three groups for non-normally distributed values. Post hoc tests with Bonferroni adjustments were performed using Dunn's and Mann–Whitney *U* tests. We considered *p* values less than 0.05 as statistically significant.

2.2 | Ethics Statement

This research was performed according to the ethical requirements of Helsinki University Hospital. The protocols were approved by the Hospital District of Helsinki and Uusimaa, Finland (no. HUS/54/2019) on February 4, 2019.

3 | RESULTS

3.1 | Women on opioid maintenance treatments

The information of MOUD and OMT are demonstrated in Table 1. Detailed history of previous substance abuse was obtained from 62/67 (93%) patients. Self-reported opioid abuse periods before the current OMT had lasted for 1–17 years, and in 51/62 (82%) for 5 years or more. Multiple previous OMT periods were more common in the methadone group than in the two buprenorphine-based groups ($p = 0.006$).

The daily dose of maintenance medication reduced towards the end of pregnancy in 41/66 (62%) women, mostly due to patients' requests. These dose reductions were most common in the buprenorphine (11/14; 79%, the reduction information was missing from one patient) and buprenorphine-naloxone (24/37; 65%) groups; and less common in the methadone group (6/15; 40%). The daily dose was increased towards the delivery in only one patient (methadone group).

Nearly all women with MOUD smoked before (97%), and during (93%) the pregnancy (Table 1). Finnish fertile-aged women smoked far less in 2018 (13% and 11%, respectively[14]). In turn, the self-reported alcohol use before the pregnancy (72%) was even lower than among general Finnish fertile-aged women (87%–89%). Approximately one in five of the patients self-reported alcohol use

16000412, 2023, 3, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1111/aogs.14497 by Duodecim Medical Publications Ltd, Wiley Online Library on [07/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 Women on opioid maintenance treatment

Basics of OMTs	Finland, %[#]	Bpnx, *n* = 37	Bp, *n* = 15	M, *n* = 15	*p* value
Self-reported opioid abuse before OMT, *n* (%)					0.106
<5 years		8 (24)	2 (14)	1 (7)	
5–9 years		10 (29)	9 (64)	9 (64)	
≥10 years		16 (47)[3]	3 (21)[1]	4 (29)[1]	
Number of previous OMT periods, *n* (%)					0.006[a]
0		0	2 (13)	0	
1		31 (84)	10 (67)	7 (47)	
2–4		6 (16)	3 (20)	8 (53)	
Duration of the last OMT before pregnancy, *n* (%)					0.727
<1 year		6 (16)	4 (31)	4 (27)	
1–4 years		19 (51)	6 (46)	7 (47)	
5–9 years		11 (30)	2 (15)	3 (20)	
≥10 years		1 (3)	1 (8)[2]	1 (7)	
Dose of OMT medication (mg), median (IQR)					
Maximum		14 (10;16)	10 (6;16)[1]	70 (56;90)	Bpnx vs. Bp 0.173
At the delivery		8 (6;12)	7 (3;8.5)	60 (40;85)	Bpnx vs. Bp 0.116
Self-reported					
Smoking before pregnancy, *n* (%)	13	35 (95)	15 (100)	15 (100)	1.000
Smoking during pregnancy, *n* (%)	11	33 (89)	15 (100)	14 (93)	0.485
Alcohol use before pregnancy, *n* (%)	87–89	23 (64)	14 (100)[1]	9 (64)[1]	0.020[b]
Alcohol use during pregnancy, *n* (%)	N/A	6 (17)[1]	3 (21)[1]	2 (18)[4]	0.900
Illicit drug use before pregnancy, *n* (%)	N/A	30 (81)	11 (79)[1]	13 (87)	0.913
Documented illicit drug use during pregnancy	N/A	13 (36)[1]	6 (43)[1]	14 (93)	0.001[c]

Abbreviations: Bpnx, buprenorphine-naloxone; Bp, buprenorphine; IQR, interquartile range; M, methadone; OMT, opioid maintenance treatment; N/A, not available; X^n, missing data, *n*.

[#]Finnish general population.[14]

[a]Bpnx vs. Bp 0.345, Bpnx vs. M 0.039; Bp vs. M 0.225.

[b]Bpnx vs. Bp 0.030; Bpnx vs. M 0.123; Bp vs. M 0.123.

[c]Bpnx vs. Bp 1.000; Bpnx vs. M < 0.001; Bp vs. M 0.015.

during the pregnancy, with no significant differences between the OMT groups. There are no comprehensive statistics on alcohol use among general Finnish women during pregnancy.

