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ORIGINAL RESEARCH ARTICLE

Maternal opioid use during pregnancy and the risk of neonatal opioid withdrawal syndrome in the offspring

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Abstract

Introduction: Neonatal opioid withdrawal syndrome (NOWS) is caused by sudden cessation from in utero exposure to opioids. The indications for opioid use during pregnancy are diverse including medication for opioid use disorder and analgesia. The opioid dose typically depends on the indication, with higher doses used for medication for opioid use disorder and lower doses used for analgesia. The aim of this study was to investigate the relationship between maternal opioid dose during pregnancy and the risk of NOWS.

Material and Methods: We conducted a historical multicenter cohort study of neonates prenatally exposed to opioids in Eastern Denmark during a six-year period from 2013 to 2018. The data was extracted from reviewing the individual's medical record(s), which were identified through a search of the Danish National Patient Register. Four groups (quartiles) according to maternal opioid dose during the last four weeks prior to delivery were compared. Unadjusted and adjusted logistic regression analyses were conducted to examine the risk of NOWS while controlling for relevant covariates.

Results: A total of 130 in utero opioid exposed neonates were included. The majority of the pregnant patients (88%) were treated with opioids for analgesic purposes. Overall, 52% of neonates developed NOWS. The cumulative incidence of NOWS was 21%, 28%, 67% and 91% at maternal average daily dose of morphine milligram equivalent during the last four weeks prior to delivery of 0.7–14 (group I), 14.3–38.6 (group II), 40–90 (group III) and 90.9–1440 (group IV), respectively. Compared to group I the adjusted odds (aOR) of NOWS increased significantly in group III (aOR 10.6 [2.9–39.1]) and group IV (aOR 37.8 [7.6–188.2]) but not in group II (aOR 1.5 [0.4–5.2]). No cases of NOWS were reported at maternal dose less than an average daily dose of five morphine milligram equivalent during the last four weeks prior to delivery. No significant changes in the incidence of NOWS were observed between 2013 and 2018.

Abbreviations: aOR, adjusted odds ratio; cOR, crude odds ratio; MME, morphine milligram equivalent; MOUD, medication for opioid use disorder; NOWS, neonatal opioid withdrawal syndrome.

Conclusions: The odds of neonatal opioid withdrawal syndrome increased significantly as the maternal average daily dose of morphine milligram equivalent during the last four weeks prior to delivery surpassed 40.

KEYWORDS
methadone, neonatal abstinence syndrome, neonatal withdrawal syndrome, opioid, opioid, opioid analgesics, pregnancy

1 | INTRODUCTION

Prenatal exposure to opioids places neonates at risk of developing neonatal opioid withdrawal syndrome (NOWS) resulting from sudden withdrawal from intrauterine opioid exposure. Neonates with NOWS typically express dysfunction of respiratory, gastrointestinal, autonomic and nervous system regulation.[1–4]

Studies from the USA have reported a marked increase in pregnancy related use of opioid analgesics over the last two decades,[3,5,6] with corresponding manifold increase in the prevalence of NOWS.[3,7,8] However, findings reported in the scientific literature are inconsistent, with some studies reporting a dose–response relationship while others did not.[1,9–11] Furthermore, it is not well described if the risk of NOWS depends on the type of prenatal opioid exposure, but a case report from Denmark described NOWS after exposure to even small doses of Tramadol.[12]

This worrying trend accentuates the need for knowledge of the relationship between maternal opioid dose and the risk of NOWS in order to offer the most accurate guidance to pregnant patients using opioids.

The objective of this study was to investigate whether a dose–response relationship exists between prenatal opioid exposure measured as maternal average daily dose of morphine milligram equivalent (MME) during the last four weeks prior to delivery and the risk of NOWS. Furthermore, we aimed to elucidate whether the risk of NOWS differed between the different types of opioids.

Key message

The odds of neonatal opioid withdrawal syndrome increased with higher maternal average daily dose of morphine milligram equivalent (MME) during the last four weeks prior to delivery, although the correlation did not become significant until average daily dose of MME exceeded 40.

