Received: 28 October 2020 | Revised: 23 August 2021 | Accepted: 30 August 2021

DOI: 10.1111/aogs.14268

AOGS Acta Obstetricia et Gynecologica Scandinavica

ORIGINAL RESEARCH ARTICLE

The association between intrapartum opioid fentanyl and early breastfeeding: A prospective observational study

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Abstract

Introduction: Intrapartum opioids in labor may interfere with the early breastfeeding phase and cause breastfeeding difficulties. This study examines the effects of intrapartum fentanyl given intravenously (IV) or through epidural analgesia (EDA) on early breastfeeding.

Material and methods: This is a prospective observational study conducted in a regional maternity unit. We included 1101 healthy mothers of term singleton babies in vertex presentation born between 2016 and 2018 (468 nulliparous and 633 multiparous). The main data were collected prospectively, and additional data were retrieved from hospital records. The main outcome measures were exclusive breastfeeding at discharge, spontaneous suckling, and breastfeeding problems after birth. We assessed the outcomes in four groups categorized by intrapartum opioid exposure: none, IV fentanyl, EDA fentanyl and IV+EDA fentanyl. We also analyzed the dose–response relation of fentanyl administered by epidural or IV and early breastfeeding. Ultimately, we dichotomized the IV fentanyl group into two groups (≤200 μg and >200 μg) to further study the effect on early breastfeeding.

Results: The odds of non-exclusive breastfeeding were doubled with EDA fentanyl (odds ratio [OR] 2.45, 95% CI 1.34–4.48, $p = 0.004$) and four times higher with IV+EDA fentanyl (OR 4.20, 95% CI 2.49–7.09, $p < 0.001$) compared with no opioid exposure. Spontaneous suckling was negatively associated with intrapartum fentanyl use ($p < 0.001$) irrespective of mode of administration. When the IV fentanyl doses exceeded 200 μg compared with less than 200 μg, we found a reduction in exclusive breastfeeding (81% vs. 89%; $p = 0.014$) and spontaneous suckling (68% vs. 83%; $p < 0.001$) and an increase in breastfeeding problems (41% vs. 27%; $p = 0.004$).

Conclusions: Fentanyl in labor is associated with breastfeeding difficulties. However, IV fentanyl in low doses (≤200 μg) seems to affect breastfeeding less than EDA fentanyl and is therefore a viable alternative when labor analgesia is needed. This could be most relevant for multiparous women, where a shorter labor is expected. More

Abbreviations: EDA, epidural analgesia; IV, intravenous; OR, odds ratio.

research is needed to determine the optimal dose and route of administration of fentanyl for labor analgesia.

KEYWORDS
breastfeeding, epidural analgesia, fentanyl, hospitalization, labor analgesia

1 | INTRODUCTION

The positive effects of breastfeeding on maternal and child health are well documented.[1] Early initiation of breastfeeding increases both the likelihood of exclusive breastfeeding and the overall duration of breastfeeding.[2] However, intrapartum opioids may interfere with the early breastfeeding phase. Observational studies have reported decreased alertness and inhibited suckling at the breast in newborns who have been exposed to opioids intrapartum, resulting in delayed initiation of breastfeeding.[3,4]

The use of labor epidural analgesia (EDA) has increased during the last 10 years as the use of intravenous (IV) opioids has declined.[5–7] However, EDA may not be desired by the woman, or may be contraindicated, technically impossible, or simply not available.[3,5] Systemic opioids are frequently used for labor analgesia when EDA is not an option. These include IV fentanyl, a synthetic opioid with a rapid onset of action, a relatively short duration, and no active metabolites.[8] All opioids readily cross the placenta by passive diffusion and have been shown to compromise fetal well-being during labor.[5,9] Researchers have raised the concern that fentanyl may disturb the sequence of nine innate, predictable newborn behavioral stages that occur when babies are in uninterrupted skin-to-skin contact with mothers during the normal period of wakefulness after birth.[5,10–13] Research has shown that attenuated neonatal neurobehavioral organization, when measured soon after birth, could be related to delayed initiation of optimal suckling behavior and self-regulation.[12,13] In addition to uninterrupted skin-to-skin care, mother–infant proximity and interaction are essential for the establishment of milk production and for sustained breastfeeding.[3,13,14] Other factors known to affect breastfeeding during hospitalization are intrapartum oxytocin use,[5] parity,[15] the father's role, and social support from nursing professionals.[16,17] While some studies have found a negative association between EDA fentanyl and both optimal suckling behavior[10,12] and exclusive breastfeeding rates at discharge,[18,19] others have found no adverse breastfeeding consequences of intrapartum doses of fentanyl up to 150 μg in an EDA solution.[10,11] These disparities show that more research is needed on the use of fentanyl in labor. In the present study, we aimed to (a) compare exclusive breastfeeding at discharge by fentanyl exposure (IV, EDA, or none); (b) examine associations between exclusive breastfeeding and clinical and demographic factors; and (c) compare spontaneous suckling, newborn temperature at 2 h, need for formula supplementation, and length of postpartum stay by fentanyl exposure.

