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Management of neonates exposed prenatally to opioids: Impact of a developmental care program implementation

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Abstract

Background:

Traditional approaches to management of neonates prenatally exposed to opioids are based on the use of pharmacotherapy (PT), adjusted to evolution of infant symptoms. Newer approaches focused on non-pharmacological care (NPC) are emerging, but there is little evidence on the active policies to implement to ensure their widespread practice. The primary objective of the study was to assess whether the implementation of a developmental care program in our neonatal medicine department had an impact on the management of these infants during hospitalization, notably exposure to NPC.

Method:

Observational study in a tertiary perinatal center. Data collected during hospitalization for infants with in utero opioid exposure included admission in the parents-infant unit (PIU) of the maternity ward, exposure to NPC and PT, occurrence of neonatal opioid withdrawal syndrome (NOWS), length of hospital stay (LOS) and feeding type at discharge. The impact of the intervention was measured by comparing three 6-year periods, the first preceding the implementation of a formalized developmental care program (2003-2008); the second following implementation of the program (2009-2014); the third after consolidation of the program (2015-2020).

Results:

258 infants prenatally exposed to opioid were recorded. From the first to the third period, admission rate in the PIU was comparable (68 % to 73 %, $p = 0.95$). Exposure to NPC (37 % to 84 %, $p < 0.001$) increased, whereas exposure to PT (40 % to 15 %, $p = 0.002$) and LOS (13 [9-18] days to 8 [6-11] days, $p = 0.003$) decreased. NOWS occurred in 141 (55 %) infants (63 % to 47 %, $p = 0.10$). In these infants, decrease in PT was also observed (64 % to 34 %, $p = 0.02$). After adjustment for perinatal confounders, hospitalization in the PIU (OR 3.23 [1.36; 7.66]; $p = 0.008$), and the 2015-2020 period (OR 5.11 [2.06; 12.64]; $p = 0.004$) were associated with absence of PT.

Conclusions:

An active policy, supporting the training and warranting the practice of NPC, is essential to reduce medication usage and length of hospitalization in infants exposed in utero to opioids.

1.Introduction

In recent years, the consumption of opioids has surged, both through illicit drug use and prescription opioids, particularly in the context of addiction treatment (medication for opioid use disorder) or non-cancer pain management [1]. Over the past two decades, the use of opioids among pregnant women has significantly increased, mirroring the epidemic seen in the general population. This trend has been most prominently observed in the United States, where the prevalence of opioid use disorder at delivery has quadrupled [2]. Similar data have also been reported in Canada and to a lesser extent in other countries [3].

Neonatal opioid withdrawal syndrome (NOWS) - characterized by the presence of at least two typical clinical signs among gastrointestinal dysfunction, hypertonia, tremor, irritability, fragmented sleep and excessive crying [4] - occurs in 48 % to 94 % of infants exposed to opioids in utero [5]. Management of infants exposed to opioids in utero involves a combination of nonpharmacological care (NPC) and pharmacotherapy (PT) [6]. Adoption of NPC in all newborns as the first-line approach is emergent strategy, which potentially allows to reduce exposure to PT for the most severe cases [7]. A few studies suggested the favorable effect of this approach, particularly in terms of parenting stress [8], while emphasizing the benefits in reducing the duration and costs of hospitalization [9–11]. However, data on efficacy and safety of this strategy are limited. Furthermore, there is limited information on the factors that contribute to the development of NOWS in this context.

Developmental care interventions, that are NPC in nature, can be condensed into five key components: protection of infant sleep; pain and stress management; developmental support activities including positioning, feeding and skin-to-skin care; integration of parents in their child's care and promotion of a healing environment [12–14]. Our neonatal medicine department transitioned to a structured practice of developmental care [15]. This was possible thanks to a training in individualized developmental care for newborns, funded by our institution. After implementation of this program and a training certification of healthcare professionals working in intensive or intermediate neonatal care units, practice of individualized developmental care was extended to all units within the department, including the parents-infant unit (PIU) of the maternity ward, where newborns exposed to opioids are typically admitted.

This study is part of a quality improvement project aimed to increase the practice of developmental care in the neonatal medicine department. The primary objective of the study was to assess whether the implementation of this developmental care program had an impact on the management of newborns exposed to opioids in utero during hospitalization, notably exposure to NPC.

2.Methods

2.1.Population

This observational study was conducted at the neonatal medicine department of a tertiary perinatal center. All live-born infants who had been exposed to opioids in utero and were admitted to the department from January 1, 2003, to December 31, 2020, were included in the study.

