Outcomes of Extremely Premature Infants Comparing Patent Ductus Arteriosus Management Approaches

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Objective To evaluate the change in the proportion of deaths/bronchopulmonary dysplasia (BPD) among premature infants (born <26 and 26-29 weeks of gestational age) following a policy change to a strict nonintervention approach, compared with standard treatment.

Study design We examined 1249 infants (341 born <26 weeks of gestational age) at 2 comparable sites. Site 1 (control) continued medical treatment/ligation, and site 2 (exposed) changed to a nonintervention policy in late 2013. Using the difference-in-differences approach, which accounts for time-invariant differences between sites and secular trends, we assessed changes in death or BPD separately among infants born 26-29 weeks and <26 weeks of gestational age in 2 epochs (epoch 1: 2011-2013; epoch 2: 2014-2017).

Results Baseline characteristics were similar across sites and epochs. Medical treatment/ligation use remained stable at site 1 but declined progressively to 0% at site 2, indicating adherence to policy. We saw no difference in death/BPD among infants born at 26-29 weeks of gestational age (12%, 95% CI -1% to 24%). However, incidence of death/BPD increased by 31% among infants born <26 weeks of gestational age (95% CI 10%-51%) in site 2, whereas there was no change in outcomes in site 1. The Score for Neonatal Acute Physiology-Version II, used as a control outcome, did not change in either site, suggesting that our findings were not due to changes in patients' severity.

Conclusions Adherence to a strict conservative policy did not impact death or BPD among 26 weeks but was associated with a significant rise in infants born <26 weeks. *(J Pediatr 2021;235:49-57)*.

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Patent ductus arteriosus (PDA) is associated with numerous complications of prematurity, including bronchopulmonary dysplasia (BPD) and death.[1,2] Although nonsteroidal anti- inflammatory medications (NSAIDs) increase ductal closure,[2,3] these medications have side effects,[3] and surgical ligation is associated with adverse outcomes.[1] Results from clinical trials show that, although successful in achieving PDA closure, medical and surgical approaches were not associated with improved outcomes.[1,2] Despite this, and that the ductus spontaneously closes in most premature newborns,[4,5] NSAIDS or ligation are commonly used in the extremely premature population. The ample evidence indicating that there are no improved long-term outcomes following medical or surgical treatment of PDA has fueled the current uncertainty surrounding management.[2,6-13] Even though few studies have documented the safety of a "conservative" approach of nonintervention with respect to BPD and mortality among premature newborns,[3] in 2016, the American Academy of Pediatrics recommended against treating the PDA during the first 2 weeks of life of extremely premature newborns.[9] This recommendation underscored the lack of evidence of improved outcomes of accelerating PDA closure, leading some centers to take a conservative approach. In this study, we applied a quasi-experimental design, the difference-in-differences (DID) approach, to evaluate whether a strict conservative approach (no intervention to accelerate closure, supplemented by other interventions such as use of diuretics or fluid restriction) to PDA management, compared with a traditional approach (treatment with NSAIDs and/or ligation to accelerate ductal closure), yielded similar outcomes in premature newborns born at 26-29 and <26 weeks of gestational age.

BPD	Bronchopulmonary dysplasia
DID	Difference-in-differences
NICU	Neonatal intensive care unit
NSAID	Nonsteroidal anti-inflammatory drug
PDA	Patent ductus arteriosus
PMA	Postmenstrual age
SGA	Small for gestational age

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Methods

A priori, we identified 2 neonatal intensive care units (NICUs) to serve as the control (site 1) and exposed (site 2) sites, respectively. For both sites, we used data from the Canadian Neonatal Network registries, which collects standardized perinatal and neonatal data on sociodemographic information, treatments, and outcomes of deliveries up to 29 weeks.[14,15] The sites, both quaternary care pediatric institutions (mother-child centers), are located in the same city and share similar characteristics with respect to (1) clinical practices (contemporaneous adoption of new oxygen saturation targets,[16] use of noninvasive continuous positive airway pressure as a primary mode of support with rescue intubation and surfactant, use of pasteurized human milk, use of similar ventilation practices); (2) comparable patient populations, in terms of socioeconomic status and risk factors (cardiac, hypoxic ischemic encephalopathy, surgical, and extremely preterm cases); (3) presence of neonatal nurse practitioners; (4) being university-affiliated institutions; and (5) presence of a neonatal transport team for admission of both inborn and outborn infants. Most of the neonatologists at both sites had been trained at their respective university, with several crossing over after their training. Site 2 was on 2 physical locations, both attended by the same medical team, until it moved to a new single-bed combined unit in mid-2015. Site 1 was on a single physical site and moved to a new single-bed unit in late 2016 (with the same team).

The study population consisted of all infants ≤29 weeks born between January 2011 and December 2018 who were admitted at either of the 2 study sites within 24 hours of birth and who did not meet the exclusion criteria, which were death within the first 24 hours of life, transfer after 24 hours of life, presence of congenital heart malformations (excluding atrial or ventricular septal defect), or other significant congenital anomaly (including genetic disorders). As we planned a priori to analyze the subset of infants born at less than 26 weeks, data are presented separately for the 2 subgroups (<26 weeks and 26 weeks or more). The study was approved by the ethics boards of the 2 hospitals.

The exposure was a clinical policy change implemented at site 2 on September 27, 2013, which established that the clinical team would adhere to a strict conservative management of PDA (ie, with no use of NSAIDs or ligation and with no "rescue" criteria for treatment). The policy was adopted after internal review of practice guidelines. Newborns at site 1 were exposed to NSAIDs and/or ligation based on previously published echocardiography criteria.[17] In this study, we categorized time "before" and "after" policy initiation as 2 epochs: epoch 1 (birth years 2011-2013) and epoch 2 (2014-2017 up to December 31, 2017).