2 | MATERIAL AND METHODS

2.1 | Setting

In Denmark, all pregnant people are offered free antenatal care including visits to midwives and doctors.

Patients treated with opioids for more than seven days during pregnancy are referred to the specialized outpatient unit called the Family Center.[13] If any midwife or doctor suspects a non-prescribed use of medicine or drugs during pregnancy, they refer the patient to a Family Center. The Family Center offers frequent prenatal visits and informs about risks for the fetus. A thorough medicine and drug history is recorded at the first visit interview, and a urine drug screening is performed. In case of a non-prescribed opioid use, the local addiction center is contacted and medication for opioid use disorder (MOUD) is initiated. The opioid use during the entire pregnancy is closely monitored at every visit along with a urine drug test if indicated. We had access to the Danish Health Data Authority national database The Shared Medication Record which holds data on all Danish citizens' electronic prescriptions and medicine purchases.

Detoxification from MOUD is generally not recommended during pregnancy due to the high risk of relapse, overdose, fluctuating opioid concentrations and potential intrauterine withdrawal for the fetus reflected in the WHO statement: "women dependent on opioids should be encouraged to use opioid maintenance treatment whenever available, rather than to attempt opioid detoxification".[5] In our setting, the most frequent indication for opioid use during pregnancy is for analgesic treatment of chronic pain conditions rather than MOUD. Some chronic pain patients express a strong desire to either reduce or taper their analgesic opioid usage before delivery. The request was accommodated, if it based on an individual assessment was deemed medically and socially safe. Tapering was conducted very gradually and closely monitored for withdrawal symptoms, compliance and signs of any additional usage. Patients were monitored through frequent consultations, adjusted to meet each patient's specific needs. In cases of even mild or short-lived withdrawal symptoms, the tapering was halted, and the dosage was adjusted until withdrawal symptoms ceased.

The national guideline of the Danish Pediatric Society recommends that neonates who have been regularly exposed to opioids prenatally within the last three weeks prior to birth are admitted to the neonatal ward for observation for NOWS for a minimum of five days.[14] Environmental care during the hospitalization includes quiet and dimly lit room, swaddling and minimization of stimuli. The neonates are evaluated for abstinence using a modified Finnegan Scale, and treated according to the score.[15]

All adults included in this study identified as women at the time of delivery. When using the term "maternal" we refer to the childbearing person, irrespective of their gender identity.

2.2 | Study design

The study was conducted as a historical multicenter cohort study of neonates prenatally exposed to opioids in Eastern Denmark.

Neonates observed for NOWS at a neonatal ward were identified by searching the Danish National Patient Register for these four ICD-10 diagnoses: DP96.1 (neonatal withdrawal symptoms from maternal use of drugs), DP96.2 (withdrawal symptoms from therapeutic use of drugs in newborn), DP04.1 (newborn affected by other maternal medication), and DZ03.8 M (observation due to suspicion of prenatal substance exposure). We defined a newborn as having NOWS when they were placed in relevant pharmacological treatment.

All neonates' medical record(s) were reviewed, and in case of prenatal opioid exposure, each and every maternal medical record(s) were reviewed to extract precise information about the maternal opioid dose during pregnancy. The medical record(s) hold information on opioids prescribed by the Family Center doctor and during hospitalization. Information obtained from The Shared Medication Record served to identify opioids prescribed by other healthcare providers, including emergency physicians and the patient's general practitioner.

The included neonates were born at six different hospitals in Eastern Denmark during the six-year period from January 1st 2013 to December 31st 2018. Eastern Denmark consists of Capital Region of Denmark, Region Zealand and Funen (Region of Southern Denmark), and during this period, 197 719 neonates were liveborn in these three regions, accounting for 55.6% of all livebirths in Denmark.[16]

The Finnegan scale has been validated for use with term neonates but not with preterm neonates.[17] It has been reported that preterm infants show different symptomatology of withdrawal than their mature counterparts, making the current scoring tools difficult to use in a preterm population,[18] we have, therefore, chosen to include only the mature and late premature neonates (gestational age ≥34 weeks and 0 days). Additionally, this represents the timepoint at which obstetric interventions to delay delivery or promote fetal lung maturation are no longer pursued. The cohort included one set of twins. Since they had identical exposure, developed NOWS at the same time and were assigned the same sex at birth, we chose to count them as one neonate.