2.2.Provision of antenatal care

Screening for drug use during pregnancy, notably prenatal opioid use, was encouraged in our country since 2005, as part of a government plan to prepare for birth and parenthood. The plan allowed for the financing of a systematic early prenatal interview during the first trimester of pregnancy, by a midwife or a physician, to assess the overall health of the pregnant woman, the medical follow-up of the pregnancy and to identify situations of vulnerability in the mother and father, including addictions. This interview allowed the woman or couple to be referred to support and assistance systems, as the “Parenting and Drug Use” unit, established in our University Hospital Centre in 1997 [16]. This interdisciplinary team comprises midwives, obstetrician- gynecologists, pediatricians, and child psychiatrists. The midwife plays a crucial role in coordinating the care provided by various health professionals, including scheduling appointments for pregnancy monitoring, drug use assessment, and adherence to medication for opioid use disorder. Additionally, the midwife provides social and psychological support, organizes addiction care with psychotropic medications if necessary, and offers guidance on childbirth preparation and postnatal infant care. Support services can be accessed through practitioners, social workers, institutions, associations, private centers, or offices. The primary objective is to collaborate with existing professionals who have established relationships with the mother or couple. Preanesthetic consultations and pediatric assessments are offered a few weeks prior to delivery, followed by a visit to the PIU to discuss hospitalization and infant care arrangements. The midwife maintains a confidential notebook containing summary personal information for the healthcare team's reference.

2.3.Provision of postnatal care

After birth, newborns exposed to opioids in utero were primarily admitted to the PIU, a specialized section of the neonatal medicine department [17]. Infants with a gestational age <34 weeks, birth weight <1800 g, or exhibiting respiratory distress, as well as those whose mother did not deliver at our institution, were initially admitted to the neonatal intensive care unit or intermediate care unit, according to somatic vulnerability. During hospital stay, the pediatrician and nurse provided ongoing support and education to the mother/couple, teaching them to recognize signs and triggers of NOWS and assisting with infant regulation.

NOWS evaluation was based on the Finnegan score [18]. NPC was the first-line approach, utilizing environmental and behavioral strategies to enhance infant comfort. A low-stimulation environment was created in individual, quiet, and dimly lit rooms, with limited access to nursing staff and visitors. Supportive care measures included swaddling, prone positioning, slow rocking, facilitated tucking, prolonged skin-to- skin contact, and non-nutritive sucking. Breastfeeding was encouraged, particularly for mothers receiving methadone or buprenorphine. Ongoing regular consumption of alcohol and ongoing use of heroin or cocaine were contraindications to breastfeeding. In cases where three consecutive Finnegan scores exceeded 8, indicative of NOWS, PT may be initiated [19]. Morphine hydrochloride was typically used as the first- line agent, with a starting dose of 0.3 mL/kg every 4 h (0.36 mg/kg/ day). Subsequent doses were increased by 0.1–0.2 mL/kg based on Finnegan score progression, up to a maximum of 0.80 mg/kg/day. When the dosage remained stable for 48 h with Finnegan scores below 8, treatment weaning commenced, consisting of a

daily reduction of 10 to 20 % in dosage as long as scores remained stable. Chlorpromazine was mostly considered as a second-line agent if morphine was insufficient in controlling withdrawal symptoms, using a 4 % oral solution administered every 8 h at a starting dosage of 1–2 mg/kg/day. Hospital discharge occurred after 2 days without treatment, provided that infant follow-up was organized through the local network, and ongoing addiction care was provided to the mother.

2.4. Implementation and dissemination of developmental care in the department of neonatal medicine

The department of neonatal medicine was awarded for Newborn Individualized Developmental Care and Assessment Program (NIDCAP) level II in 2008. This program integrates all aspects of developmental care, it increases maternal closeness and involvement in infant care and parental confidence in caregiving [20–22]. The program in the department is overseen by a steering committee that convenes quarterly. The committee facilitated the establishment of a developmental care network, comprising nurses who have received training in developmental care provided by NIDCAP-certified professionals. Regular training sessions have been conducted since 2014 to ensure a minimum of 10 referent nurses are part of the network. This network has played a crucial role in disseminating newborn behavior observation skills and providing developmental care across all functional units of the department, including the PIU of the maternity ward [15].

2.5. Data collection

Neonates exposed to opioids in utero were identified from our hospital-based database. The “Parenting and Drug Use” unit collected antenatal data using a standardized questionnaire. Routine urine drug screening during pregnancy is not performed in our country. When the interdisciplinary prenatal team suspected under-reporting of consumption by the mother, the coordinating midwife mentioned to carry out drug testing on the neonate in the confidential notebook. This information was provided to the mother before birth and the sample was collected after maternal consent.

In-utero exposure to opioids was defined as at least one of the following: maternal heroin use, medication for opioid use disorder with methadone or buprenorphine, or prescription of opioids for analgesic purposes. Multiple drug consumption by the mother was defined as the use of at least two substances, including an opioid and excluding tobacco. Associated substances considered were alcohol, cocaine, cannabis, and benzodiazepines [23].

2.6. Outcome measures

The primary end-point was the proportion of infants exposed to NPC, whether or not they developed NOWS. Exposure to NPC was determined based on nurses' documentation of supportive or developmental care. All nursing records, whether digital or paper-based, were meticulously reviewed, including observations, supervision notes, patient knowledge, or transmission pieces. NPC was defined as a supportive care to soothe the infant, adapt feeding or environment, or advice to parents to help them to assist their infant.

Secondary outcomes included the incidence of PT, feeding type at discharge, and hospital length-of-stay (LOS). Pharmacotherapy was defined as the use of a medication, opioid or non-opioid, to treat NOWS. Feeding type at discharge, considered in the absence of contraindication to breastfeeding, was classified into 3 categories: exclusive breastfeeding, combination of formula and breastfeeding and exclusive formula. LOS was calculated from the birth date to home discharge. LOS for children transferred to another hospital, to a social hotel, or to a family for legal placement was not considered because these durations are affected by issues unrelated to opioid withdrawal.