The primary outcome was a composite of death or BPD, defined as any respiratory support or oxygen supplementation (including low flow nasal cannula) at 36 weeks of postmenstrual age (PMA), or at the time of NICU discharge, if discharge occurred before 36 weeks of PMA.[18]

Statistical Analyses

We used Fisher exact and χ^2 tests to evaluate differences in categorical characteristics between the 2 centers, and Student *t* test and Wilcoxon Mann-Whitney tests to compare parametric and nonparametric continuous variables, respectively, between centers and between epochs. We applied the DID approach (**Figure 1**; available at www.jpeds.com), a quasi-experimental method, to estimate the impact on death or BPD of changing to a strict conservative PDA management approach, compared with standard care (NSAIDs and/or ligation).[19] The crucial assumptions of the DID model is that the policy change was independent of unobserved time-varying factors and that other relevant factors were comparable between the 2 groups across the study epochs (additional details available in the **Appendix** [available at www.jpeds.com]).[19] We chose this design to control for secular trends and avoid confounding by indication.

Rates of the outcomes of interest were modeled by linear regression of observed outcomes for each subject, as binary variables, on the binary inputs of site (site 1 vs site 2), epoch (epoch 1 vs epoch 2), and exposure to the change in practice (change in practice at site 2, as an interaction term for site and epoch).[20] Linear regression is preferred for such binary-on-binary regression models, as the regression coefficients directly correspond to the magnitude of the effect of each variable on the probability of the outcome of interest.[21] In addition, we modeled the relative change in outcome using Poisson regression with robust covariance matrix estimators (Eicker–Huber–White SEs).[22-25] The potential impact of factors that varied between epochs or sites was assessed in regression models that included those factors as independent variables. We visually evaluated the assumption of parallel trends in epoch 1 based on the logarithm scale (**Appendix**).

By examining an outcome not expected to change as a result of the change in PDA policy ("placebo" outcome), we further assessed whether omitted variables may have influenced our results.[26] We used a Score for Neonatal Acute Physiology (an indicator of baseline neonatal illness) above 20 as the placebo endpoint.[27] Additional details are included in the **Appendix**. All analyses were carried out using R (v 3.4.4, Open-Source International Collaborative) and R Studio (v 1.0.143, Open-Source International Collaborative).

Results

During the study period, a total of 1298 babies with gestational age at birth of ≤29 weeks were admitted to the study NICUs. Of these, 49 (including 18 born at a gestational age of <26 weeks) met exclusion criteria: 16 died within 24 hours of birth, 9 were admitted >24 hours after birth, and 24 had a major congenital anomaly. The final analytic sample comprised 1249 infants, including 341 (27.3%) born <26 weeks of gestational age. Average gestational age was similar at each site in the 2 epochs in both the <26 and ≥26 weeks subsets of infants (**Table I**; available at www.jpeds.com). Demographic and clinical characteristics, as well

Table II. Characteristics of the study population by site and epoch

	Site 1 (control) Epoch 1	Site 2 (exposed) Epoch 1		Site 1 (control) Epoch 2	Site 2 (exposed) Epoch 2	
<26 wk of gestational age						
	n = 75	**n = 44**	***P* value**	**n = 139**	**n = 83**	***P* value**
Baseline and pretreatment variables						
Gestational age (wk)	24.5 (0.7)	24.3 (0.7)	.31	24.3 (0.7)	24.2 (0.7)	.44
Birth weight (g)	718 (119)	732 (102)	.50	718 (146)	700 (118)	.35
Male sex	42 (56)	25 (57)	1.00	72 (52)	48 (58)	.41
Cesarean delivery	36 (49)	20 (45)	.70	89 (64)	52 (63)	.89
Apgar at 5 min <7	45 (63)	23 (52)	.33	88 (64)	59 (71)	.31
Outborn	5 (7)	3 (7)	1.00	17 (12)	8 (10)	.66
Singleton	56 (75)	31 (70)	.67	96 (69)	70 (84)	.02
SGA	6 (8)	1 (2)	.26	12 (9)	5 (6)	.61
SNAP-II score >20	42 (56)	25 (57)	1.00	70 (50)	41 (51)	1.00
Antenatal steroids	65 (89)	39 (89)	1.00	120 (86)	76 (92)	.29
Maternal hypertensive disorder	9 (13)	1 (2)	.09	13 (10)	8 (10)	1.00
Antenatal antibiotic used	50 (68)	33 (75)	.53	105 (78)	69 (84)	.38
ROM ≥24 h	19 (26)	17 (39)	.21	39 (29)	37 (46)	.01
Surfactant used	64 (85)	44 (100)	.007	113 (81)	75 (90)	.08
Treatment variables						
Ibuprofen used	43 (57)	33 (75)	.07	91 (65)	9 (11)	<.0001
Indomethacin exposure	3 (4)	0 (0)	.29	7 (5)	0 (0)	.047
NSAIDS used or ligation	50 (67)	33 (75)	.41	96 (69)	9 (11)	<.0001
Ligation	21 (28)	6 (14)	.11	19 (14)	0 (0)	.0001
Outcomes						
IVH grade 3 or more	17 (23)	14 (32)	.34	32 (23)	16 (21)	.73
NEC	17 (23)	5 (11)	.15	21 (15)	7 (8)	.21
ROP stage 3 and more	18 (13)	9 (20)	.46	34 (17)	14 (17)	.11
ROP treated	10 (29)	6 (14)	1.00	28 (20)	3 (4)	.0002
Nosocomial infection	43 (57)	18 (41)	.09	70 (50)	35 (42)	.27
Early onset sepsis	3 (4)	2 (5)	1.00	3 (2)	4 (5)	.43
Postnatal systemic steroids	42 (56)	27 (61)	.7	101 (73)	50 (60)	.07
Ventilation d	25 (7-43)	18 (8-21)	.31	23 (10-41)	18 (6-37)	.19
Length of stay in alive at discharge	141 (38)	132 (62)	.28	131 (28)	28 (43)	.57
BPD	35 (80)	6 (19)	<.0001	71 (73)	35 (56)	.03
Death	33 (44)	13 (30)	.13	47 (34)	21 (25)	.23
Death or BPD	66 (88)	19 (43)	<.0001	113 (81)	55 (66)	.02
≥26 wk of gestational age						
	n = 308	**n = 112**	***P* value**	**n = 310**	**n = 178**	***P* value**
Baseline and pretreatment variables						
Gestational age (wk)	27.7 (1.1)	27.7 (1.0)	.91	27.7 (1.1)	27.6 (1.1)	.26
Birth weight (g)	1080 (265)	1070 (257)	.74	1057 (272)	1083 (255)	.31
Male sex	172 (56)	66 (59)	.58	161 (52)	88 (49)	.66
Cesarean delivery	201 (65)	76 (68)	.64	230 (74)	116 (65)	.04
Apgar at 5 min < 7	127 (41)	41 (37)	.43	117 (38)	79 (44)	.19
Outborn	18 (6)	15 (13)	.02	33 (10)	27 (15)	.19
Singleton	238 (77)	82 (73)	.46	222 (72)	131 (74)	.71
SGA	35 (11)	16 (14)	.52	55 (18)	14 (8)	.004
SNAP-II score >20	60 (19)	24 (22)	.73	55 (18)	28 (16)	.66
Antenatal steroids	289 (94)	100 (90)	.27	289 (91)	161 (90)	1.00
Maternal hypertensive disorder	70 (23)	21 (19)	.53	59 (19)	30 (17)	.61
Antenatal antibiotic used	176 (57)	61 (56)	.82	182 (60)	116 (68)	.09
ROM ≥24 h	80 (26)	33 (30)	.55	67 (22)	52 (29)	.08
Surfactant used	158 (51)	77 (69)	.002	180 (58)	90 (50)	.13
Treatment variables						
Ibuprofen used	78 (25)	38 (34)	.11	101 (33)	10 (6)	<.0001
Indomethacin exposure	1 (1)	0 (0)	1.00	7 (2)	0 (0)	.05
Ligation	28 (9)	2 (2)	.01	4 (1)	0 (0)	.30
NSAIDS used or ligation	84 (27)	38 (34)	.23	107 (35)	10 (6)	<.0001
Outcomes						
IVH grade 3 or more	27 (9)	14 (13)	.32	22 (7)	21 (12)	.11
NEC	34 (11)	8 (7)	.32	21 (7)	4 (2)	.05
ROP stage 3 and more	12 (4)	4 (4)	1.00	7 (3)	5 (3)	.76
ROP treated	1 (1)	0 (0)	1.00	3 (3)	2 (4)	1.00
Nosocomial infection	82 (27)	27 (24)	.69	58 (19)	39 (22)	.46
Early onset sepsis	3 (1)	5 (4)	.06	4 (1)	3 (2)	.71
Postnatal systemic steroids	71 (23)	29 (26)	.63	75 (24)	39 (22)	.64