To quantify prenatal opioid exposure, we calculated the cumulative maternal opioid dose during the entire pregnancy and during the last four weeks prior to delivery. For the latter we derived the average daily dose by dividing the cumulative dose by 28. As a result, patients with the same average daily dose of MME received the same cumulative dose over the four-week period, even though the actual daily dose may have varied during that time.

For comparison across different types of opioids average daily dose was converted to morphine milligram equivalents (MME), using a conversion table that corresponds to the CDC Guideline for Prescribing Opioids for Chronic Pain (Table S1).[19]

2.3 | Statistical analyses

The study population was divided into quartiles according to cumulative maternal opioid dose during the last four weeks prior to delivery. Group I represented the lowest doses, while Group IV represented the highest doses.

A univariate logistic regression analysis was conducted to evaluate the relationship between the maternal opioid dose and the corresponding crude odds of NOWS in the neonate.

Multivariable logistic regression was conducted in order to adjust for the following, pre-selected, binary covariates; cigarette smoking at the time of birth, prior history of non-prescribed opioid use, use of psychoactive drugs at any time during the pregnancy that may contribute to neonatal maladaptation syndrome or withdrawal symptoms (psychotropic drugs, antidepressant medications including selective serotonin reuptake inhibitor, antiepileptic medications, gabapentin, benzodiazepines, or hypnotics), infant sex assigned at birth, and breastfeeding. Subsequently, we conducted a sensitivity analysis excluding breastfeeding.

To assess the extent to which unmeasured confounding may have affected the associations, we calculated the E-value based on the ORs.[20]

Logistic regression was conducted using Rstudio 4.1.2. (R Foundation for Statistical Computing, Vienna, Austria). Incidences were calculated using Microsoft Excel 2016.

3 | RESULTS

The search in the Danish National Patient Register yielded 533 neonates with one of the four predefined diagnoses. Of these, 142 had prenatally been exposed to opioids during the last four weeks prior to birth and had been admitted to the neonatal ward for NOWS observation. Twelve were excluded. Six due to insufficient information regarding maternal opioid dose during the pregnancy. Five due to prematurity and one twin. In total 130 neonates were included in the study (Figure 1). Basic characteristics and covariates are summarized in Table 1.

In total, 115 (88%) of the pregnant patients were treated with analgesic opioids due to either pre-existing chronic pain conditions ($n=86$) or pain conditions that developed during pregnancy ($n=29$). One was treated for chronic diarrhea with opium drops. Fourteen pregnant patients received MOUD with methadone or buprenorphine. Three of the chronic pain patients had previously received MOUD.

Overall, 122 (94%) of the pregnant patients were treated with only one type of opioid during the last four weeks prior to delivery.