Key message

Fentanyl in labor in doses up to 200 μg may be less harmful to breastfeeding than higher doses, whether given intravenously or by epidural. In cases where epidural is not available or desired, IV fentanyl can be an option for pain relief in labor.

2 | MATERIAL AND METHODS

2.1 | Design and setting

We conducted a prospective observational study between October 1, 2016 and December 31, 2018. Participants were consecutively evaluated before labor. Eligible participants were healthy mothers with a single pregnancy, planned vaginal birth, and no language barrier or cognitive impairment. The women received oral and written information about the study in pregnancy week 36 and on admission to the labor department. All the participants gave written consent before labor. The criteria for inclusion in the analyses were low-risk vaginal births from 37 to 42 weeks of gestation and healthy babies weighing at least 2500 g at birth and cared for with the mother on the postnatal ward. Of 1271 eligible mother–newborn pairs, 170 (13.4%) were excluded for reasons listed in Figure 1.

Sørlandet Hospital has 1800–2000 deliveries per year. Intravenous fentanyl was introduced in our labor ward more than 10 years ago in connection with a research project. This had an impact on EDA use at our hospital, which, in 2017, was lower than the average use in Norwegian hospitals (19% vs. 32%).[7] The level of parents' education is high in Norway in general.[7] All families are covered by comprehensive social security benefits, so there are no financial barriers to accessing maternity care.[7] A national survey on infant nutrition showed that four out of five infants were still breastfed at the age of 6 months.[20]

The midwives at Sørlandet Hospital are trained to leave the newborn undisturbed on the mother's chest for at least 2 h after birth or long enough to self-attach to the mother's breast. In the postnatal department, rooming-in is practiced during the hospital stay, with an option for the mother's partner to stay with her and the baby if space permits. The mother–newborn pairs in our study group were not separated at any time during their hospital stay.