(*continued*)

Table II. Continued

	Site 1 (control) Epoch 1	Site 2 (exposed) Epoch 1		Site 1 (control) Epoch 2	Site 2 (exposed) Epoch 2	
	<26 wk of gestational age					
	n = 75	n = 44	*P* value	n = 139	n = 83	*P* value
Ventilation d	3 (0-14)	3 (1-12)	.73	2 (0-10)	2 (0-7)	.23
Length of stay in alive at discharge	75 (41)	74 (38)	.76	81 (41)	73 (38)	.05
BPD	101 (37)	22 (21)	.002	108 (38)	35 (21)	<.0001
Death	43 (14)	6 (5)	.02	28 (9)	9 (5)	.11
Death or BPD	135 (44)	28 (25)	<.0001	133 (43)	43 (24)	<.0001

IVH, intraventricular hemorrhage; *NEC*, necrotizing enterocolitis (stage 2 or above per Bell criteria, nosocomial infections diagnosed 2 days after birth with positive blood or cerebrospinal fluid culture); *ROM*, rupture of membranes; *ROP*, retinopathy of prematurity; *SNAP-II score*, Score for Neonatal Acute Physiology, Version II.
Expressed as mean (SD) or count (%).
P value for differences between sites. Fisher exact test for categorical variables; Student *t* test (for gestational age, birth weight, and length of stay in alive at discharge) and Wilcoxon Mann-Whitney test (for ventilation days).

as neonatal outcomes during hospitalization, are shown in Table II. Gestational age at birth, birth weight, infant sex, and steroids exposure before and after birth were similar between sites and subsets (<26 and ≥26 weeks of gestational age) in each epoch. Among babies ≥26 weeks of gestational age, outborn status was more frequent in epoch 2 at site 1 and cesarean delivery and small for gestational age (SGA) were less common in epoch 2 at site 2. Among babies born <26 weeks of gestational age, the proportion of singletons was slightly higher at site 2 in epoch 2 (84% vs 69% at site 1). Newborns <26 weeks of gestational age at site 2 were more frequently exposed to prolonged rupture of membranes, compared with newborns at site 1 in epoch 2. In epoch 1, newborns at site 2 were more frequently exposed to surfactant replacement therapy than those at site 1 (≥26 weeks: 51% vs 69%; <26 weeks: 85% vs 100%). Finally, although numbers were small, retinopathy of prematurity requiring treatment in infants born at <26 weeks of gestational age appeared to be less common in epoch 2 at site 2 (6/44 [14%] vs 3/83 [4%]).