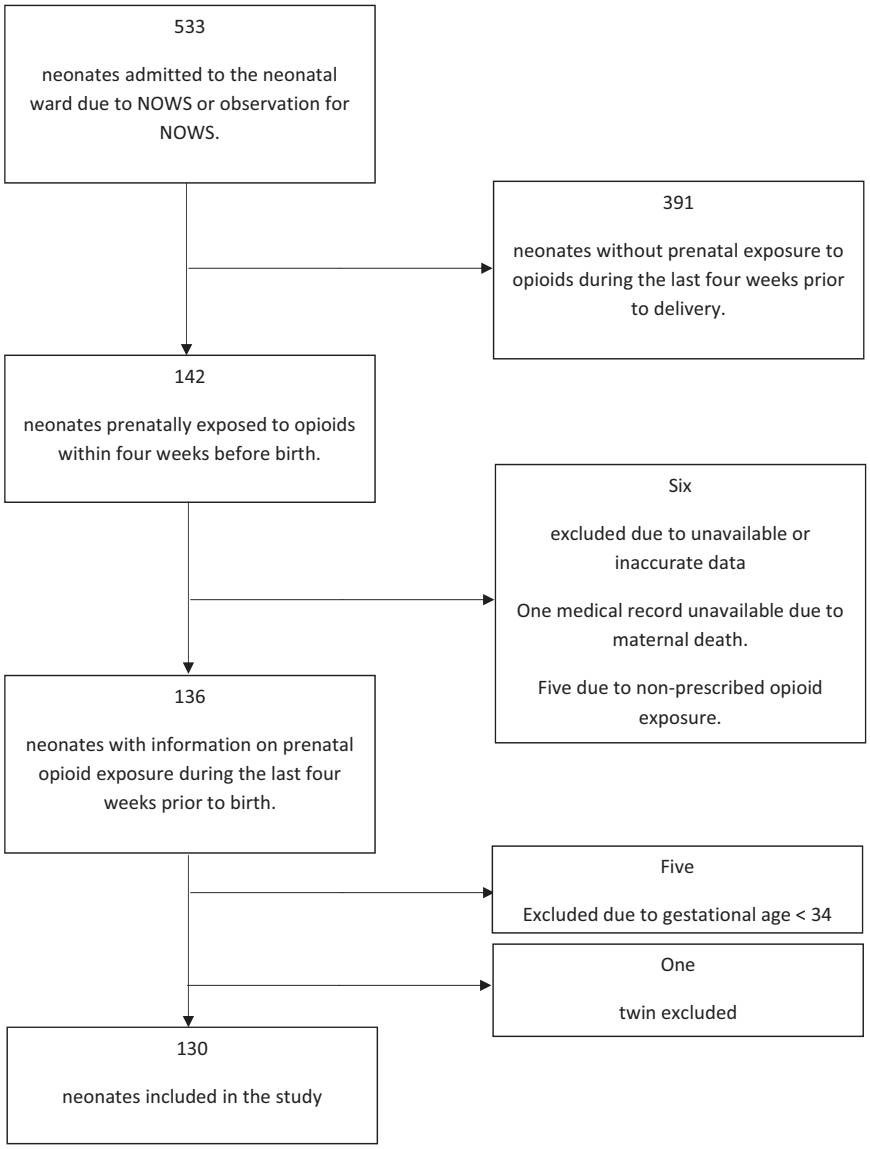

FIGURE 1 Flowchart, inclusion of neonates. NOWS, Neonatal opioid withdrawal syndrome.

Three of the 46 pregnant patients in the methadone group concurrently received codeine or morphine, but since the methadone dose accounted for >95% of MME these pregnant patients were included in the methadone group and not the poly-opioid group (Table 2).

Pregnant patients with a cumulative intake of more than 5000 MME during the last four weeks prior to delivery, corresponding to an average daily dose of 179 MME, or more than 50 000 MME throughout the entire pregnancy all received methadone or buprenorphine.

In total, 67 of the 130 neonates developed NOWS requiring pharmacological treatment (51.5%). In our study population, no cases of NOWS were reported with a maternal dose less than an average daily dose of five MME during the last four weeks prior to delivery.

The crude odds of NOWS did not differ significantly in group II compared to group I corresponding to an average daily dose of 14.3–38.6 MME (crude OR [cOR] 1.5 [0.5–4.5]). However, the odds of NOWS increased significantly in group III corresponding to an average daily dose of 40.0–90.0 MME (cOR 7.4 [2.5–22.4]) and group IV corresponding to an average daily dose of 90.9–1440.0 MME (cOR 35.9 [8.4–153.4]). After multivariable logistic regression analysis, the adjusted odds of NOWS remained significantly higher in group III (adjusted OR [aOR] 10.6 [2.9–39.1] $p < 0.001$) and group IV (aOR 37.8 [7.6–188.2] $p < 0.001$) compared to group I.

A sensitivity analysis was conducted by excluding breastfeeding from the multivariable logistic regression. The aOR decreased slightly, suggesting a limited confounding effect (Table 3). From the ORs of group III and IV (OR 8.5 and 32.9, respectively), E-values of 16.5 and 45.3 were obtained, indicating that the observed ORs of 8.5 and 32.9 could potentially be explained by an unmeasured confounder, that was associated with both the treatment and the outcome by ORs of, respectively, 16.5 and 45.3; however, weaker confounding could not do so.