The illicit drug use was high before and during the pregnancy (Table 1 and Figure 2). Drug screens at the maternity outpatient clinic were voluntary. Six women (6/65, 9%) gave no samples, but three of them self-reported concomitant drug use. When combining the self-reports and the positive urine tests, the drug abuse rate was 33/65 (51%) in the entire study population during the current pregnancy. It was significantly more common in the methadone group than in the buprenorphine-based groups throughout the pregnancy (p = 0.001). During the third trimester, 80% (9/15) of the methadone group patients used illicit drugs, whereas the proportions in the buprenorphine-naloxone and buprenorphine only groups were 22% (8/37) and 20% (3/15), respectively (p = 0.066). Furthermore, the women in the methadone group used significantly more benzodiazepines, cannabis, and stimulants than the patients in the other groups (p = <0.001; p = 0.020; p = 0.002, respectively, Figure 3). Over half of the patients with prescribed benzodiazepines, 11/21 (52%), also acquired them from other sources.

Psychiatric medication was prescribed for 43/65 (66%) of the patients, and 20/66 (30%) had a psychiatric comorbidity diagnosis, most commonly in the methadone group (Table 2). The most frequent International Classification of Diseases 10th revision diagnoses were depressive (F32; 6/66; 9%), anxiety (F41; 4/66; 6%), attention deficit hyperactivity (F90; 4/66; 6%), and specific personality (F60; 7/66;10%) disorders.

The prevalence of relatively common chronic somatic diseases, such as diabetes mellitus type 1 (no cases) and type 2 (1/67, 2%), hypothyroidism, epilepsy, migraine, hypertension, and asthma in women on OMT was of same magnitude as in the general Finnish female population. Instead, substance use-related somatic diseases

16000412, 2023, 3, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1111/aogs.14487 by Duodecim Medical Publications Ltd, Wiley Online Library on [07/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

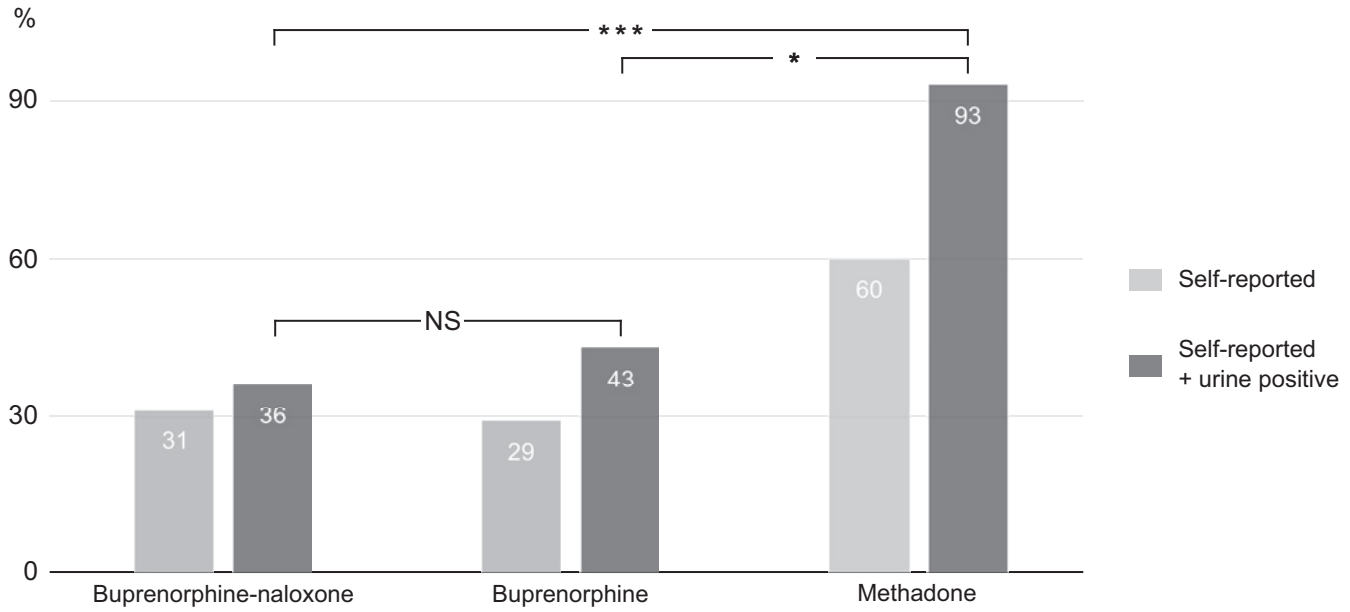


FIGURE 2 Illicit drug use. Self-reported and documented illicit drug use during pregnancy in the opioid maintenance treatment groups. When combining self-reports and positive urine tests, women in the methadone group used significantly more illicit drugs than women in the buprenorphine-based groups. ***p=<0.001, *p=<0.05, NS: no significance (p=0.659).