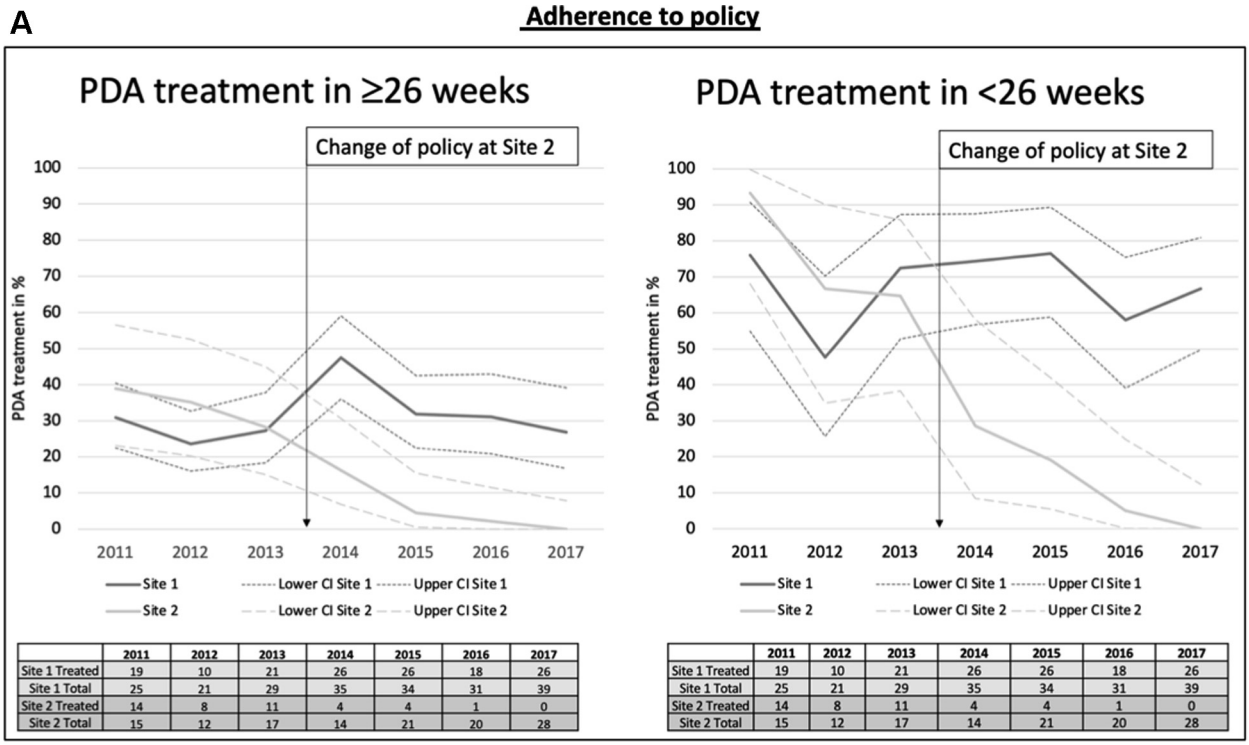
In both, the <26 and 26-29 weeks of gestational age strata, use of NSAIDS or ligation decreased progressively to reach 0% at the end of epoch 2 at site 2 (birth year 2017). In site 1, use of NSAIDS remained constant between epochs 1 and 2, Figure 2, A. Surgical ligation of PDA decreased at site 1 from 13% to 5% from epoch 1 to epoch 2, and from 5% to 0% at site 2.

The proportion of the composite death or BPD outcome at the 2 sites in each epoch is shown in Figure 2, B. As per standard practice, we visually confirmed the parallel trends assumption between sites on the linear and relative scale prior to the adoption of the policy (Figure 2 and Figure 3 [available at www.jpeds.com]). In the ≥26-week subset, the proportion of death or BPD remained stable between the 2 epochs at each site: 135 of 308 (44% of site 1) patients vs 28 of 112 (25% of site 2) in epoch 1 and in 133 of 310 (43% of site 1) vs 43 of 178 (24% of site 2) in epoch 2. In the <26-week subset, death or BPD occurred in 66 of 75 (88% of site 1) patients vs 19 of 44 (43% of site 2) in epoch 1 and in 113 of 139 (81% of site 1) vs 55 of 83 (66% of site 2) in epoch 2. Results of the DID model for the outcome of death or BPD are presented in Table III. The DID interaction term estimate for the more mature infants indicated an effect on the outcome between −1% and 24% (β 12%), potentially suggestive of a modest increase in this group (nonsignificant). However, their observed proportions of death or BPD appeared to be stable (Figure 2). Among babies born <26 weeks of gestational age, we saw an absolute increase of 31% (95% CI 10%-51%) in the occurrence of death or BPD following the policy change. In the overall cohort, not stratified by gestational age, there was no difference in primary outcome following the policy change (Table III).The relative risk, by the Poisson model, increased by 66% (relative risk 1.66 [95% CI 1.13-2.46]) (Table III). Models adjusted for surfactant and singleton status in the <26-week group and for surfactant, outborn status, SGA status, and cesarean delivery in the ≥26-week group did not improve the fit of the unadjusted models.

The proportion of newborns with a Score for Neonatal Acute Physiology, Version II score above 20 ("placebo outcome") remained stable in both sites and was similar between epochs (Figure 4; available at www.jpeds.com). Table IV (available at www.jpeds.com) shows that, for this outcome, the interaction terms were not different from 0 in either the ≥26 weeks or the <26 weeks.

Discussion

In this study of 1249 newborns admitted at 2 comparable sites, a strict PDA nonintervention policy did not meaningfully affect the incidence of death or BPD among infants born at 26-29 weeks of gestational age but was associated with higher incidence of death or BPD among those born before 26 weeks of gestational age (n = 341). This finding was consistent across all sensitivity analyses. Although there have been sparse reports on premature infants managed conservatively,[4,5,13,28] this large cohort of newborns was evaluated using a DID model, which accounts for time-invariant differences between sites and secular trends. Our overall finding of no benefit of NSAIDs for death or BPD among infants born ≥26 weeks of gestational age is consistent with the results of 2 meta-analyses that summarized the findings of



	2011	2012	2013	2014	2015	2016	2017
Site 1 Treated	19	10	21	26	26	18	26
Site 1 Total	25	21	29	35	34	31	39
Site 2 Treated	14	8	11	4	4	1	0
Site 2 Total	15	12	17	14	21	20	28

	2011	2012	2013	2014	2015	2016	2017
Site 1 Treated	19	10	21	26	26	18	26
Site 1 Total	25	21	29	35	34	31	39
Site 2 Treated	14	8	11	4	4	1	0
Site 2 Total	15	12	17	14	21	20	28