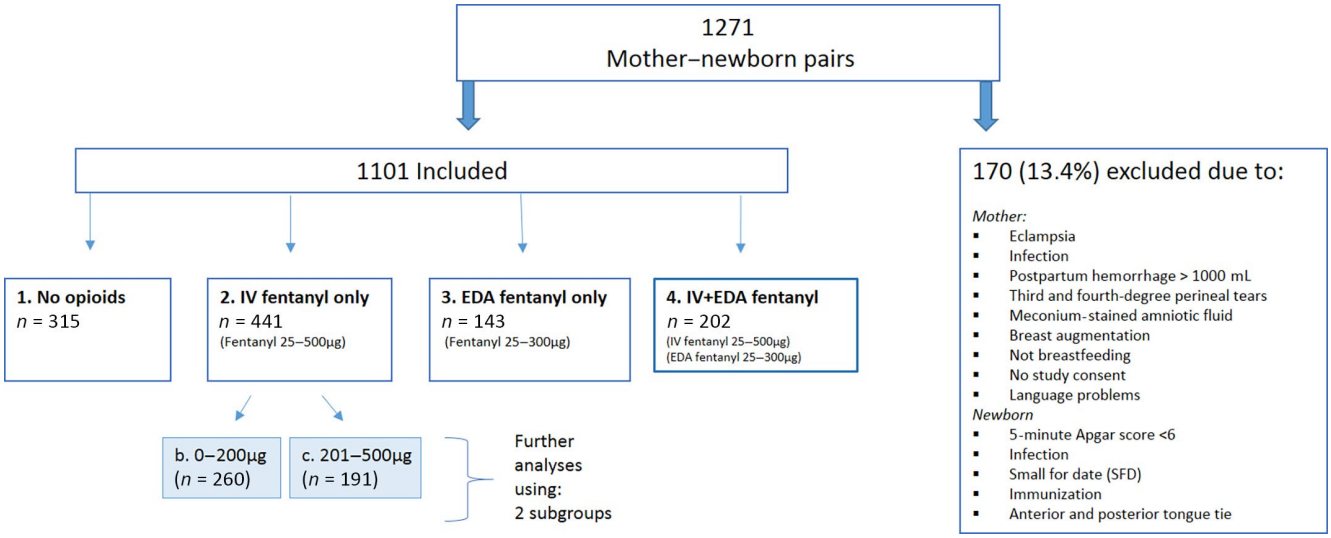

FIGURE 1 Flow chart about the analysis process [Color figure can be viewed at wileyonlinelibrary.com]

All the mothers received information about normal infant signs of readiness to feed and guidance on how to find an optimum position for breastfeeding and ensure that the baby is suckling effectively. Staff were available to observe and guide mothers on breastfeeding throughout their stay. Formula milk was given to breastfed babies only on medical indication or the mother's wish because of breastfeeding problems. The staff were instructed not to influence patients' choice of pain relief during labor.

2.2 | EDA and IV fentanyl

The labor unit's standard 50-ml epidural mixture consists of 100 µg fentanyl, 50 mg ropivacaine, and 43 ml NaCl 0.9% and is administered by a continuous infusion pump at rates from 8 to 15 ml/h with bolus doses given as needed. The maximum allowable EDA fentanyl dose is 300 µg, which is reached if the woman receives 150 ml of the mixture.

Pharmacological properties of fentanyl (rapid metabolism and no active metabolites) are such that half-life elimination for adults takes 3–4 h.[21] The blood fentanyl concentration from fentanyl in EDA is dependent on conversion by the cytochrome system in liver and excretion of inactive breakdown products.[22] Intravenous fentanyl administered by midwives starts with bolus doses of 25 µg, administered four times within 20 min (25 µg × 4). After the bolus doses (100 µg), 25 µg can be given every 20 min based on the mother's need for pain relief. The maximum allowable IV fentanyl dose is 500 µg and the last dose is given no later than 30 min before expected time of birth.

2.3 | Study measures

We developed a questionnaire to be filled in by the midwife in charge because the hospital records did not give us all the required data. The items included in the questionnaire were based on previous breastfeeding and fentanyl labor analgesia studies.[5,6] Exclusive breastfeeding at discharge was the primary outcome variable, based on the WHO/UNICEF Baby Friendly Hospital Initiative.[23] Other variables included (a) patient demographics and labor characteristics (Table 1), (b) labor analgesia data, and (c) breastfeeding data (time, duration, and quality of first feed; prevalence of breastfeeding problems noted during the postpartum stay; use of formula milk or nipple shield because of breastfeeding problems; length of stay; and whether or not the mother was given an appointment at the breastfeeding follow-up clinic). Ten midwives working in the maternity unit tested the questionnaire before it was administered, and the final version was adjusted according to their feedback. In addition, relevant obstetric data (parity; induction; operative delivery; and obesity, defined as body mass index ≥35 kg/m^2) were collected from the program PARTUS™, which is the data program used for patient documentation in the labor department.

2.4 | Fentanyl exposure during labor

The choice of analgesia was based on the mother's wishes and her need for pain relief during the active phase of labor (established labor: from 4 cm cervical dilation and regular contractions). The participants were divided into four groups according to intrapartum opioid exposure during the active phase of labor: (a) no opioids, (b) IV fentanyl only, (c) EDA fentanyl only, and (d) IV+EDA fentanyl.

2.5 | Statistical analyses

Descriptive statistics are used to present the demographic and clinical characteristics of the sample. Continuous variables are described as median and range and categorical variables as numbers and percentages, as well as *t* test, chi-squared test, and Pearson's correlation

TABLE 1 Patient demographics, labor characteristics of the study groups (*N* = 1101)