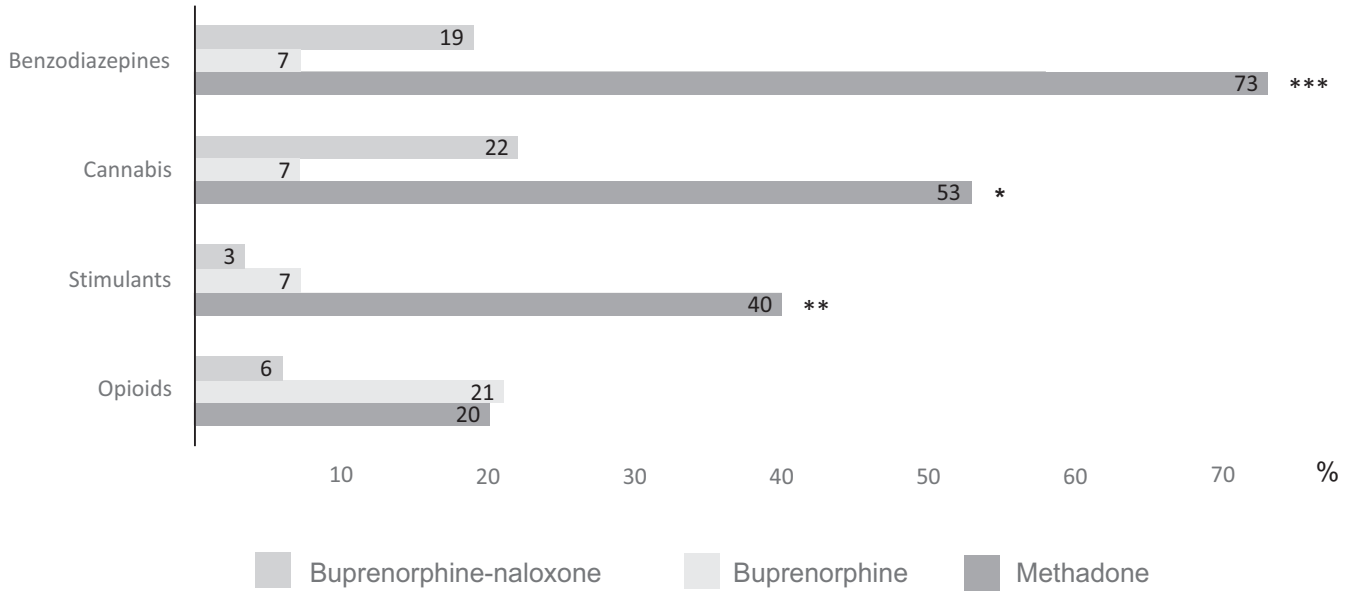


FIGURE 3 Most frequently used illicit drugs during pregnancy in the opioid maintenance treatment groups. ***p=<0.001, **p=<0.01, *p=<0.05.

were common: (a) three patients in the methadone group (3/15, 20%) had a history of acute endocarditis and two of them had prosthetic heart valves; (b) three in the methadone group (3/15, 20%) had suffered from venous thrombosis, and one of them also from pulmonary embolism; (c) two patients had been operated on after needle-stick injuries; one had undergone fasciotomy because of compartment syndrome (buprenorphine-naloxone group, 1/37, 3%) and one's fingers were amputated (methadone group, 1/15, 7%); (d) nearly all (91%) had positive hepatitis C virus (HCV) antibodies and 46% had active HCV (data not available in eight patients). One patient (methadone group) had a history of hepatitis B, but none was hepatitis B surface antigen positive. One patient was on medication for HIV infection (Table 2).

Three women (5%) had visited the emergency room because of violence during the pregnancy; one from the buprenorphine group and two from the methadone group. Patients from the methadone group also reported other violent experiences, one person several times during the current pregnancy. One intoxication occurred in

16000412, 2023, 3, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1111/aogs.14487 by Duodecim Medical Publications Ltd, Wiley Online Library on [07/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 Medical diagnoses of the women on the opioid maintenance treatment

Disease	Finland, incidence[#]	Final study population	Bpnx, *n* = 37	Bp, *n* = 15	M, *n* = 15	*p* value
Psychiatric comorbidity, *n* (%)	N/A	20 (30)[1]	11 (30)	1 (7)[1]	8 (53)	0.025[a]
Psychopharmacy, *n* (%)	N/A	43 (66)	24 (67)[1]	7 (47)[1]	12 (80)	0.232
HCV antibodies positive, *n* (%)	N/A	60 (91)[1]	33 (89)	12 (86)[1]	15 (100)	0.060
Active HCV infection, *n* (%)	21/100 000	27 (46)[8]	13 (39)	3 (25)[3]	11 (79)[1]	0.013[b]
Active HBV infection, *n* (%)	0.07/100 000	0	0	0	0	1.000
HIV infection, *n* (%)	<5/100 000	1 (1)	0	0	1 (7)	1.000

Abbreviations: Bp, buprenorphine; Bpnx, buprenorphine-naloxone; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; M, methadone; N/A, not available; X^n, missing data (*n*).

[#]Finnish general population.

[a]Bpnx vs. Bp 0.426; Bpnx vs. M 0.327; Bp vs. M 0.042.

[b]Bpnx vs. Bp 1.000; Bpnx vs. M 0.042; Bp vs. M 0.018.

gestational week 8 (methadone group). No suicide attempts were reported.