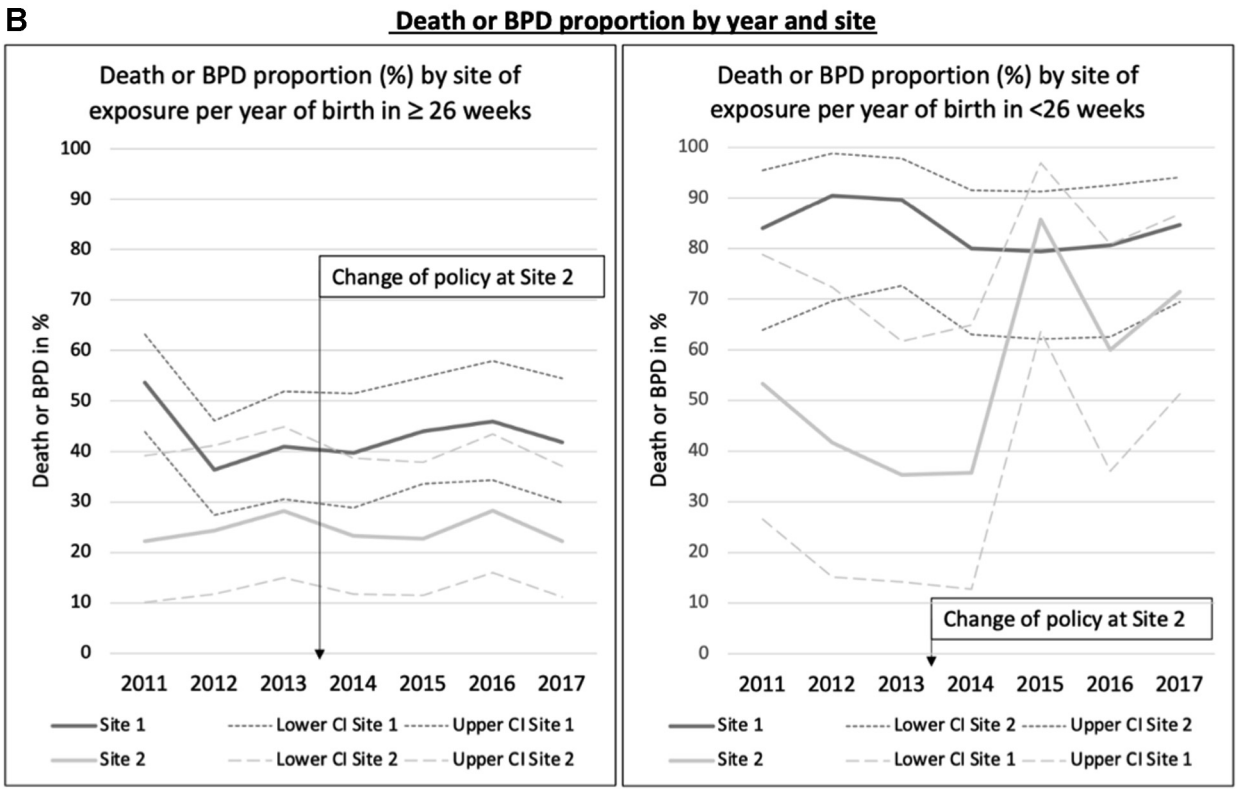


Figure 2. **A,** Adherence to policy. Proportion exposed to NSAIDs or ligation by site and year. 908 newborns were born at 26-29 weeks and 341 at <26 weeks. Site 1 (*control, dark gray*), site 2 (*exposed, light gray*). The 95% CIs are indicated by dashed lines. Lines were obtained joining yearly averages. **B,** Death or BPD rate by year and site. Proportion of newborns who died or developed BPD by site and year. In total, 908 newborns were born at 26-29 weeks and 341 at <26 weeks. Site 1 (*control, dark gray*), site 2 (*exposed, light gray*). The 95% CIs are indicated by dashed lines. Lines were obtained joining yearly averages.

Table III. Primary outcome by DID model using linear and Poisson regression

DID linear regression for outcome: death or BPD			
	Coefficients Death or BPD	Point Estimate (β)	95% CI
<26 wk	Intercept	0.88	0.81- 0.95
	Site	−0.45	−0.61 to −0.28
	Epoch	−0.07	−0.17 to 0.03
	Interaction term (DID estimator)	0.30	0.09-0.50
≥26 wk	Intercept	0.44	0.38-0.49
	Site	−0.19	−0.29 to −0.09
	Epoch	−0.009	−0.09 to 0.07
	Interaction term (DID estimator)	0.0009	−0.13 to 0.13
≤29 wk (pooled data from the overall population)	Intercept	0.52	0.47-0.57
	Site	−0.22	−0.31 to −0.14
	Epoch	0.02	−0.05 to 0.09
	Interaction term (DID estimator)	0.05	−0.06 to 0.17
DID Poisson regression for outcome: death or BPD			
	Coefficients Death or BPD	**Relative risk**	**95% CI**
<26 wk	Intercept	0.88	0.81-0.96
	Site	0.49	0.34-0.70
	Epoch	0.92	0.82-1.04
	Interaction term (DID estimator)	1.66	1.13-2.46
≥26 wk	Intercept	0.44	0.39-0.50
	Site	0.57	0.40-0.80
	Epoch	0.98	0.82-1.17
	Interaction term (DID estimator)	0.99	0.63-1.55
≤29 wk (pooled data from the overall population)	Intercept	0.52	0.48-0.58
	Site	0.57	0.44-0.74
	Epoch	1.04	0.92-1.19
	Interaction term (DID estimator)	1.19	0.87-1.60