We were unable to conduct the intended analysis on the different types of opioids and the odds of NOWS due to small sample size. Table 2 shows the available descriptive data for the different types of opioids. It is noteworthy that the interval between the lowest dose causing NOWS and the highest dose without NOWS is very

TABLE 1 Maternal and neonatal characteristics stratified by quartiles of opioid dose.

Group	All	I	II	III	IV
Neonates, *N*	130	33	32	33	32
Cumulative maternal MME dose during the last four weeks prior to delivery. Median (range) [IQR]	1100 (20–40320) [2136]	270 (20–392) [140]	560 (401–1080) [320]	1680 (1120–2520) [815.5]	6720 (2545–40320) [9395]
Maternal average daily dose of MME during the last four weeks prior to delivery. Median (range) [IQR]	39.3 (0.7–1440) [76.3]	9.6 (0.7–14) [5]	20 (14.3–38.6) [11.4]	60 (40–90) [29.1]	240 (90.9–1440) [335.5]
Cumulative maternal MME dose during the entire pregnancy. Median (range) [IQR]	10515 (52.5–521640) [24474]	1065 (52.5–23720) [3434.5]	5754 (605–15900) [5700]	14140 (1615–81636) [10394.5]	69420 (4250–521640) [89805]
Gestational age (weeks) Median (range)	38.9 (34.7–41.9)	38.6 (35.3–40.6)	38.9 (34.7–39.3)	38.7 (35.0–41.6)	38.9 (34.7–41.9)
Maternal cigarette smoking at delivery, *N*	44	9	9	10[a]	16[a]
Maternal history of opioid use disorder, *N*	17	1	1	2	13
Maternal use of psychoactive drugs during pregnancy, *N*	51	8	13	14	16
Breastfed on day five after birth, *N*	83	19[a]	24	23	17
Male sex, *N*	65	17	16	13	19

Abbreviations: IQR, interquartile range; MME, morphine milligram equivalent.
[a]Missing data for one mother.

large for the majority of the different types of opioid. For all other types than oxycodone and codeine it is seen that the same dose could cause NOWS in one neonate, but not in another.

As shown in Table S2 we did not observe any significant changes in the incidence of NOWS between 2013 and 2018.

4 | DISCUSSION

The odds of NOWS increased significantly as the maternal average daily dose of MME during the last four weeks prior to delivery increased, and an average daily dose of five MME was the lowest dose observed to cause NOWS.

We found that the neonates exposed to the highest quartile doses of average daily dose of MME (group IV) had a 37 times higher adjusted odds of NOWS compared to the neonates born to the quarter who took the lowest doses (group I). The neonates from group III had 10 times higher adjusted odds of NOWS compared to group I. However, we were unable to show a significant difference in the adjusted odds of NOWS in the neonates from group II compared to group I.

Thus, we are unable to demonstrate the hypothesized linear dose–response relationship between maternal average daily dose of MME during the last four week prior to delivery.

Several other studies have likewise demonstrated a significant increase in the risk of NOWS with increasing maternal opioid dose,[21–24] whereas others have not.[1,9–11] A possible explanation to why the latter studies were unable to demonstrate a significant correlation can be found in their study design. The studies included only patients in MOUD with methadone or buprenorphine which explains the much higher opioid doses compared to the analgesic doses in our study. In addition to the MOUD, some of the pregnant patients had a non-prescribed drug use,[1,9] which makes the calculation of the exact maternal opioid dose troublesome. The mean daily methadone dose was >75 mg[1,9,10] and mean daily buprenorphine dose 16.6 mg.[11] Using the conversion factor from Table S1 this corresponds to >900 MME which would place the patients in group IV, where the incidence of NOWS in our data was >90%. This was also mentioned by Seligman et al. as they referred to several studies that included a "low" daily dose group of <30 mg methadone and reported a positive correlation between maternal methadone dose and NOWS.[9]

The fact that the lowest average daily dose of MME during the last four weeks prior to delivery reported to cause NOWS in the present study was only five, accentuates the importance of being aware of the risk of NOWS, even when treating pregnant patients with low doses of opioid. To the best of our knowledge no previous study has reported such low opioid dose to cause NOWS.