3.2 | Obstetrical outcomes

The women on OMT were of the same age as Finnish parturients in general, but they tended to be less often primiparas, 16% vs. 41% (Table 3). The pregnancy follow up started during the first trimester with the majority of patients (41/63, 65%). The methadone group tended to start the visits later – 47% started their visits in the second or third trimester – whereas the proportions in the buprenorphine-naloxone and buprenorphine groups were 34% and 23%, respectively, but the differences were statistically insignificant.

Pregnancy complications occurred with the same rates as in the general population,[14] and the deliveries were mainly uneventful. The proportion of spontaneous vaginal deliveries was 53/67 (79%), and the cesarean section rate was 13/67 (19%), of which 4/13 (31%) were elective (6% of all deliveries).

3.3 | Newborns

Most neonates (64/67, 96%) were born full-term (>37^{+0} weeks of gestation) and in good condition (Table 4). None had Apgar scores below 5. One neonate in the buprenorphine-naloxone group (3%) and two in the methadone group (13%) had 5-minute Apgar scores of 5 or 6, which forms 5% of the total study population. In 2018, of all Finnish newborns 2.2% had 5-minute Apgar scores from 4 to 6.[14]

The birth sizes were smaller than in the general Finnish population (Table 4, Figure 4). Furthermore, 15/67 (22%) had a small-for-gestational-age diagnosis: 7/37 (19%) in the buprenorphine-naloxone group, 3/15 (20%) in the buprenorphine group; and 5/15 (33%) in the methadone group. The newborns in the methadone group tended to be smallest, especially in having a small head circumferences (Figure 4).

There were a few minor congenital malformations in every OMT group, but without statistically significant differences between the groups ($p = 0.522$). These malformations were of skin, urinary tract, and skeletal origin. Both neonates with urinary tract anomalies were in the buprenorphine-naloxone group (one hypospadia, and one horseshoe kidney with congenital prolapse of the urinary meatus). Furthermore, one child in the methadone group had congenital club-foot. No obvious fetal alcohol syndrome signs were observed in the newborns.

All neonates were monitored for NOWS symptoms.[15] The need for pharmacological treatment for NOWS was lowest in the buprenorphine-naloxone group and highest in the methadone group (51% vs. 67% vs. 87%, $p = 0.054$). When combining buprenorphine-based groups the difference between them and the methadone group was significant (29/52 vs. 13/15; 56% vs. 87%, $p = 0.029$). Of neonates with fetal exposure to illicit drugs, those in the methadone group most often experienced NOWS with a need for pharmacological treatment ($p = 0.048$). In the buprenorphine-based groups the difference between exposed and non-exposed was statistically insignificant (buprenorphine-naloxone $p = 0.406$, buprenorphine $p = 1.000$).

4 | DISCUSSION

In the present paper, we demonstrate that OMT with buprenorphine-naloxone appears to be as safe during pregnancy as buprenorphine monotherapy for both mother and newborn. Women on methadone OMT carry marked risks and require particularly cautious follow up. Illicit drug use is common in all OMT groups despite seemingly committed patients.

Studies on relatively new OMT, such as buprenorphine-naloxone, are urgently needed.[3,13,16–18] However, research on drug abuse issues is challenging because of recruitment problems, social stigma, dropouts, compliance issues, and confounding factors. In this study, we aimed at investigating OMT groups that were as pure as possible by including only mothers, who used the same OMT throughout

16000412, 2023, 3, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1111/aogs.14487 by Duodecim Medical Publications Ltd, Wiley Online Library on [07/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 3 Obstetrical outcomes

Outcome	Finland, mean OR, %[a]	Bpnx, *n* = 37	Bp, *n* = 15	M, *n* = 15	*p* value
Age (y) at the delivery, median (IQR)	31	29 (20–38)	32 (27–34)	30 (28–32)	0.660
Parity one	29	28 (26–33)	33 (32–36)	28 (28–28)	0.257
Multipara	N/A	30 (27–33)	29 (26–34)	30 (25–36)	0.920
Ethnic: Caucasian, *n* (%)	N/A	36 (97)	15 (100)	15 (100)	1.000
Partus, *n* (%)					0.367
Parity one	41	6 (16)	4 (27)	1 (7)	
Multipara	59	31 (84)	11 (74)	14 (93)	
First visit to maternal outpatient clinic, *n* (%)					0.647
First trimester	N/A	23 (66)[2]	10 (77)[2]	8 (53)	
Second trimester	N/A	6 (17)	2 (15)	5 (33)	
Third trimester	N/A	6 (17)	1 (8)	2 (13)	
Pregnancy complications, *n* (%)					0.138
Gestational diabetes mellitus	21	5 (14)	4 (27)	4 (27)	
Pre-eclampsia	4	0	1 (7)	0	
Premature rupture of membranes		1 (3)	2 (13)	0	
Placenta previa		0	1 (7)	0	
Other[b]		4 (11)	0	1 (7)	
Mode of delivery, *n* (%)					0.698
Vaginal	74	30 (81)	11 (73)	12 (80)	
Instrumental	9	0	1 (7)	0	
Cesarean section	17	7 (19)	3 (20)	3 (20)	
Emergency, *n*		4	2	3	
First stage of the delivery (min), median (IQR)					
Parity one	N/A	594 (201;730)	510 (450;510)	N/A	0.724
Multipara	N/A	323 (196–652)[1]	483 (234–746)	280 (160–350)	0.189
Second stage of the delivery (min), median (IQR)					
Para one	N/A	23 (13–36)	45 (34–45)	N/A	0.077
Multipara	N/A	9 (7–19)[1]	14 (6–31)	17 (8–25)	0.544