Three six-year periods were established (Fig. 1):

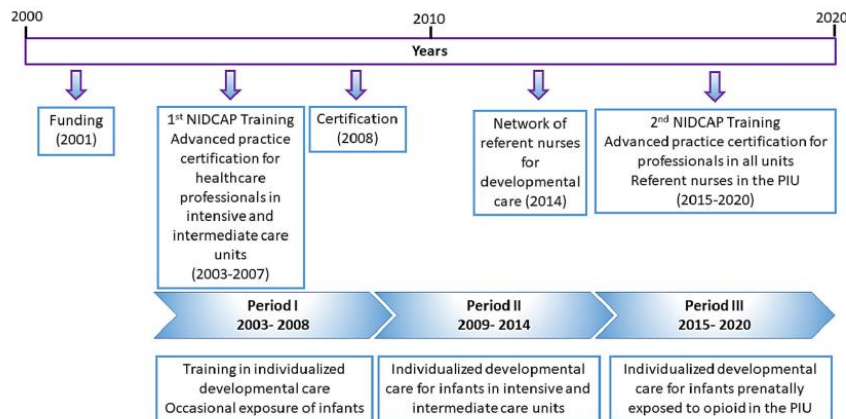


Fig. 1. Implementation and consolidation of the developmental care program in the neonatal medicine department and exposure of infants to developmental care during the study periods, according to the units of hospitalization.
NIDCAP: newborn individualized developmental care and assessment program; PIU: parents-infant unit of the maternity ward.

Period 1 (2003–2008): training to a structured developmental care program (NIDCAP), with professionals certified to advanced practice in individualized developmental care in the neonatal intensive care and intermediate care units at the end of the period. During this period, newborns hospitalized in these units were occasionally exposed to individualized developmental care, ie, developmental care based on behavioral observation, mainly for the purposes of training health professionals. Newborns hospitalized in other units of the department, including the PIU, were not exposed to individualized developmental care. However, they were occasionally exposed to developmental care, but not based on formal behavioral observation.

Period 2 (2009–2014): implementation of a network of referent nurses for developmental care in the neonatal intensive care and intermediate care units. During this period, newborns hospitalized in neonatal intensive care and intermediate units were regularly exposed to individualized developmental care, notably those below 28 weeks gestation or with major illnesses. Newborns hospitalized in other units were occasionally exposed.

Period 3 (2015–2020): second NIDCAP training to extend advanced practice certification in individualized developmental care to professionals of all units of the department, including the PIU, and extension of the network of referent nurses to the PIU. During this period, newborns hospitalized in the PIU were regularly exposed to individualized developmental care, notably those prenatally exposed to opioids.

2.7. Statistics

Between-period comparisons were made using Kruskal-Wallis and the chi-squared test. In cases of significant difference, paired comparisons were made for with Bonferroni method correction to account for the multiplicity of tests. Univariate and multivariate logistic regression analyses were performed to study the influence of each covariate on the judgment criteria. The model was constructed by a step-by-step procedure based on the likelihood ratio test (input and output thresholds =0.20). The adjusted odds ratios and their 95 % confidence intervals were calculated. The quality of the model was estimated by the Hosmer- Lemeshow adequacy test. Values are expressed as numbers (%) or medians (Q25; Q75). $P < 0.05$ were considered statistically significant. Statistical analysis was performed with SAS Version 9 software (SAS Institute, Cary, NC).

2.8. Ethical considerations

The study was approved by the institutional review board of our University Hospital Centre (IRB-MTP-2020-12-202000670). In accordance with national legislation and institutional requirements, written informed consent to participate in this study was not required from the participants or the participants' legal guardians.

3. Results

3.1. Population

From January 2003 to December 2020, 258 neonates (from 250 pregnancies), born after in utero opioid exposure, were admitted to the department of neonatal medicine. >85 % of pregnancies had regular follow-up. Delivery took place in our institution in 228 cases (inborn neonates, 88 %). For neonates, sex ratio was 0.93, and gestational age at birth 38.7 [36.7–40.0] weeks, including 28 % of preterm birth. Birthweight was 2710 [2270–3150] g, including 20 % of intrauterine growth restriction, according to Olsen curves [24]. In most cases (71 %), newborns were hospitalized in the PIU, while hospitalization in neonatal intensive care unit or intermediate care unit was required for prematurity, low birthweight or congenital malformation. Death occurred in 3 neonates (1.2 %): 1 neonate (40+3 weeks) from multiple organ failure following severe birth asphyxia; 1 neonate (36+0 weeks) from bilateral congenital thrombosis of the renal veins and cerebral haemorrhagic lesions; 1 very premature infant (27+6 weeks) from severe necrotizing enterocolitis. Perinatal characteristics were comparable across the study periods (Table 1).

Table 1
Perinatal characteristics.