DID (with linear regression or Poisson regression) with the primary outcome of death and/or BPD modeled for the exposure to the site, epoch (2011-2013 vs 2014-2017) and interaction between site and epoch. The interaction term between epoch and site exposure is not significantly associated with the primary outcome in the 26- to 29-week gestational age at birth newborns. The interaction terms (without any adjustment) between epoch and site exposure are significantly associated with the primary outcome in the ˂26-week newborns. Pooled data from the overall cohort is also presented, indicating that pooling the data across gestational ages may conceal a potentially important difference in outcome, as the small at-risk population (<26 weeks) is diluted with more mature infants for whom the change in intervention is of little or no consequence.

several trials.[2,29] Most of the studies included infants born between 28 and 32 weeks, and many had a high open-label use of NSAIDs in the placebo/no treatment groups or included NSAIDs use for infants in the placebo arm in a stepwise manner.[30]

In a multicenter aggregated data study of the California Perinatal Quality Care Collaborative,[31] adjusted mortality increased by 0.21% (95% CI 0.06%-0.33%) for each percentage-point decline in unit-specific proportion of NSAIDs or ligation use among infants weighing 400-749 g at birth. The same study reported a significant reduction of NSAIDs use between 2008 and 2015 in all weight strata (400-1499 g). Among infants weighing 1000-1499 g, there was an association between decreased ligation rate and death or BPD. These findings were replicated in a geographically distinct population of extremely small newborns (400-749 g) from the Pediatrix Clinical Data Warehouse between 2006 and 2016.[32] Results from these studies are consistent with our findings that a nonintervention policy was not associated with an increase in death or BPD among babies ≥26 weeks of gestational age but may adversely impact babies <26 weeks of gestational age. In contrast, a study that evaluated 61 520 inborn infants from the Pediatrix group, born between 23 and 30 weeks of gestational age from 2006 to 2015, reported a stable rate of BPD (21%-19%) and a significant decrease in mortality (13%-10%), whereas the use of NSAIDs and ligation steadily declined over the studied period (32%-18% and 8%-3%, respectively).[33] Another pre-post study compared a nonintervention approach with a previous mandatory closure approach in 178 infants <26 weeks of gestational age who required mechanical ventilation and had a significant PDA (≥2 mm in size).[34] In the first epoch, a large proportion were exposed to NSAIDs (64%) or ligation (82%; at 12 ± 7 days of post-natal life), vs none in epoch 2. The authors reported a decline in the rate of BPD (58% to 38%) and stable mortality during hospitalization. The results of these 2 later reports diverge from our findings but may suffer from the inherent limitations of pre-post studies. Benitz et al recognized that extremely premature newborns had not been adequately represented in trials and that they may (or may not) benefit from early closure.[2] As shown in our study, pooling the data across gestational ages may conceal a potentially important difference in outcome, as a small at-risk population (<26 weeks of gestational age) is diluted with more mature infants for whom the change in intervention is of little or no consequence. This mechanism may explain the negative results of prior randomized trials.

Several studies have suggested that a strict conservative management policy may be associated with worse outcomes in the most premature newborns. In an observational study of infants <28 weeks of gestational age comparing 2 epochs (prophylactic indomethacin vs treatment after the first week of life), permanent PDA closure was achieved earlier during the prophylactic indomethacin epoch, whereas death or BPD was higher in the later treatment epoch.[35] These results are similar to those of a recent cohort study of over 39 000 infants born at 24-28 weeks of gestational age, which reported that both low and high rates of PDA treatment were associated with adverse outcomes (death or severe neurological injury), whereas a moderate treatment approach was associated with better outcome.[36] These studies suggest that extremes in approaches regarding PDA-targeted interventions should be thoroughly evaluated before systematic implementation.

An unblinded multicenter trial (PDA-TOLERATE - PDA: TO LEave it alone or Respond And Treat Early - Trial[37]) among infants born at <28 weeks who had not been treated in the first week of life reported no difference in outcomes between the treatment and no treatment arms; however, about one-half of the infants born at <26 weeks had received "rescue" PDA treatment. Outcomes were more favorable among the 181 infants who had been excluded from the trial because of physicians' lack of equipoise on treatment indication, which suggests a degree of consistency in identifying a "significant" duct requiring treatment.[38] These results highlight the need to better evaluate the impact of PDA-related interventions in the most immature newborns. These infants were underrepresented in the meta-analysis on which the American Academy of Pediatrics recommendations were based.

The main strength of our study is the use of a quasi-experimental approach to evaluate a policy of nonintervention for the PDA. This design uses changes in pre- and post-intervention trends, comparing patients from one study center to a similar population not exposed to the policy change and allows for better control of confounding by indication, as it avoids comparing individual patients with and without NSAIDs/ligation. In addition, the design avoids the underlying assumption of pre-post studies, which assumes no underlying secular trends and no time-varying confounders.[19,20] The 2 study centers were similar with respect to organization and the patient populations they served and, because both provide data to the Canadian Neonatal Network, the definition and collection of variables were standardized. We saw no evidence of violations of the DID assumptions. We observed a difference in the absolute change of death or BPD between the 2 centers for the 2 strata of gestational age, but trends across the 2 centers were parallel in epoch 1. As such, we are confident that the only consequential time-varying change was the PDA management policy adoption. In addition, the results were similar with and without adjustments for identified time-varying characteristics (surfactant and singleton status in <26 weeks; and for surfactant, outborn status, SGA status, and caesarean delivery in the ≥26 weeks). All sensitivity analysis corroborated the main finding of a rise in the primary outcome with conservative management in the <26 weeks strata. The main limitation was the small number of sites and, consequently, of infants. We only included 2 centers because of their high level of comparability. We also had no information on the cumulative dose of steroids and/or NSAIDs per patient. Neither site had an official protocol for PDA screening in place during the entire study period. Hence, we could not ascertain the incidence of PDA and hemodynamically significant PDA, nor time to closure. Granular information about the severity of the respiratory illness and the causes of death in our population was not available. Thus, with the evolution of populations and management strategies, the study would not have captured changes over time in the severity of BPD (even within the "severe" BPD stratum). Although BPD was diagnosed at 36 weeks of PMA or discharge, whichever came first, infants born at less than 26 weeks of gestational age are not transferred to other sites before 36 weeks. We had no information about discharge on home oxygen, but length of stay was similar across sites and epochs. We had no detailed information about presence of pulmonary hemorrhage, timing of PDA treatment, and number of doses for infants exposed to NSAIDs. However, these factors, despite being informative for the overall population, do not influence the assessment of a policy change impact. The change in outcome was not immediate, reflecting the fact that PDA treatment at site 2 did not stop all at once. (**Figure 2**). Indeed, there was a large reduction in PDA treatment at site 2, from 67% among babies born in 2013 to 29% among those born in 2014, with only a small increase in death or BPD observed in the latter birth year. The delayed rise in death or BPD may be because in the initial period following the policy change, some of the most vulnerable babies still had their PDA treated. However, the significance of this observation is uncertain, as well as limited by the small number of newborns <26 weeks per individual year. Furthermore, we did not take into account any clustering by neonatologist or clinical team member exposure. By evaluating the average change by site, rather than by exposure at the individual level, we avoid confounding by indication. Finally, we used a composite outcome (with its inherent limitations) because variations in survival may result in variations in the incidence of BPD. We believe that this does not detract from the key result of this study because site 2 made the decision to systematically avoid therapeutic closure of the PDA during epoch 2, including among infants <26 weeks, a rarely pursued approach that ought to be studied in the context of the current controversies regarding PDA management.