	Non-opioid (*n* = 315)	IV fentanyl (*n* = 441)	EDA fentanyl (*n* = 143)	EDA +IV fentanyl (*n* = 202)	*p* value
Age (year), mean	32	31	30	30	0.161
Smoking, *n* (%)	9 (3)	18 (4)	6 (4)	7 (4)	0.731
Education, *n* (%)					0.397
Primary school	26 (8)	34 (8)	9 (6)	19 (10)	
High school	103 (33)	148 (34)	50 (35)	76 (38)	
College, university	179 (58)	246 (56)	84 (59)	104 (52)	
Nationality, *n* (%)					0.593
Norwegian	258 (82)	368 (84)	119 (83)	173 (87)	
Non-Norwegian	57 (18)	72 (16)	24 (17)	27 (14)	
Para, *n* (%)					<0.001
Nulliparous	79 (25)	181 (41)	81 (60)	127 (63)	
Multiparous	236 (75)	260 (59)	62 (43)	75 (37)	
BMI >35, *n* (%)	6 (2)	11 (3)	11 (8)	14 (7)	<0.001
Induction, *n* (%)	49 (16)	116 (26)	69 (48)	81 (40)	<0.001
Intrapartum oxytocin use, *n* (%)	16 (5)	55 (13)	56 (39)	69 (35)	<0.001
Operative delivery[a], *n* (%)	9 (3)	32 (7)	40 (28)	47 (23)	<0.001
5 min Apgar score ≤7	0	2	3	5	0.009
Newborn rectal temperature (°C), mean	37.1	36.8	36.8	36.7	0.511
Length of postpartum stay (days), mean					
Nulliparous	2.7	2.8	3.0	3.1	<0.001
Multiparous	1.8	2.0	2.3	2.6	<0.001

[a]Forceps or vacuum delivery.

coefficient, as appropriate. On means and percentages, 95% CI are given. To explore the dose–response relation of fentanyl administered by epidural or IV and early breastfeeding, we modeled IV fentanyl and EDA fentanyl as two separate continuous values, each able to independently contribute to the binary outcomes modeled to examine the continuous effect of fentanyl. We also subdivided the IV fentanyl group into two groups (≤200 μg and 201–500 μg) to further study the effect on early breastfeeding. (Figure 1). The value was chosen because this refers to two ampoules of fentanyl, which is usually offered as a "2-h pain relief package" in daily clinical practice where a shorter labor is expected. Our primary aim was to construct a model to assess possible associations between discretized and continuous fentanyl and breastfeeding and adjust it for possible confounders. Possible associations between exclusive breastfeeding and relevant variables and between spontaneous suckling and relevant variables were modeled using binary logistic regression analysis. Variables that were known to be possible confounders, and therefore tested in our model, were age, obesity, oxytocin use, operative delivery, parity, induction, education, and opioid exposure. Variables tested for association with the outcome in univariate analyses that reached the level of statistical significance ($p < 0.05$) were entered into a multiple regression model, where dichotomized fentanyl (≤200 μg and 201–500 μg) was used to model the outcome. In the dose–response model of fentanyl, interactions between IV fentanyl and EDA fentanyl as continuous quantities and their respective intercept terms (ie, presence or absence of IV fentanyl and EDA fentanyl) were explored and removed from the model when highly non-significant. In some cases non-significant associations were retained in dose–response models to assure appropriate adjustment or to clarify interpretation of other model parameters. For exclusive breastfeeding, we included operative delivery and oxytocin use in the multivariate model despite these variables not being significant in the univariate analyses because the literature shows that they are known to be associated with receiving EDA and IV fentanyl. The strengths of association in all models were measured on the odds ratio (OR) scale with 95% CI. Values of *p* less than 0.05 were considered significant. The statistical software used was SPSS version 25 for PC (IBM Corporation, Armonk, NY, USA) and R version 3.6 (R Core Team, 2020).

2.6 | Ethical approval

The study followed the Helsinki Protocol (WMA Declaration of Helsinki at www.wma.net). The study was approved by the Regional Committee for Ethics in Medical Research, Region South on

April 8, 2016 (2016/1349 B) and the Norwegian Data Inspectorate (2017/53515).

3 | RESULTS

Of the 1101 participants, 441 (40%) received IV fentanyl, 143 (13%) EDA fentanyl, 202 (18%) IV+EDA fentanyl and 315 (29%) did not receive any intrapartum opioids. In the IV+EDA fentanyl group, the last IV fentanyl dose was given more than 8 h before birth in 37 (18%) cases. The women's demographics and labor characteristics are described in Table 1. More than 88% had a normal spontaneous vaginal delivery, and the rest were vacuum- or forceps-assisted vaginal deliveries. Our data, which included only healthy newborns, gave no indication of any association between intrapartum fentanyl and respiratory depression. No baby required naloxone.