Abbreviations: Bpnx, buprenorphine-naloxone; Bp, buprenorphine; IQR, interquartile range; M, methadone; N/A, not available; X^n, missing data (*n*).

[a]Finnish general population.[14]

[b]Other pregnancy complications include hypertension, infections, blood-stained discharge, Rhesus immunization, hepatogestosis, oligohydramnios, fetal growth retardation (*n* = 1), and intrauterine asphyxia.

the pregnancy, and their newborns. Aiming at the purity of the study groups leads to limited size of the study population. Although the basic population in the current population-based region is large (1.7 million), the number of women fulfilling the final inclusion criteria was small, and therefore the study may not have been powerful enough to discover all clinically significant factors. Hence, even though our population was larger than in many previous reports, specifically with buprenorphine-naloxone studies,[13,17] it was still small. Furthermore, the care of pregnant women with OUD is organized differently in different countries, which also may influence the results. Therefore, larger multicenter studies are needed before more precise conclusions are drawn.

The patient groups were relatively homogeneous and committed to OMT and follow up. The pregnancy monitoring, the deliveries, and neonatal care were performed in standardized circumstances. Several potential confounding factors were ruled out with the study design, which is a strength.

The concomitant illicit drug use is a potential confounding factor. Although we had assumed some illicit drug use, its magnitude during pregnancy was unexpectedly high.[19,20] Moreover, the actual use may have been even higher because the data are based on the patients' own reports and voluntary urine tests, when the fear of child protection services involvement may have hindered truthful reporting. The role of the OMT dosage reduction in illicit drug use also remains uncertain. On the one hand, it did not seem to solely explain the high rate of illicit drug use, as 56% of the women with reduced doses did not use illicit drugs, but on the other hand, 44% did. In any case, the OMT dosing role needs to be clarified in future

16000412, 2023, 3, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1111/aogs.14487 by Duodecim Medical Publications Ltd, Wiley Online Library on [07/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 4 Newborns of the mothers on opioid maintenance treatment

Outcome	Finland, % or mean[a]	Bpnx, *n* = 37	Bp, *n* = 15	M, *n* = 15	*p* value
Gender male, *n* (%)	52	21(57)	6 (40)	8 (53)	0.546
Gestational age (wk), median (IQR)		39 + 6(38 + 6; 41 + 5)	39 + 6(39 + 1; 41 + 1)	39 + 3(38 + 1; 40 + 4)	0.318
$<37^{+0}$	5	2 (5)	1 (7)	0	0.838
Meconium-stained amniotic fluid, *n* (%)	N/A	1 (3)[4]	2 (15)[2]	3 (21)[1]	0.139
Apgar 1 min, mean		8.7 (±0.1)	8.4 (±0.2)	8.3 (±0.2)	0.594
Apgar 5 min, mean		9.1 (±0.1)	8.7 (±0.5)	8.1 (±0.4)	0.277
Apgar 10 min, mean		9.3 (±0.2)	8.3 (±0.6)	8.4 (±0.4)	0.367
Umbilical artery pH, median (IQR)		7.24 (7.19–7.28)	7.26 (7.19–7.33)	7.27 (7.25– 7.31)	0.366
Umbilical artery BE, median (IQR)		−3.5 (−4.8 to −1.2)	−4.1 (−5.8 to −3.0)	−2.0 (−4.8 to −0.9)	0.408
Birthweight (g), median (IQR)	3526	3435 (2570–3819)	3330 (2678–3605)	3205 (2775–3600)	0.928
Neonatal length (cm), median (IQR)		49 (47.5–51)	49 (48–50)	48 (45–50)	0.561
Neonatal head circumference (cm), median (IQR)		34.5 (33–36)	35 (34–36)	34 (32–35)	0.182
Finnegan scoring, *n* (%)		37 (100)	15 (100)	15 (100)	1.000
Medical treatment for NOWS, *n* (%)		19 (51)	10 (67)	13 (87)	0.054

Abbreviations: BE, base excess; Bp, buprenorphine; Bpnx, buprenorphine-naloxone; IQR, interquartile range; M, methadone; N/A, not available; NOWS, neonatal opioid withdrawal syndrome; pH, potential of hydrogen; X^n, missing data, (*n*).