Breastfeeding has previously been shown to reduce the risk of NOWS.[21,25,26] However, in our analysis, breastfeeding on the fifth day of life was only a weak confounder.

Many previously published studies on pregnant patients using opioids focus primarily on MOUD, leaving a knowledge gap in the evidence-based guidance of patients being treated with lower analgesic opioid doses. Since our results are based primarily on neonates

TABLE 2 Incidence of neonatal opioid withdrawal syndrome (NOWS), time from birth until initiation of treatment and the lowest dose with development of NOWS and highest dose without development of NOWS stratified by the different types of opioids.

Type of opioid the neonate was prenatally exposed to during the last four weeks prior to delivery	Neonates	Cumulative incidence of NOWS		Hours from birth until initiation of NOWS treatment.			Lowest cumulative maternal MME during the last four weeks prior to delivery with development of NOWS	Highest cumulative maternal MME during the last four weeks prior to delivery without development of NOWS
	N	*N*	%	Earliest	Latest	Median		
Methadone	46	33	72	4	100	26	140	6850
Morphine	20	7	35	17	66	35	280	3360
Tramadol	22	7	32	16	38	32	350	2520
Oxycodone	12	5	42	7	40	26	1575	1155
Codeine	10	2	20	28	32	30	578	315
Buprenorphine	10	7	70	11	34	20	2016	33600
Fentanyl	1	1	100			36	3360	
Oral opium solution	1	0	0					280
Poly-opioid[a]	8	5	63	25	55	36	348	500

Abbreviations: NOWS, neonatal opioid withdrawal syndrome; MME, morphine milligram equivalents.

[a]Neonates prenatally exposed to more than one type of opioid during the last four weeks prior to delivery. Three neonates were included in "methadone" group instead of the "poly-opioid" group since methadone accounted for >95% of the cumulative MME.

TABLE 3 Cumulative incidence, covariates and risk estimates of neonatal opioid withdrawal syndrome (NOWS) based on maternal average daily dose of morphine equivalents during the last four weeks prior to delivery.

	Neonates	Cumulative incidence of NOWS		Univariate logistic regression			Multivariable logistic regression including breastfeeding[a]			Multivariable logistic regression without breastfeeding[b]		
	N	*N*	%									
Total	**130**	**67**	**51.5**	**cOR**	**95% CI**	***p* value**	**aOR**	**95% CI**	***p* value**	**aOR**	**95% CI**	***p* value**
Groups												
I	33	7	21.2									
II	32	9	28.1	1.5	0.5–4.5	0.52	1.5	0.4–5.2	0.53	1.3	0.4–4.6	0.65
III	33	22	66.7	7.4	2.5–22.4	<0.001	10.6	2.9–39.1	<0.001	8.5	2.5–29.0	<0.001
IV	32	29	90.6	35.9	8.4–153.4	<0.001	37.8	7.6–188.2	<0.001	32.9	6.8–158.8	<0.001

Abbreviations: aOR, adjusted odds ratio; cOR, crude odds ratio; CI, confidence interval; NOWS, neonatal opioid withdrawal syndrome.

[a]Adjusted for the following binary covariates: cigarette smoking at the time of birth, prior history of non-prescribed opioid use, use of psychoactive drugs, breastfed on the fifth day of life and infant sex assigned at birth.

[b]Adjusted for the following binary covariates: cigarette smoking at the time of birth, prior history of non-prescribed opioid use, use of psychoactive drugs and infant sex assigned at birth.

born to pregnant patients being treated with analgesic doses (87%), our findings can serve to fill out this gap.

Our experience is that the majority of pregnant patients being treated with analgesic opioids are highly motivated to reduce their opioid dose in order to minimize their offspring's risk of NOWS. Based on our findings, the risk of NOWS plateaus below an average daily dose of 40 MME, rendering it questionable whether reducing the dosage below this dose will significantly decrease the risk of NOWS. Therefore, attempting to taper below this dose may pose an unnecessary risk to the pregnant person and the fetus, unless the individual's condition or indication for analgesic opioids calls for cessation. This aspect should be further explored in future studies.