The median IV fentanyl dose was 175 μg (range 25–500 μg). The mean length of time from the first to the last dose of IV fentanyl was 2:04 h. The median dose of EDA fentanyl was 100 μg (range 10–320 μg) and the mean length of use was 6:35 h, with an average infusion rate of 10 mL/h. The mean time from last dose IV fentanyl to birth was 1:9 h.

Intrapartum opioid exposure was negatively associated with exclusive breastfeeding at discharge ($p < 0.001$) with ORs of 1.80 (95% CI 1.09–2.97) for IV fentanyl, 2.45 (95% CI 1.34–4.48) for EDA fentanyl, and 4.20 (95% CI 2.49–7.09) for IV+EDA fentanyl, compared with non-exposed mothers in the univariate analysis (Tables 2, 3). Dose–response analyses showed that each additional microgram of IV fentanyl or milliliter of EDA fentanyl was associated with a statistically significant increase in risk for non-exclusive breastfeeding (Table 2). Because EDA does not include only fentanyl, we cannot compare the relative effect sizes of the estimated parameters for EDA and IV fentanyl (μg for IV fentanyl and mL for EDA) against one other.

Other variables significantly associated with exclusive breastfeeding were parity, education, and induction. In the multivariable logistic regression analysis, education, and opioid exposure remained significantly associated with exclusive breastfeeding (Table 2). Although the use of IV fentanyl was less common among the nulliparas than the multiparas (41% vs. 59%), the use of EDA fentanyl was significantly higher among the nulliparas (60%) than among the multiparas (43%) ($p < 0.001$).

Exclusive breastfeeding at discharge was strongly correlated with spontaneous suckling in the first 3 h postpartum (Tables 2 and 3). The proportion of babies not suckling at all in the first 3 h, either spontaneously or with active intervention to help them attach to the breast, was lowest (12%, $n = 38$; 95% CI 8%–15%) in the non-opioid group and highest (45%, $n = 91$; 95% CI 38%–49%) in the IV+EDA fentanyl group (Table 3). When the suckling occurred, the time from birth to first suckling and duration showed the same trend in the four groups (Table 3). There was a significant difference in spontaneous suckling between the groups (no opioids vs. IV fentanyl vs. EDA fentanyl vs. IV+EDA fentanyl), both among nulliparas (76% vs. 64% vs. 63% vs. 54%; $p = 0.014$) and multiparas (93% vs. 88% vs. 76% vs. 57; $p < 0.001$). Dose–response analyses showed that for each additional microgram of IV fentanyl the risk of failure to suckle spontaneously increased a statistically significant amount. Interestingly, however, the number of milligrams of EDA fentanyl did not change the expected outcome, only the presence of lack of EDA fentanyl (Table 2).

In the IV fentanyl group, 58% ($n = 250$) of the participants received less than 200 μg IV fentanyl. Analyses of the IV fentanyl subgroups (≤200 μg, median 115, range 25–200 μg vs. 201–500 μg, median 310, range 225–500 μg) (Figure 1) showed that there was a clear reduction in exclusive breastfeeding (89% vs. 81%; $p < 0.001$) and spontaneous suckling (83% vs. 68%; $p < 0.001$), and an increase in breastfeeding problems (27% vs. 41%; $p = 0.01$) when the IV fentanyl doses exceeded 200 μg. However, the difference between the groups in terms of the use of formula supplement was not significant ($p = 0.161$).

The use of formula milk as the result of breastfeeding problems during hospitalization was also significantly associated with opioid use (Table 3). Nobody in the no opioid group used a nipple shield, compared with 10 (2%) in the IV fentanyl group, 5 (3%) in the EDA fentanyl group, and 12 (6%) in the the IV+EDA fentanyl group. Follow up at the hospital outpatient breastfeeding clinic was required less often by mothers in the no opioid group (6%, $n = 19$) than in the IV fentanyl group (11%, $n = 46$), EDA fentanyl group (13%, $n = 19$), and IV+EDA fentanyl group (15%, $n = 31$) ($p < 0.005$). The mean length of hospital stay was 2.2 days for multiparas and 2.9 days for nulliparas (Table 1).

4 | DISCUSSION

Intrapartum opioid fentanyl exposure was significantly associated with reduced exclusive breastfeeding at discharge irrespective of mode of administration among healthy nulliparous and multiparous mothers with vaginal delivery at Sørlandet Hospital. There was also a significant reduction in spontaneous suckling and an increase in breastfeeding problems and use of formula milk when IV fentanyl above 200 μg, EDA fentanyl, or IV +EDA fentanyl were used.