[a]Finnish general population.[14]

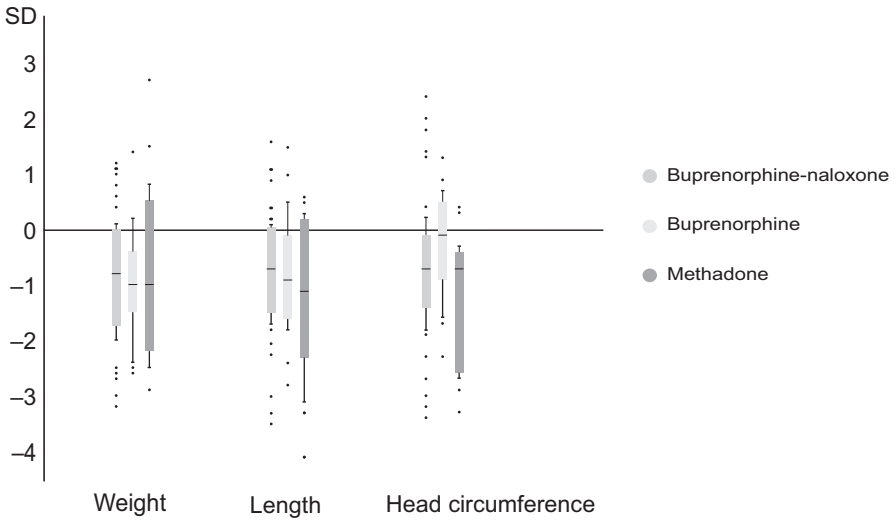


FIGURE 4 Proportional birth sizes. Anthropometric data of the newborns compared with 2011 updated Finnish childhood growth curves using relative measures expressed as standard deviation (SD).

studies, not only because of the possible effects on illicit drug use, but also because constant dosing has been suggested to be more beneficial for both mother and fetus than decreasing doses.[2]

The most-used illicit drugs are in line with the previous literature,[21,22] except that cocaine was rarely used. Furthermore, mothers from buprenorphine-based groups may have additionally used illicit buprenorphine, which is difficult to detect in the tests (as the tests are anyway positive for buprenorphine as the OMT). Of note, the reason for preferring buprenorphine-naloxone as OMT and performing the present study, is this parenteral abuse potential of oral buprenorphine.

The illicit drug use was concerning in the research cohort. The methadone group was most complicated, not only with their most frequent illicit drug use, but also because of the overall situation. Their backgrounds were more severe, and they had more previous OMT periods as well as psychiatric comorbidities and medications. Furthermore, they suffered more from substance-use-related somatic diseases and experiences of violence. They also tended to start their visits to the maternity outpatient clinic later. Hence, their risk profiles were highly complex and may have, in a multifactorial way, affected the well-being, health and other outcomes of the women and their fetuses. Therefore, the interpretation of the methadone group requires caution because the outcomes may be caused by their overall complex situation rather than the methadone medication alone.

Smoking was common in all OMT groups, which is in accordance with previous publications.[21,22] Alcohol use, in turn, was far

16000412, 2023, 3, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1111/aogs.14487 by Duodecim Medical Publications Ltd, Wiley Online Library on [07/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

more moderate and of the same level as in the Norwegian study.[19] We believe that this may be at least close to the truth. Although the alcohol consumption was based on women's own reports, they had reported illicit drug use in higher numbers. Hence, one could assume that they would also report alcohol use, especially as in Finland, alcohol is legal whereas non-prescribed drugs and cannabis are not.

Maternal pregnancy complications and relatively common somatic diseases were as prevalent as in the general population. As expected, psychiatric comorbidities were more common,[22,23] as were certain generally rare somatic conditions that are likely to be associated with the history of injection drug use and associated lifestyle,[24,25] such as amputations, fasciotomy, endocarditis, thrombosis, pulmonary embolism and HCV. Considering heavy smoking, it was a slight surprise that placental abruption was not more common.[26] The deliveries were also mostly uneventful. These patients, like all mothers in Finland, received free-of-charge high-quality maternal care, as indicated by the relatively low frequency of cesarean sections and low perinatal mortality (3.7/1000 neonates in Finland, 0 in the final study population[14]). The thorough follow up and planned labor modes may have resulted in these relatively safe pregnancies and deliveries.

The neonates were mainly born full-term, in good condition and without major defects. Hence, earlier single investigations suggesting higher risk for prematurity in OMT pregnancies,[2] lower Apgar scores with buprenorphine-naloxone than with buprenorphine treatment,[18] and increased risk for congenital defects[27] were not supported by our research. In our original study population was one stillbirth, which was most likely explained by maternal injecting amphetamine use followed by septicemia rather than OMT, and the case was excluded from the final analysis. An assumption stating that it is unlikely to have a causal link between OMT substances and birth abnormalities[2,27] is supported by this paper. However, one must keep in mind the limited power of the reported studies, including ours.