In regards to the American studies[3,5–8] reporting marked increases in pregnancy related use of opioid analgesics and prevalence of NOWS over the last two decades, we were unable to show a similar increase in the Danish population during our study period.

This present study has several strengths and limitations. One of the most noteworthy strengths is that the knowledge of the maternal opioid dose arises from frequent clinical contact with real-time reports on the use of opioids throughout the pregnancy, rather than large register based data on redeemed prescriptions.[22,23] Access to The Shared Medication Record made it possible to monitor if the patient received opioid prescriptions from other doctors than the Family Center doctor. In addition, patients with a confirmed or suspected non-prescribed use were excluded, both increasing the data accuracy. Non-prescribed use, however, cannot be entirely ruled out. Another strength is that the study was conducted as a multicenter study with every center complying with the same nationally accepted treatment guideline thus ensuring comparability. The historical design and the sample size of 130 is a major limitation that is reflected in the width of the confidence intervals, which limits interpretation of the effect estimates. However, it is noteworthy that the search to identify the neonates prenatally exposed to opioid was based on data of >50% of all births in Denmark over a consecutive period of six years. Due to the observational nature of the study unmeasured confounding (residual confounding) may play a role and cannot be ruled out.

5 | CONCLUSION

Our analysis showed that the odds of NOWS increased with increasing maternal average daily dose of MME during the last four weeks prior to delivery, but the correlation did not reach significance until the average daily dose of MME exceeded 40. The lowest average daily dose of MME during the last four weeks prior to delivery observed to cause NOWS was five. The vast majority of the included neonates were born to pregnant patients being treated with analgesic opioids rather than MOUD. We did not observe an increase in NOWS during the six-year study period.

AUTHOR CONTRIBUTIONS

Conceived and designed the study: Vibeke Vestermark and Ulrik Schiøler Kesmodel. Data collection: Anna Warncke Kristensen, Vibeke Vestermark, Anette Kjærbye-Thygesen and Maria-Christina Eckhardt. Analysis and interpretation of results: Anna Warncke Kristensen, Vibeke Vestermark and Ulrik Schiøler Kesmodel. Drafted original manuscript: Anna Warncke Kristensen and Vibeke Vestermark. Revised and edited: Anna Warncke Kristensen, Vibeke Vestermark, Anette Kjærbye-Thygesen, Maria-Christina Eckhardt and Ulrik Schiøler Kesmodel. Figure design; Anna Warncke Kristensen. Funding acquisition: Vibeke Vestermark.

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CONFLICT OF INTEREST STATEMENT

The authors have no financial or non-financial interests to disclose.

ETHICS STATEMENT

The Danish Data Protection Agency (file no. 18–000315/082) and the Danish Patient Safety Authority (file no. 3–3013-2538/1) approved the present study on September 5, 2018.

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REFERENCES

1. Jansson LM, DiPietro JA, Elko A, Velez M. Infant autonomic functioning and neonatal abstinence syndrome. *Drug Alcohol Depend*. 2010;109:198-204.
2. McQueen K, Murphy-Oikonen J. Neonatal abstinence syndrome. *N Engl J Med*. 2016;375:2468-2479.
3. Anbalagan S, Mendez MD. *Neonatal Abstinence Syndrome*. StatPearls; 2023 http://www.ncbi.nlm.nih.gov/pubmed/31285356
4. Hudak ML, Tan RC, Frattarelli DAC, et al. Neonatal drug withdrawal. *Pediatrics*. 2012;129:e540-e560.
5. 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.
6. Epstein RA, Bobo WV, Martin PR, et al. Increasing pregnancy-related use of prescribed opioid analgesics. *Ann Epidemiol*. 2013;23:498-503.
7. Brandt L, Finnegan LP. Neonatal abstinence syndrome: where are we, and where do we go from here? *Curr Opin Psychiatry*. 2017;30:268-274.
8. Hirai AH, Ko JY, Owens PL, Stocks C, Patrick SW. Neonatal abstinence syndrome and maternal opioid-related diagnoses in the US, 2010-2017. *JAMA*. 2021;325:146-155.
9. Seligman NS, Almario CV, Hayes EJ, Dysart KC, Berghella V, Baxter JK. Relationship between maternal methadone dose at delivery and neonatal abstinence syndrome. *J Pediatr*. 2010;157:428-433.e1.
10. Jones HE, Jansson LM, O'Grady KE, Kaltenbach K. The relationship between maternal methadone dose at delivery and neonatal outcome: methodological and design considerations. *Neurotoxicol Teratol*. 2013;39:110-115.
11. Jones HE, Dengler E, Garrison A, et al. Neonatal outcomes and their relationship to maternal buprenorphine dose during pregnancy. *Drug Alcohol Depend*. 2014;134:414-417.
12. Vestermark V, Nielsen SM. Abstinenser hos nyfødte eksponeret for tramadol. [Abstinences in neonates exposed to tramadol] (In Danish, no abstract available). *Ugeskr Læger*. 2014;176:2-3.