In conclusion, although the PDA has been associated with several adverse outcomes of prematurity, previous studies have failed to show an improvement with the use of NSAIDs or ligation. Current guidelines recommend against the use of active PDA treatment of premature newborns in the first 2 weeks of life, regardless of gestational age at birth. The findings of our quasi-experimental study suggest that a strict

nontreatment conservative management policy of the PDA may be associated with a rise in death or BPD in infants born at less than 26 weeks, but not in babies that are 26-29 weeks. Our analysis seems to support a management approach that eliminates PDA treatment had no adverse impact on subjects ≥26 weeks gestation, and that trials of interventions for infants with persistent PDA (whether to accelerate closure or manage its effects otherwise) should focus on infants born <26 weeks of gestational age. Our results encourage adoption of less interventional strategies in the more mature preterm infants born 26-29 weeks of gestational age. In the absence of evidence of benefit, we should encourage equipoise in enrollment of infants in well-structured trials to determine whether the suggested benefit for PDA intervention in the most premature infants is corroborated. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

References

1. Benitz WE. Patent ductus arteriosus in preterm infants. Pediatrics 2016;137:e20153730.
2. Benitz WE, Bhombal S. The use of nonsteroidal anti-inflammatory drugs for patent ductus arteriosus closure in preterm infants. Semin Fetal Neonatal Med 2017;22:302-7.
3. Prescott S, Keim-Malpass J. Patent ductus arteriosus in the preterm infant: diagnostic and treatment options. Adv Neonatal Care 2017;17:10-8.
4. Rolland A, Shankar-Aguilera S, Diomandé D, Zupan-Simunek V, Boileau P. Natural evolution of patent ductus arteriosus in the extremely preterm infant. Arch Dis Child Fetal Neonatal Ed 2015;100:F55-8.
5. Sung SI, Chang YS, Kim J, Choi JH, Ahn SY, Park WS. Natural evolution of ductus arteriosus with noninterventional conservative management in extremely preterm infants born at 23-28 weeks of gestation. PLoS One 2019;14:e0212256.
6. Clyman RI, Chorne N. Patent ductus arteriosus: evidence for and against treatment. J Pediatr 2007;150:216-9.
7. Perez KM, Laughon MM. What is new for patent ductus arteriosus management in premature infants in 2015? Curr Opin Pediatr 2015;27:158-64.
8. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol 2010;30:241-52.
9. Benitz WE , Committee on F, Newborn AAoP. Patent ductus arteriosus in preterm infants. Pediatrics 2016;137.
10. Chock VY, Punn R, Oza A, Benitz WE, Van Meurs KP, Whittemore AS, et al. Predictors of bronchopulmonary dysplasia or death in premature infants with a patent ductus arteriosus. Pediatr Res 2014;75:570-5.
11. Benitz WE. Patent ductus arteriosus: to treat or not to treat? Arch Dis Child Fetal Neonatal Ed 2012;97:F80-2.
12. Benitz WE. Learning to live with patency of the ductus arteriosus in preterm infants. J Perinatol 2011;31(Suppl 1):S42-8.
13. Semberova J, Sirc J, Miletin J, Kucera J, Berka I, Sebkova S, et al. Spontaneous closure of patent ductus arteriosus in infants ≤1500 g. Pediatrics 2017;140:e20164258.
14. CNN. Patient log. Admission screen definitions. Canadian Neonatal Network. Abstractor's Manual 2012:1-93.
15. Investigators CNN. Canadian Neonatal Network-Annual Report 2018; 2018.
16. Askie LM, Darlow BA, Davis PG, Finer N, Stenson B, Vento M, et al. Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants. Cochrane Database Syst Rev 2017;4: Cd011190.
17. Kluckow M, Jeffery M, Gill A, Evans N. A randomised placebo-controlled trial of early treatment of the patent ductus arteriosus. Arch Dis Child Fetal Neonatal Ed 2014;99:F99-104.
18. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82:527-32.
19. Saeed S, Moodie EEM, Strumpf EC, Klein MB. Evaluating the impact of health policies: using a difference-in-differences approach. Int J Public Health 2019;64:637-42.
20. Dimick JB, Ryan AM. Methods for evaluating changes in health care policy: the difference- in-differences approach. JAMA 2014;312:2401-2.
21. Gomila R. Logistic or linear? Estimating causal effects of experimental treatments on binary outcomes using regression analysis. J Exp Psychol Gen 2021;150:700-9.
22. Lechner M. The estimation of causal effects by difference-in-difference methods. Foundations Trends Econometr 2011;4:165-224.
23. White H. A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. Econometrica 1980;48:817-38.
24. Huber PJ. The behavior of maximum likelihood estimates under nonstandard conditions. Proceedings of the fifth Berkeley symposium on mathematical statistics and probability: University of California Press; 1967. p. 221-33.
25. Eicker F. Limit theorems for regressions with unequal and dependent errors, Proceedings of the fifth Berkeley symposium on mathematical statistics and probability. Berkeley, CA: University of California Press; 1967. p. 59-82.
26. Wing C, Simon K, Bello-Gomez RA. Designing difference in difference studies: best practices for public health policy research. Annu Rev Public Health 2018;39:453-69.
27. Beltempo M, Shah PS, Ye XY, Afifi J, Lee S, McMillan DD. SNAP-II for prediction of mortality and morbidity in extremely preterm infants. J Matern Fetal Neonatal Med 2019;32:2694-701.
28. Letshwiti JB, Semberova J, Pichova K, Dempsey EM, Franklin OM, Miletin J. A conservative treatment of patent ductus arteriosus in very low birth weight infants. Early Hum Dev 2017;104:45-9.
29. Mitra S, Florez ID, Tamayo ME, Mbuagbaw L, Vanniyasingam T, Veroniki AA, et al. Association of placebo, indomethacin, ibuprofen, and acetaminophen with closure of hemodynamically significant patent ductus arteriosus in preterm infants: a systematic review and meta-analysis. JAMA 2018;319:1221-38.
30. Gersony WM, Peckham GJ, Ellison RC, Miettinen OS, Nadas AS. Effects of indomethacin in premature infants with patent ductus arteriosus: results of a national collaborative study. J Pediatr 1983;102:895-906.
31. Hagadorn JI, Bennett MV, Brownell EA, Payton KSE, Benitz WE, Lee HC. Covariation of neonatal intensive care unit-level patent ductus arteriosus management and in-neonatal intensive care unit outcomes following preterm birth. J Pediatr 2018;203:225-33.e1.
32. Hagadorn JI, Tolia V, Shaffer ML. Covariation of PDA management and outcomes of infants born 400-749 grams in Pediatrix Neonatal ICUs. Pediatric Academic Societies (PAS) 2020 Meeting (Cancelled) Online Program Guide; 2020. Poster Session, Poster 3926.459.
33. Bixler GM, Powers GC, Clark RH, Walker MW, Tolia VN. Changes in the diagnosis and management of patent ductus arteriosus from 2006 to 2015 in United States neonatal intensive care units. J Pediatr 2017;189:105-12.
34. Sung SI, Chang YS, Chun JY, Yoon SA, Yoo HS, Ahn SY, et al. Mandatory closure versus nonintervention for patent ductus arteriosus in very preterm infants. J Pediatr 2016;177:66-71.e1.