Over half of the infants needed pharmacological treatment for NOWS. The need was lower in the buprenorphine-based groups than in the methadone group, which is in line with the clinical experience and the literature (maternal buprenorphine associated with less severe NOWS).[8,28,29] Of note, even though the average daily dose of buprenorphine during the pregnancy was higher in the buprenorphine-naloxone group than in the buprenorphine-monotherapy group, the former infants did not suffer more from NOWS than the latter.

The neonates in all groups were born relatively small, although mostly within normal range. This is in line with previous literature[7,8,13,22] and could, at least partly, be explained by tobacco exposure.[30] However, other risk factors, such as alcohol[31] and poly-substance use, poor nutrition, as well as OMT medication[8,32] are also possible explanations. Additionally, because of limited human safety data,[12] the role of naloxone needs further confirmation. Several studies, including ours, show similar outcomes with buprenorphine-naloxone and other forms of OMT,[13] indicating that naloxone causes no additional harm. Nevertheless, solid scientific evidence is needed. Furthermore, the long-term clinical, developmental, and social effects of OMT on both mother and child require evaluation in future studies.

5 | CONCLUSION

In this study, buprenorphine-naloxone maintenance treatment seems equal to buprenorphine monotherapy for mother and newborn. Future studies with larger data are needed to confirm the results. With lower parenteral abuse risk than with buprenorphine, buprenorphine-naloxone could be considered as useful medication for OMT during pregnancy. Women on methadone OMT have a more severe substance abuse problem with marked overall risk profile, so they require particularly cautious follow up. Furthermore, the ongoing illicit drug use is worryingly common even among committed patients. Hence, routine drug screening for women and neonates should be available, and NOWS needs to be diagnosed, if the mother is on OMT or any suspicion of fetal drug exposure exists.

AUTHOR CONTRIBUTIONS

MMK contributed to project development, data collection and management, data analysis, and manuscript writing and editing. SJT contributed to project development, data collection, and manuscript editing. EMN contributed to project development and manuscript editing. KMR contributed to project development, data management and analysis, and manuscript writing and editing. HKK contributed to project development, data analysis, and manuscript writing and editing.

ACKNOWLEDGMENTS

We thank registered nurse Hilkka Puttonen, Helsinki University, for collecting part of the data and biostatistician Paula Bergman, Helsinki University Biostatistics Consulting, for statistical consulting.

FUNDING INFORMATION

This work was supported by Foundation for Pediatric Research (Finland), and by the Päivikki and Sakari Sohlberg Foundation (Finland).

ORCID

Minna M. Kanervo https://orcid.org/0000-0002-0373-9500
Hanna K. Kahila https://orcid.org/0000-0001-9658-1193
Krista M. Rantakari https://orcid.org/0000-0002-4218-0391

REFERENCES

1. *Guidelines for the Identification and Management of Substance use and Substance use Disorders in Pregnancy*. World Health Organization; 2014.
2. ACOG Committee Opinion No. 711: opioid use and opioid use disorder in pregnancy. *Obstet Gynecol*. 2017;130:e81-e94.
3. Rausgaard NLK, Ibsen IO, Jørgensen JS, Lamont RF, Ravn P. Management and monitoring of opioid use in pregnancy. *Acta Obstet Gynecol Scand*. 2020;99:7-15.