	2003–2020	2003–2008	2009–2014	2015–2020	P
Maternal characteristics	<i>N</i> = 250	<i>N</i> = 84	<i>N</i> = 89	<i>N</i> = 77	
Social data					
Age, years	32 [27–36]	31 [27–35]	32 [27–36]	31 [29–37]	0.45
Living in a couple	203 (85)	67 (88)	72 (85)	64 (83)	0.70
Precarious housing ^a	18 (7)	4 (5)	5 (6)	9 (12)	0.21
Medical background					
Psychiatric illness	27 (11)	9 (11)	8 (9)	10 (13)	0.64
Other chronic disease	74 (30)	26 (31)	23 (26)	25 (32)	0.61
Previous pregnancies					
Miscarriage	87 (36)	34 (42)	23 (27)	30 (41)	0.09
Intrauterine fetal death	17 (7)	7 (9)	7 (8)	3 (4)	0.46
NOWS	28 (14)	6 (10)	12 (17)	10 (15)	0.51
Pregnancy					
Parity ^b	3 [2–4]	3 [2–4]	3 [2–4]	3 [2–4]	0.41
Normal course	155 (62)	58 (69)	49 (55)	48 (62)	0.17
Late/irregular follow-up	37 (15)	9 (11)	14 (16)	14 (18)	0.38
Multiple pregnancy	8 (3)	3 (4)	1 (1)	4 (5)	0.32
Threatened premature labor	49 (20)	14 (17)	19 (21)	16 (21)	0.72
Preeclampsia	6 (2)	3 (4)	1 (1)	2 (3)	0.60
Diabetes ^c	11 (4)	5 (6)	5 (6)	1 (1)	0.29
Newborn characteristics	<i>N</i> = 258	<i>N</i> = 87	<i>N</i> = 90	<i>N</i> = 81	
Birth					
Inborn ^d	228 (88)	77 (89)	81 (90)	70 (86)	0.76
Unplanned home birth	5 (2)	2 (2)	1 (1)	2 (3)	0.74
Cesarian delivery	92 (36)	31 (36)	31 (34)	30 (37)	0.92
Gestational age, weeks	38.7 [36.7; 40.0]	39.0 [36.6–40.3]	38.7 [36.7–39.9]	38.6 [36.7–39.9]	0.57
Preterm birth	71 (28)	23 (27)	24 (27)	24 (30)	0.89
Male	124 (48)	40 (46)	41 (46)	43 (53)	0.68
Birth weight, g	2710 [2270–3150]	2880 [2330–3240]	2770 [2260–3130]	2590 [2200–3040]	0.23
IUGR ^e	52 (20)	14 (16)	23 (26)	15 (19)	0.27
Birth head circumference, cm	33 [32–34]	33 [32–34]	33 [32–34]	33 [31–34]	0.31
Microcephaly ^f	29 (12)	9 (11)	8 (9)	12 (15)	0.55
5 min Apgar score	10 [8–10]	10 [8–10]	10 [9–10]	10 [9–10]	0.79
Hospitalization					
Initial admission					0.95
PIU of the maternity ward	182 (71)	59 (68)	64 (71)	59 (73)	
Other units	76 (29)	28 (32)	26 (29)	22 (27)	
Congenital malformation	15 (6)	3 (3)	4 (4)	8 (10)	0.21
In-hospital death	3 (1)	1 (1)	2 (2)	0 (0)	0.78
Discharge					0.51
Home	199 (77)	65 (75)	73 (81)	61 (75)	
Transfer to another hospital	33 (13)	14 (16)	7 (8)	12 (15)	
Social hostel	15 (6)	6 (7)	5 (6)	4 (5)	
Legal infant placement in a family	8 (3)	1 (1)	3 (3)	4 (5)	

Values are medians [Q25, Q75] or numbers (%).

Abbreviations: NOWS, neonatal opioid withdrawal syndrome; IUGR, intrauterine growth restriction; PIU: parents-infant unit.

^a Homelessness or homeless hostel.

^b Including the current pregnancy.

^c Including gestational diabetes.

^d Defined as occurring in our University Hospital Centre.

^e Defined as birth weight < 3rd centile according to Olsen curves [24].

^f Defined as head circumference < 3rd centile according to Olsen curves [24].

3.2. Substances used during pregnancy

Daily use of opioids throughout pregnancy was reported in 237 (95 %) mothers, mainly methadone (46 %) and buprenorphine (44 %). Multiple drug consumption was observed in 52 % of pregnancies, and 22 % of mothers used 2 opioids or more. The associated substances were, in order of frequency, cannabis (26 %), cocaine or crack and alcohol (16 % each), and benzodiazepine (8 %). From the first to the third period, the most notable changes were a decline in the use of buprenorphine, while the usage of opioid analgesics exhibited an increase (Table 2). Drug testing were carried out on 105 (42 %) infants, including 38 (44 %) performed in period 1, 34 (38 %) in period 2, and 33 (41 %) in period 3 ($p = 0.73$). They showed the presence of an undeclared substance in 9 cases (8.6 %): opioids -excluding a medication for maternal opioid use disorder- in 8 cases and a drug containing a benzodiazepine in 1 case.

Table 2
Substances used during pregnancy.