Our findings of a negative association between EDA fentanyl and both non-exclusive breastfeeding rates at discharge[18,19] and optimal suckling behavior support the findings of earlier studies.[10,12] The dose–response analyses indicated that increasing intrapartum opioid fentanyl use regardless of route of administration was associated with risk for non-exclusive breastfeeding. Previous studies[10,11] have found that intrapartum EDA fentanyl doses up to 150 μg have no adverse breastfeeding consequences and that total fentanyl dose has a stronger impact on breastfeeding than the duration of exposure.[10] By contrast, in our study, where the mean EDA fentanyl dose was only 127 μg, we found a significant association with early breastfeeding problems. This difference might be explained by the fact that our study had more participants than previous studies. While some absorption of fentanyl from the epidural space occurs with EDA fentanyl, we were only able to estimate this amount because

TABLE 2 Associations of non-exclusive breastfeeding at discharge and failure to suckle spontaneously within 3 hours after birth; dichotomized fentanyl models and dose–response models

	Univariate analysis			Multivariable analysis			Dose-response models		
Variables	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Non-exclusive breastfeeding									
Age	0.99	0.95–1.03	0.65				0.02		0.38
Obesity	0.51	0.26–1.06	0.07						
Oxytocin use	1.17	0.76–1.79	0.48	0.79	0.50–1.26	0.33	−0.27	−0.76 to 0.20	0.27
Operative delivery	1.21	0.73–1.99	0.46	0.87	0.51–1.51	0.63	0.22	−0.33 to 0.82	0.45
Parity	0.67	0.48–0.94	0.021	1.28	0.89–1.86	0.19	−0.20	−0.61 to 0.22	0.35
Induction	1.84	1.30–2.61	0.001	1.51	0.99–2.32	0.06	0.57	0.20–0.93	0.003
Education			0.030			0.033	−0.40	−0.66 to 0.13	0.003
Primary school	1.00								
High school	1.23	0.25–6.13	0.80	1.03	0.20–5.26	0.97			
University level	1.05	0.24–4.89	0.95	0.87	0.18–4.15	0.86			
Opioid exposure			<0.001			<0.001	NA	NA	NA
No	1.00								
IV fentanyl	1.80	1.09–2.97	0.021	1.68	1.01–2.80	0.046			
EDA fentanyl	2.45	1.34–4.48	0.004	2.19		0.018			
IV+EDA fentanyl	4.20	2.49–7.09	<0.001	3.65	1.15–4.20	<0.001			
Opioid exposure (dose–response)					2.07–6.42				
IV fentanyl (μg) (slope)							0.003	0.001–0.38	<0.001
EDA fentanyl (ml) (slope)							0.001	0.0005–0.002	<0.001
Failure to suckle spontaneously									
Age	0.97	0.34–1.00	0.038				00.02	−0.05 to 0.01	0.18
Education			0.28				0.20	−0.02 to 4.31	0.08
Primary school	1.00								
High school	0.41	0.13–1.32	0.14						
University level	0.49	0.15–1.60	0.24						
Obesity	0.56	0.29–1.07	0.08						
Induction	1.38	1.03–1.86	0.032	1.07	0.78–1.48	0.68	−0.07	−0.40 to 2.56	0.66
Oxytocin use	1.81	1.30–2.53	<0.001	1.01	0.69–1.47	0.98	0.12	−0.26 to 5.14	0.53
Operative delivery	2.11	1.44–3.11	<0.001	1.09	0.71–1.68	0.70	0.03	−0.41 to 4.71	0.88
Parity	3.28	2.46–4.37	<0.001	2.64	1.94–3.60	<0.001	0.96	0.62–1.31	3.78
Opioid exposure			<0.001			<0.001			
No	1.00								
IV fentanyl	2.18	1.44–3.29	<0.001	1.86	1.23–2.88	0.003	NA	NA	NA
EDA fentanyl	3.53	2.15–5.80	<0.001	2.57	1.50–4.42	<0.001			
IV+EDA fentanyl	6.31	4.05–9.84	<0.001	4.32	2.67–6.98	<0.001			
Opioid exposure (dose-response)									
IV fentanyl (μg) (intercept)							−0.08	−0.54 to 0.37	0.73
EDA fentanyl (ml) (intercept)							−0.92	−1.42 to 0.44	<0.001