16000412, 2023, 3, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1111/aogs.14487 by Duodecim Medical Publications Ltd, Wiley Online Library on [07/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. *Jama*. 2012;307:1934-1940.
5. Yeoh SL, Eastwood J, Wright IM, et al. Cognitive and motor outcomes of children with prenatal opioid exposure: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2:e197025.
6. Czynski AJ, Davis JM, Dansereau LM, et al. Neurodevelopmental outcomes of neonates randomized to morphine or methadone for treatment of neonatal abstinence syndrome. *J Pediatr* 2020;219:146-151.e1.
7. Nguyen L, Lander LR, O'Grady KE, et al. Treating women with opioid use disorder during pregnancy in Appalachia: initial neonatal outcomes following buprenorphine+naloxone exposure. *Am J Addict*. 2018;27:92-96.
8. Wiegand SL, Stringer EM, Stuebe AM, Jones H, Seashore C, Thorp J. Buprenorphine and naloxone compared with methadone treatment in pregnancy. *Obstet Gynecol*. 2015;125:363-368.
9. McCance-Katz EF, Sullivan LE, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. *Am J Addict*. 2010;19:4-16.
10. Orman JS, Keating GM. Buprenorphine/naloxone: a review of its use in the treatment of opioid dependence. *Drugs*. 2009;69:577-607.
11. Seligman NS, Rosenthal E, Berghella V, Saxon AJ, and Friedman M. Overview of management of opioid use disorder during pregnancy[Internet] 2019 [cited 2022 Sep 29]. Available from: https://scholar.googleusercontent.com/scholar.bib?q=info:XOgb2v5PDkAJ:scholar.google.com/&output=citation&scisdr=CgVA2JCVEI7956fa_hU:AAGBfm0AAAAAYzXc5hWJ0b47tgvXEmJStJ91Vg_RfP0i&scisig=AAGBfm0AAAAAYzXc5pTL4MKd1TfLqHWjEEea7Md1Jupc&scisf=4&ct=citation&cd=-1&hl=fi
12. Wiegand S, Swortwood M, Huestis M, Thorp J, Jones H, Vora N. Naloxone and metabolites quantification in cord blood of prenatally exposed newborns and correlations with maternal concentrations. *Am J Perinatol Rep*. 2016;23(6):e385-e390.
13. Link HM, Jones H, Miller L, Kaltenbach K, Seligman N. Buprenorphine-naloxone use in pregnancy: a systematic review and metaanalysis. *Am J Obstet Gynecol MFM*. 2020;2:100179.
14. Finnish Institute for Health and Welfare (THL), Finland. Perinatal statistics - parturients, delivers and newborns - THL [Internet]. [cited 2022]. Available from: https://thl.fi/en/web/thlfi-en/statistics-and-data/statistics-by-topic/sexual-and-reproductive-health/parturients-deliveries-and-births/perinatal-statistics-parturients-delivers-and-newborns
15. Finnegan LP, Connaughton JFJ, Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. *Addict Dis*. 1975;2:141-158.
16. Link HM, Jones HE, Miller LA, Kaltenbach K, Seligman NS. Buprenorphine-naloxone use in pregnancy: a subgroup analysis of medication to treat opioid use disorder. *Am J Obstet Gynecol MFM*. 2021;3:100369.
17. Debelak K, Morrone WR, O'Grady KE, Jones HE. Buprenorphine + naloxone in the treatment of opioid dependence during pregnancy-initial patient care and outcome data. *Am J Addict*. 2013;22:252-254.
18. Lund IO, Fischer G, Welle-Strand GK, et al. A comparison of buprenorphine + naloxone to buprenorphine and methadone in the treatment of opioid dependence during pregnancy: maternal and neonatal outcomes. *Subst Abuse Res Treat*. 2013;7:61-74.
19. Welle-Strand GK, Skurtveit S, Jones HE, et al. Neonatal outcomes following in utero exposure to methadone or buprenorphine: a National Cohort Study of opioid-agonist treatment of pregnant women in Norway from 1996 to 2009. *Drug Alcohol Depend*. 2013;127:200-206.
20. Jansson LM, Velez ML, McConnell K, et al. Maternal buprenorphine treatment and infant outcome. *Drug Alcohol Depend*. 2017;180:56-61.
21. Keegan J, Parva M, Finnegan M, Gerson A, Belden M. Addiction in pregnancy. *J Addict Dis*. 2010;29:175-191.
22. Metz V, Jagsch R, Ebner N, et al. Impact of treatment approach on maternal and neonatal outcome in pregnant opioid-maintained women. *Hum Psychopharmacol*. 2011;26:412-421.
23. Jansson LM, Velez ML. Infants of drug-dependent mothers. *Pediatr Rev*. 2011;32:5–12; quiz 12–3.
24. Prasad M, Jones M. Medical complications of opioid use disorder in pregnancy. *Semin Perinatol*. 2019;43:162-167.
25. Kimmel SD, Del Rio C. Improving outcomes for people with injection drug-related endocarditis: are medications for opioid use disorder enough? *J Addict Med*. 2020;14:280-281.
26. Tikkanen M. Placental abruption: epidemiology, risk factors and consequences. *Acta Obstet Gynecol Scand*. 2011;90:140-149.
27. Lind JN, Interrante JD, Ailes EC, et al. Maternal use of opioids during pregnancy and congenital malformations: a systematic review. *Pediatrics*. 2017;139:e20164131.
28. Piske M, Homayra F, Min JE, et al. Opioid use disorder and perinatal outcomes. *Pediatrics*. 2021;148:e2021050279.
29. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med*. 2010;363:2320-2331.
30. Rumrich I, Vähäkangas K, Viluksela M, Gissler M, de Ruyter H, Hänninen O. Effects of maternal smoking on body size and proportions at birth: a register-based cohort study of 1.4 million births. *BMJ Open*. 2020;10:e033465.
31. Treit S, Zhou D, Chudley AE, et al. Relationships between head circumference, brain volume and cognition in children with prenatal alcohol exposure. *PLoS ONE*. 2016;11:e0150370.
32. Zedler BK, Mann AL, Kim MM, et al. Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: a systematic review and meta-analysis of safety in the mother, fetus and child. *Addict Abingdon Engl*. 2016;111:2115-2128.

How to cite this article: Kanervo MM, Tupola SJ, Nikkola EM, Rantakari KM, Kahila HK. Buprenorphine-naloxone, buprenorphine, and methadone throughout pregnancy in maternal opioid use disorder. *Acta Obstet Gynecol Scand*. 2023;102:313-322. doi:10.1111/aogs.14497

16000412, 2023, 3, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1111/aogs.14497 by Duodecim Medical Publications Ltd, Wiley Online Library on [07/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License