	2003–2020 (n = 250)	2003–2008 (n = 84)	2009–2014 (n = 89)	2015–2020 (n = 77)	P
Opioids					
Daily consumption during pregnancy	237 (95)	80 (95)	87 (98)	70 (91)	0.60
Opioid substance					
Heroin	54 (22)	23 (27)	16 (18)	15 (19)	0.36
Buprenorphine	111 (44)	51 (61)	37 (42)	23 (30)	<0.01 ^a
Median dosage (mg/d)	4 [2–8]	4 [1–8]	4 [2–8]	5 [2–8]	0.50
Medadone	116 (46)	32 (38)	41 (46)	43 (56)	0.08
Median dosage (mg/d)	60 [31–90]	50 [35–100]	55 [35–70]	60 [30–90]	0.94
Analgesic opioids	37 (15)	5 (6.0)	12 (13)	20 (26)	<0.01 ^a
MDC	129 (52)	41 (49)	41 (46)	47 (61)	0.13
≥2 Opioids	56 (22)	21 (25)	16 (18)	19 (25)	0.46
Opioid + non opioid	108 (43)	37 (44)	34 (38)	37 (48)	0.43
Non opioid substances					
Alcohol	39 (16)	12 (14)	14 (16)	13 (17)	0.90
Cocaine (and crack)	41 (16)	7 (8.3)	18 (20)	16 (21)	0.05
Cannabis	64 (26)	17 (20)	17 (19)	30 (39)	0.01
Benzodiazepine	21 (8)	9 (11)	5 (5.6)	7 (9.1)	0.47
Tobacco	198 (79)	62 (74)	69 (78)	67 (87)	0.11

Values are medians (Q25, Q75) or numbers (%).

Abbreviations: MDC, multiple drug consumption.

Paired comparisons with Bonferroni method correction: ^ap < 0.05 between 2003 and 2008 and 2015–2020.

3.3. Management of infants exposed to opioids in utero

In the overall population, NPC ($p < 0.001$) increased, whereas PT ($p = 0.002$) and LOS ($p = 0.003$) decreased from the first to the third period. Maximal values for Finnegan scale were comparable ($p = 0.42$). Exclusive formula at discharge was less frequent ($p = 0.04$), but without significant difference between periods (Fig. 2).

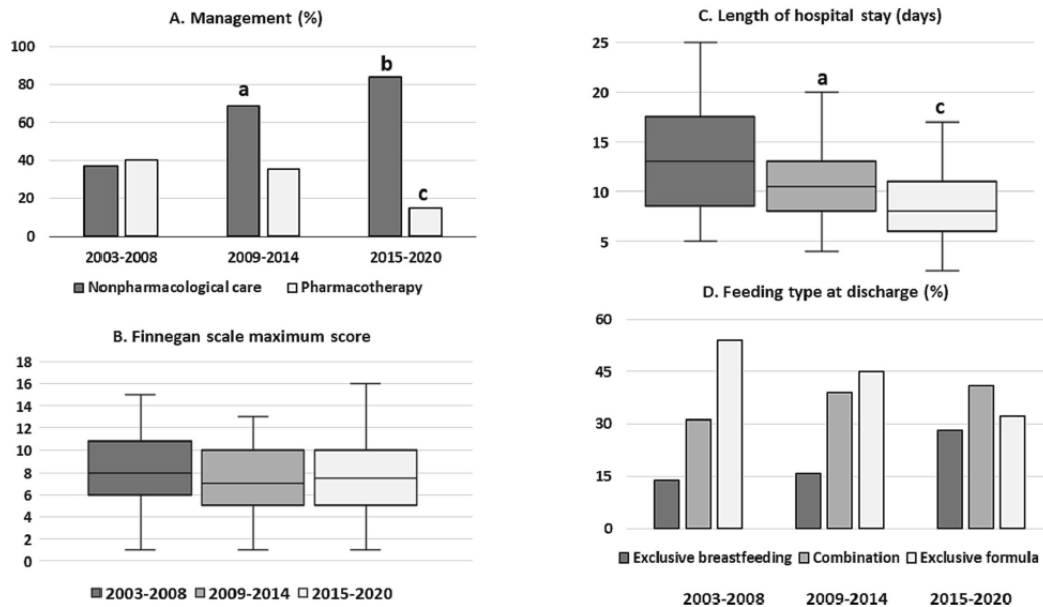


Fig. 2. Evolution of hospitalization characteristics in infants exposed to opioids in utero (2003–2020). 1 A. Nonpharmacological care and pharmacotherapy (N = 258). 1B. Maximal values for Finnegan scale (N = 258). 1C. Length of hospital stay among neonates admitted in the parent-infant unit (PIU) of the maternity ward and discharged home (N = 181). 1D. Feeding type at discharge excluding infants with contraindication to maternal breastfeeding (N = 179).

The line within the box shows the median value, while the box indicates the interquartile distance (25th and 75th centiles).

Paired comparisons with Bonferroni method correction: ^ap < 0.05 between 2003 and 2008 and 2009–2014, ^bp < 0.05 between 2003 and 2008 and 2015–2020, ^cp < 0.05 between 2003 and 2008 and 2015–2020 and between 2009 and 2014 and 2015–2020.