13. Familieambulatorie-guideline; Håndtering af gravide med risikoforbrug af potentielt vanedannende medicin, alkohol eller andre rusmidler. [Family Center guideline; Management of pregnant women with risk- consumption of potentially addictive medicine, alcohol or other substances] (In Danish). (Accessed May 12, 2023) https://static1.squarespace.com/static/5467abcce4b056d72594db79/t/56547a00e4b00b10016240a6/1448376832106/Familieambulatorieguideline+25.03.15.pdf
14. Neonatale Abstinenser [Neonatal abstinenses] (In Danish). Accessed May 12, 2023. https://paediatri.dk/images/dokumenter/Retningslinjer_2021/DPS_NAS_11.01.2020.pdf
15. Finnegan LP. Neonatal abstinence. In: Nelson NM, ed. *Current Therapy in Neonatal–Perinatal Medicine*. 2nd ed. BC Decker Inc; 1990.
16. Statistics Denmark. Accessed May 12, 2023. https://www.statistikbanken.dk/statbank5a/selectvarval/saveselections.asp
17. Finnegan LP, Kron RE, Connaughton JF, et al. A scoring system for evaluation and treatment of the neonatal abstinence syndrome: a new clinical and research tool. *Basic and Therapeutic Aspects of Perinatal Pharmacology*. Raven Press; 1975:139-153.
18. Allocco E, Melker M, Rojas-Miguez F, Bradley C, Hahn KA, Wachman EM. Comparison of neonatal abstinence syndrome manifestations in preterm versus term opioid-exposed infants. *Adv Neonatal Care*. 2016;16:329-336.
19. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain-United States, 2016. *JAMA*. 2016;315:1624-1645.
20. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167:268-274.
21. Dryden C, Young D, Hepburn M, MacTier H. Maternal methadone use in pregnancy: factors associated with the development of neonatal abstinence syndrome and implications for healthcare resources. *BJOG*. 2009;116:665-671.
22. Patrick SW, Dudley J, Martin PR, et al. Prescription opioid epidemic and infant outcomes. *Pediatrics*. 2015;135:842-850.
23. Desai RJ, Huybrechts KF, Hernandez-Diaz S, et al. Exposure to prescription opioid analgesics in utero and risk of neonatal abstinence syndrome: population based cohort study. *BMJ Clin Res*. 2015;350:h2102.
24. Shirel T, Hubler CP, Shah R, et al. Maternal opioid dose is associated with neonatal abstinence syndrome in children born to women with sickle cell disease. *Am J Hematol*. 2016;91:416-419.
25. Mangat AK, Schmölzer GM, Kraft WK. Pharmacological and non-pharmacological treatments for the neonatal abstinence syndrome (NAS). *Semin Fetal Neonatal Med*. 2019;24:133-141.
26. McQueen K, Taylor C, Murphy-Oikonen J. Systematic review of newborn feeding method and outcomes related to neonatal abstinence syndrome. *J Obstet Gynecol Neonatal Nurs*. 2019;48:398-407.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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