(Continues)

TABLE 2 (Continued)

	Univariate analysis			Multivariable analysis			Dose-response models		
Variables	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
IV fentanyl (μg) (slope)							−0.003	−0.01 to 0.002	<0.001
EDA fentanyl (ml) (slope)							−0.004	−0.01 to 0.004	0.30
IV EDA interaction (slope)							0.00003	0–0.00007	0.05

TABLE 3 Outcome variables in four intrapartum opioid analgesia groups (*N* = 1101)

Four intrapartum opioid analgesia groups (*N* = 1101)					
	Non-opioid (*n* = 315) 0 μg	**IV fentanyl (*n* = 441) 185 μg (175–195 μg)**	**EDA fentanyl (*n* = 143) 126 μg (116–138 μg)**	**EDA +IV fentanyl (*n* = 202) 316 μg (289–344 μg)**	
Fentanyl μg, Mean (CI)	**% (95% CI) *n***	**% (95% CI) *n***	**% (95% CI) *n***	***% (95% CI) n***	***p value***
Exclusive breastfeeding	92 (90–96) 291	87 (84–90) 384	83 (76–89) 119	74 (68–80) 150	<0.001
Suckling spontaneously[a]	88 (85–92) 277	78 (74–82) 343	69 (60–76) 98	55 (48–62) 111	<0.001
Time (min) from birth to first suckling (mean)	0:52	1:04	1:11	1:11	
Total suckling time (min) after birth (mean)	0:34	0:33	0:26	0:26	
Breastfeeding problems	19 (18–27) 61	32 (23–35) 143	45 (40–48) 64	48 (40–54) 97	<0.001
Formula milk because of breastfeeding problems[b]	10 (7–16) 30	18 (16–25) 88	26 (25–38) 37	25 (23–32) 551	<0.001

[a]Spontaneous suckling: Ability of infants to initiate spontaneous feeding behavior unassisted when placed in a prone position between their mother's breasts. Suckling and rooting movements began at a mean of 15 min, hand-to-mouth movements at 34 min, and spontaneous suckling at 55 min.[40]

[b]Newborns needing formula milk for medical reasons not included.

the concentration in maternal blood was not simultaneously measured. With IV fentanyl, the dose added to maternal blood is known. Our results indicate that there is an association between fentanyl dose during labor and early breastfeeding and that the dose, route of administration, and duration of EDA and IV fentanyl exposure may all be important factors. The fact that the last dose of IV fentanyl is given at least 30 min before birth and EDA is continued until just after birth may also play a role. In our study, the mean time from last dose IV fentanyl to birth was 1:9 h. The clinical impact of the added effect of IV and EDA fentanyl in group 4 was striking: these babies seldom suckled spontaneously had more difficulty feeding effectively, and were least likely to be exclusively breastfed on discharge. Their mothers had received by far the largest cumulative doses of fentanyl. Our EDA use began to rise to national levels around 2018, and reached 33% in 2019 (EDA use in all Norwegian hospitals was 35.5% in 2019).

Many women appreciate some form of pain relief in labor and prefer a choice of options.[24] Knowledge about the breastfeeding consequences of alternative pharmacologic routes of administration, such as IV fentanyl, is therefore needed. Current opinion holds EDA as the reference standard for pain relief during labor, but compared with IV opioid analgesia it also requires more resources to implement and to manage its adverse effects (low blood pressure, loss of bladder control, itchy skin, and headache are all more common with EDA)[25] The possible adverse effects of IV fentanyl are sedation, nausea or vomiting, itchy skin, and respiratory depression.[26] In addition, the presence of additional IV lines and catheter(s) when EDA is used, compared with IV fentanyl, is likely to affect the mother's ability to follow WHO recommendations on mobility and an upright position during labor (which has been shown to reduce the need for cesarean sections).[27] Therefore, IV fentanyl may be a viable alternative, especially if a short labor is anticipated, EDA is contraindicated, or the availability of anesthetist services is limited. Healthcare providers should counsel women on the potential side effects of opioids and on the alternative pain relief options available, as well as the advantages of low EDA fentanyl doses (i.e., "walking epidural"), which allow an active labor.[24] However, it is important to keep in mind that unwanted pain might interfere with bonding and lactation even more than treatment for pain relief. The right choice of pain relief method is important because IV fentanyl alone may not be sufficient to relieve pain in all labors, particularly induced labor and operative vaginal delivery, where EDA may help women to cope better.