NOWS occurred in 141 (55 %) newborn infants (Table 3). Maternal opioid use was known before birth for all but two newborns, where this use was reported after the onset of symptoms. In this patient population, we observed from the first to the third period an increase in management with NPC only ($p = 0.003$), with a decrease in the prescription of PT (0.022). These changes in practice did not impact the maximum weight loss during hospitalization ($p = 0.53$) or hospital LOS ($p = 0.36$).

Table 3
Care provided in infants exposed to opioids in utero with NOWS.

	2003–2020 (n = 258)	2003–2008 (n = 87)	2009–2014 (n = 90)	2015–2020 (n = 81)	P
NOWS occurrence	141/258 (55)	55/87 (63)	48/90 (53)	38/81 (47)	0.10
Management					
Exposure to NPC	112 (79)	32 (58)	42 (87)	38 (100)	<0.01 ^{a, b}
NPC only	62 (44)	20 (36)	16 (33)	26 (68)	<0.01 ^{a, c}
PT	79 (56)	35 (64)	32 (67)	12 (32)	<0.01 ^{a, c}
Medications					
Age at start of treatment, day	3 [2–4]	3 [2–4]	2 [1–3]	2 [0–5]	0.27
Treatment duration, day	12 [9–15]	11 [9–14]	12 [9–13]	19 [12–37]	0.04
Number of medications					<0.01
One	61 (43)	32 (58)	23 (48)	6 (16)	
Two or more	18 (13)	3 (5)	9 (19)	6 (16)	
First-line agent					
Morphine hydrochloride	68 (48)	29 (53)	30 (63)	9 (24)	<0.01 ^{a, c}
Maximum dosage (mg/kg/d)	0.36 [0.30–0.49]	0.33 [0.30–0.44]	0.39 [0.30–0.50]	0.40 [0.36–0.63]	0.19
Chlorpromazine	6 (4.2)	4 (7.3)	1 (2.1)	1 (2.7)	0.51
Maximum dosage (mg/kg/d)	1.3 [1.0–2.0]	1.7 [1.3–2.3]	1.0 [1.0–1.0]	1.3 [1.3–1.3]	0.43
Sufentanil	5 (3.6)	2 (3.7)	1 (2.1)	2 (5.3)	0.85
Maximum dosage (µg/kg/h)	0.20 [0.09–0.38]	0.20 [0.01–0.40]	0.38 [0.38–0.38]	0.14 [0.09–0.20]	0.74
Clinical end-points					
Maximum weight loss (% birthweight)	7.8 [6.0–9.8]	8.6 [5.4–10.3]	7.1 [6.4–9.2]	8.3 [5.8–9.3]	0.53
Management with NPC only (%)	7.4 [6.1–9.2]	7.2 [5.4–9.4]	7.2 [6.8–9.2]	8.3 [6.4–9.3]	0.87
Management with NPC and PT (%)	8.1 [5.8–10.1]	9.5 [5.5–11.5]	7.0 [6.0–9.3]	8.1 [5.5–9.2]	0.25
Seizures	2 (1.4)	1 (1.8)	1 (2.1)	0 (0)	0.63
Discharge					
Length of hospital stay, days	14 [11–19]	16 [12–19]	15 [11–19]	12 [10–23]	0.36
Treatment at hospital discharge					
Morphine hydrochloride	6 (4.3)	4 (7.3)	2 (4.2)	0 (0)	0.24
Chlorpromazine	9 (6.4)	2 (3.7)	4 (8.3)	3 (7.9)	0.57

Values are medians (Q25, Q75) or numbers (%).

Abbreviations: NOWS, neonatal opioid withdrawal syndrome; NPC, nonpharmacologic care; PT, pharmacotherapy.

Paired comparisons with Bonferroni method correction: ^a $p < 0.05$ between 2003 and 2008 and 2015–2020, ^b $p < 0.01$ between 2003 and 2008 and 2009–2014, ^c $p < 0.01$ between 2009 and 2014 and 2015–2020.

3.4. Factors associated with NOWS

A summary of univariate analyses examining factors associated with the occurrence of NOWS can be found in Table 4 (left panel). In multivariate analysis, factors associated with NOWS were single motherhood (OR 2.54 [1.11; 5.81]; $p = 0.03$), maternal methadone use during pregnancy (OR 3.10 [1.77; 5.45]; $p < 0.01$), increased gestational age (per week) at birth (OR 1.16 [1.05; 1.27]; $p < 0.01$), and the 2003–2008 period compared to the most recent 2015–2020 period (OR 2.64 [1.32; 5.27]; $p = 0.02$). The area under the curve of the model was 0.71, with chi-squared value of Hosmer-Lemeshow goodness-of-fit test equal to 5.31 ($p = 0.62$).

3.5. Factors associated with PT in neonates with NOWS

Univariate analyses for PT in neonates with NOWS are summarized in Table 4(right panel). In multivariate analysis, factors associated with the need for PT were maternal benzodiazepine use during pregnancy (OR 15.15 [1.83; 125.08]; $p = 0.01$), absence of hospitalization in the PIU (OR 3.23 [1.36; 7.66]; $p = 0.008$), and the 2003–2014 periods compared to the most recent 2015–2020 period (OR 5.11 [2.06; 12.64]; $p = 0.004$). The area under the curve of the model was 0.74, with chi-squared value of Hosmer-Lemeshow goodness-of-fit test equal to 1.23 ($p = 0.75$).

Table 4
Factors associated with NOWS and with the need for PT in neonates with NOWS.
Univariate analyses.

	<i>Factors associated with NOWS</i> <i>Whole population (N = 258)</i>			<i>Factors associated with PT</i> <i>Infants with NOWS (N = 141)</i>		
	NOWS Absent (n = 117)	NOWS Present (n = 141)	P	PT No (n = 62)	PT Yes (n = 79)	P
Maternal characteristics (n = 250)						
Single motherhood	15 (13)	32 (23)	0.04	16 (26)	16 (20)	0.56
Substances used during pregnancy						
Heroin	19 (16)	35 (25)	0.12	12 (19)	23 (29)	0.14
Buprenorphine	55 (47)	56 (40)	0.29	23 (37)	33 (42)	0.70
Methadone	37 (32)	79 (56)	<0.01	35 (56)	44 (56)	1.00
Analgesic opioids	23 (20)	14 (10)	0.04	10 (16)	4 (5.1)	0.05
MDC	50 (43)	79 (56)	0.04	32 (52)	47 (59)	0.44
≥ 2 Opioids	18 (15)	38 (27)	0.04	14 (23)	25 (32)	0.31
Alcohol	19 (16)	20 (14)	0.78	10 (16)	10 (13)	0.73
Cocaine (and crack)	19 (16)	22 (16)	1.00	8 (13)	14 (18)	0.58
Cannabis	25 (21)	39 (28)	0.31	19 (31)	20 (25)	0.61
Benzodiazepine	4 (3.4)	17 (12)	0.02	1 (2)	16 (20)	<0.01
Tobacco	85 (73)	113 (80)	0.20	54 (87)	59 (75)	0.10
Newborn characteristics						
Gestational age, weeks	37.4 ± 3.3	38.5 ± 2.6	<0.01	38.5 ± 2.5	38.5 ± 2.7	0.90
IUGR (<3rd centile)	24 (21)	28 (20)	1.00	8 (13)	20 (25)	0.10
Care course characteristics						
Inborn delivery	105 (90)	123 (87)	0.67	59 (95)	64 (81)	0.02
Hospitalization in the PIU of maternity ward	86 (73)	96 (68)	0.42	50 (81)	46 (58)	<0.01
Periods			0.12			<0.01
2003–2008	32 (27)	55 (39)		20 (32)	35 (44)	
2009–2014	42 (36)	48 (34)		16 (26)	32 (41)	
2015–2020	43 (37)	38 (27)		26 (42)	12 (15)	

Values are means ± standard deviation or numbers (%).

Abbreviations: NOWS, neonatal opioid withdrawal syndrome; PT: pharmacotherapy; MDC, multiple drug consumption; IUGR: intrauterine growth restriction; PIU: parents-infant unit.

4. Discussion

Our study demonstrates that the management of infants exposed to opioids in utero admitted to our institution has undergone significant changes over the past 18 years. Adoption of NPC has become widespread, hospitalization length of stay has shortened, and the prescription of PT has decreased by 50 %.

Data about psychoactive drug use during pregnancy are sparse in our country. A recent study carried out among pregnant women in care centers specializing in drug addiction observed a decline in the use of heroin and medication for opioid use disorder, while cannabis and cocaine use increased, to a similar extent as we noted in our study [25]. We observed consistent levels of in utero opioid exposure across the three study-periods. We estimated an incidence rate of 1.2–1.4 per 1000 births, out of an annual 10–12,000 births referred to our institution for these situations. These rates are significantly lower than those reported in the United States over the past 20 years but align with the rates observed in Europe [3,26].

Our study showed a decline in buprenorphine use, likely due to changes in access to methadone. The introduction of methadone syrup in our country in 1995 was accompanied by strict supervision of access, managed by specialized addiction treatment centers. The introduction of methadone capsules in 2008 made methadone more accessible to the general population, including pregnant women. From 2009 to 2020, the prevalence of methadone use doubled, with two-thirds of users in 2020 consuming the capsule form [27]. Our national addict-vigilance network highlights the high proportion of women involved in drug abuse reports with analgesic opioids [28]. We also observed an increasing consumption of these drugs in our cohort. A national retrospective study among pregnant women reported that analgesic opioids were prescribed and dispensed to nearly 2 % of them during the first trimester and 1 % during the third trimester [29].

Despite regular monitoring for the majority of pregnancies, the rate of premature births (28 %) was 4 times higher than the national average during this period [30]. The incidence of preterm births has been reported to vary widely, ranging from 12 % to 52 %. This variation is influenced by factors such as the type of medication used for opioid use disorder, multiple drug consumption, socioeconomic status, maternal stress, and access to prenatal care [31,32]. In our population, the rate of induced prematurity was 40 %, with severe intrauterine growth restriction as the main cause. Previous research described higher risk of poor foetal growth and low birth weight in infants born to opioid-exposed mothers [33].