To the best of our knowledge, no studies have explored the effects of both IV fentanyl and EDA fentanyl on early breastfeeding

in a large group of parturients. By including women not exposed to fentanyl intrapartum, we were able to assess the effect of any intrapartum fentanyl exposure on breastfeeding, in addition to comparing IV and EDA fentanyl. The relatively large IV fentanyl use in our hospital allowed analysis of the dose–response relation between IV fentanyl and early breastfeeding, on which we found no previous reports. Our study included only healthy mothers with a singleton low-risk vaginal birth and healthy babies. In addition, over 13% of the mother–newborn pairs were excluded from the study for various reasons that may have affected breastfeeding. All maternity units in Norway follow the same national guidelines for obstetric care, so we believe that the findings can be generalized to the entire country. The use of a standardized questionnaire made it possible to collect data on important breastfeeding variables rather than relying on data retrieved retrospectively from hospital records, which often lack information.

A limitation of the present study is the small sample sizes of nulliparas with no opioid exposure and multiparas with EDA fentanyl exposure, respectively. This may have prevented the findings from reaching statistical significance for some variables in the groups of nulliparas and multiparas alone. It should also be noted that this is a single-center study undertaken at a hospital with a clinical tradition that differs from most hospitals in the country regarding the use of IV fentanyl. Furthermore, this was not a randomized controlled trial, so the groups may have differed in ways not captured in the study. One smaller study has shown that a combination of multiple interventions during labor may be associated with a shorter duration of exclusive breastfeeding.[28] In our study, the IV+EDA fentanyl group had the highest number of inductions, the highest intrapartum oxytocin use, the most operative deliveries, and the most instances of obesity. Factors such as age, obesity, parity, induction, and operative delivery may have had effects on breastfeeding that were not revealed in the regression analysis. Results of previous studies do not confirm the effect of intrapartum oxytocin on breastfeeding;[5,29] however, almost any intervention on the natural process of birthing interferes with the evolution of bonding and lactation. [28] Another limitation is that our results are based on fentanyl administered by midwives, so our findings may not be extrapolated to countries with patient-controlled epidural and IV analgesia. Pain is a multifaceted concept, and there are many aspects we have not been able to uncover in this study. One question remains unanswered in our study: did the women in the IV+EDA fentanyl group have more difficult, painful labors, or were they less tolerant of pain and so in need of stronger analgesia?

5 | CONCLUSION

Our data show that IV fentanyl up to 200 μg in labor was associated with a lower prevalence of early breastfeeding problems than EDA fentanyl, regardless of dose. Therefore, IV fentanyl can be a viable alternative for labor analgesia, especially if a short labor is anticipated. The association between fentanyl exposure by different routes and negative effects on breastfeeding should be considered when establishing guidelines for fentanyl use and when informing mothers about the risks and benefits of various forms of pain relief in labor. We have now changed our policy on analgesia in labor to encourage earlier use of EDA in cases where the midwife anticipates a prolonged labor or if 200 μg fentanyl is not sufficient. The findings from our study can also be used to ensure that mothers exposed to higher amounts of intrapartum opioids, and therefore at risk of experiencing breastfeeding problems, are identified, that they receive support during an important time for the mother and for her bonding with the newborn, and to avoid negative breastfeeding outcomes. More research is needed to determine the optimal dose and route of administration of fentanyl for labor analgesia.

ACKNOWLEDGMENTS

We would like to thank all the staff in the study hospital for their assistance in conducting the study.

AUTHOR CONTRIBUTIONS

HO, TOT, LTE, RM and IV planned and designed the study. HO carried out the data collection. HO, LTE and IV performed the quantitative data analysis. HO drafted the paper. HO, TOT, LTE, RM and IV contributed to writing the manuscript. DMS performed the dose-response analysis. All the authors reviewed and approved the final manuscript.

CONFLICTS OF INTEREST

None.

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How to cite this article: Oommen H, Oddbjørn Tveit T, Eskedal LT, Myr R, Swanson DM, Vistad I. The association between intrapartum opioid fentanyl and early breastfeeding: A prospective observational study. *Acta Obstet Gynecol Scand*. 2021;00:1–9. https://doi.org/10.1111/aogs.14268