Management of infants exposed to opioids in utero dramatically changed during the study period, with much more systematic exposition to NPC and a massive reduction in the use of PT. Our logistic regression analyzes data showed the favorable effect of the wider application of NPC in the PIU during the last period (2015–2020) on the risk of Nows occurrence, as on the risk of severe Nows requiring PT. Prior studies have shown the benefits of training programs aimed at improving the family centered care of opioids exposed newborns. Holmes et al. reported that rooming-in with family and decreased use of neonatal intensive care unit beds reduced PT and LOS [34]. Comparable results were found by Grossman et al., when they focused their interventions on NPC such as a low-stimulation environment, continuous parental engagement to infant's care, and breastfeeding promotion [10]. Our study highlights the importance of ensuring NPC practice and convincing caregivers of its effectiveness in preventing and treating Nows. Although NPC has been recommended for these patients in

our PIU since 1997 [17,19], its widespread application has been achieved through an active policy supported by the steering committee and a network of referent nurses [15]. Our strategy, based on the adaptation of NPC and PT to the clinical behavior of each infant, has similarities with the Eat, Sleep, Console approach [11]. Both methods prioritize NPC and family empowerment by interpreting each infant's behavioral cues [20,35]. These approaches currently seem to be the most effective strategies for the management of opioid-exposed infants [36]. The policy that emphasized NPC as the standard treatment, particularly through prolonged skin-to-skin contact, could also contribute to increase breastfeeding at discharge [37].

The other results of our logistic regression analyses confirmed the risk of methadone, compared to buprenorphine, on NOWS occurrence [38,39], and the generally milder courses of withdrawal associated with prematurity [40]. The relationship between NOWS and maternal lifestyle could be due to the positive influence of the father's presence, for maternal support as well as for active participation to NPC [41]. We also found a risk of pharmacologically treated NOWS in case of concomitant antenatal opioid and benzodiazepine exposure, a finding consistent with data from a large population-based study in the United States that highlighted the risks of this association among others intrauterine polysubstance exposures [42].

Our study has several limitations, which first include a limited number of patients. Nonetheless, it presents distinct advantages compared to population-based studies. The "Parenting and Drug Use" unit is a well-recognized facility among perinatal healthcare professionals and general practitioners in the local network, and its establishment in our institution predates the period under investigation by several years. We believe that the consistent support provided to mothers and couples throughout pregnancy facilitated reliable reporting of opioid and illicit drug consumption, owing to the trust built with healthcare professionals during monthly appointments.

Being an observational, single-center study, its results may be challenging to generalize to other centers. The Eat, Sleep, Console approach is in increasing use in the USA for the management of infants exposed in utero to opioids [11,35,36]. The application of a developmental care program for caring these infants, such as NIDCAP at our center, share similarities with this method, particularly for maximizing non-pharmacological interventions and increasing family involvement in infant care [43]. But there are also differences, notably the use of the Finnegan score, since we continue to use it to identify NOWS and to decide on possible pharmacotherapy. However, care of these infants in our department is not based on this score, but on behavioral observation, which allows to develop individualized care plans. Accordingly, NPC was always considered in first-line and recourse to PT, 15 % in opioid-exposed infants during the third period, was very close to the rate observed with Eat, Sleep, Console approach in a recent trial [36].

As for any observational study, the suggested relationships between patient management and outcomes are hypothetical. Implementing a developmental care program can have a direct influence on infant behavior, but may also influence the healthcare providers perception of these infants. The extensive 18-year study duration could have been influenced by numerous shifts in daily clinical practices within the PIU. Nonetheless, the admission criteria to the PIU, including lower limits of gestational age and birth weight, as well as the reasons for admission, remained the same throughout. The Finnegan scale was the sole tool utilized to assess withdrawal symptoms in newborns, yet concerns have been raised regarding the

accuracy and consistency of scoring among caregivers [44]. The COVID-19 pandemic widely disrupted many aspects of the health care system. Our results remained consistent over the last 6-year period, suggesting that our program was sufficiently consolidated to withstand the most critical moment of the crisis, that occurred in our country in 2020. Future studies are needed to affirm the sustainability of this program in the current context of nursing crisis.

5. Conclusion

In conclusion, our study underscores the critical role of an active policy in promoting and ensuring the consistent practice of developmental care, particularly in facilitating effective exposure to NPC for all newborns exposed in utero to opioids. In these patients, our results found reductions in medication use and length of hospitalization. Future studies in this area will be essential to assess whether optimizing NPC impacts parent-infant bonding [45] and long-term outcomes of these infants [46].

CRedit authorship contribution statement

Gilles Cambonie: Writing – original draft, Validation, Methodology, Investigation, Conceptualization.

Lison Aujogues dit Baron: Writing – original draft, Validation, Methodology, Investigation.

Clementine Combes: Writing – review & editing, Validation, Methodology, Formal analysis.

Corinne Chanal: Writing – review & editing, Validation, Investigation.

Evelyne Mazurier: Writing – review & editing, Validation, Investigation.

Rose-Marie Toubin: Writing – review & editing, Validation, Investigation.

Mathilde Fortier: Writing – review & editing, Validation, Resources, Investigation.

Angelo Polito: Writing – original draft, Validation, Methodology.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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