35. Liebowitz M, Clyman RI. Prophylactic indomethacin compared with delayed conservative management of the patent ductus arteriosus in extremely preterm infants: effects on neonatal outcomes. J Pediatr 2017;187:119-26.e1.
36. Isayama T, Kusuda S, Reichman B, Lee SK, Lehtonen L, Norman M, et al. neonatal intensive care unit-level patent ductus arteriosus treatment rates and outcomes in infants born extremely preterm. J Pediatr 2020;220:34-9.e5.
37. Clyman RI, Liebowitz M, Kaempf J, Erdeve O, Bulbul A, Hakansson S, et al. PDA- TOLERATE Trial: an exploratory randomized controlled trial of treatment of moderate-to- large patent ductus arteriosus at 1 week of age. J Pediatr 2019;205:41-8.e6.
38. Liebowitz M, Katheria A, Sauberan J, Singh J, Nelson K, Hassinger DC, et al. Lack of equipoise in the PDA-TOLERATE Trial: a comparison of eligible infants enrolled in the trial and those treated outside the trial. J Pediatr 2019;213:222-6.e2.

50 Years Ago in *The Journal of Pediatrics*

Noninvasive Blood Pressure Measurement in Neonates

McLaughlin GW, Kirby RR, Kemmerer WT, DeLemos RA. Indirect measurement of blood pressure in infants utilizing Doppler ultrasound. J Pediatr 1971;79:300-3.

In the neonatal intensive care unit, blood pressure is used as an indirect measure of organ perfusion. Fifty years ago in *The Journal*, McLaughlin et al proposed a solution to the contemporary problem that the sphygmomanometric method for blood pressure measurement could not be applied to newborn infants. The reason for this was that the sound from the neonatal arteries could not be heard with a stethoscope. Thus, instead of using a stethoscope, McLaughlin et al applied Doppler ultrasound to detect the systolic and diastolic end points. Indirect systolic and diastolic blood pressures were compared with arterial measurements in 15 infants with a weight range of 1000-3000 g. Doppler ultrasound systolic blood pressure correlated well with arterial values, whereas Doppler diastolic blood pressure measurement was feasible only in the largest infants.

Today, oscillometric blood pressure measurement is standard in the neonatal intensive care unit. The first automated method for oscillometric blood pressure measurement was published in 1979,[1] 8 years after McLaughlin's "Brief clinical and laboratory observation" on Doppler ultrasound was published in *The Journal*. The oscillometric method is superior to the Doppler method in newborn infants, as it is accurate and provides mean and diastolic blood pressure values, in addition to the systolic blood pressure provided by the Doppler method.[2] In the past 50 years, other technological advancements in the assessment of neonatal organ perfusion have included functional echocardiography, electrical impedance cardiometry, near-infrared spectroscopy, and novel Doppler ultrasound technology.[3]

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References

1. Ramsey M 3rd. Noninvasive automatic determination of mean arterial pressure. Med Biol Eng Comput 1979;17:11-8.
2. Nuntnarumit P, Yang W, Bada-Ellzey HS. Blood pressure measurements in the newborn. Clin Perinatol 1999;26:981-96.
3. Vik SD, Torp H, Follestad T, Stoen R, Nyrnes SA. NeoDoppler: new ultrasound technology for continuous cerebral circulation monitoring in neonates. Pediatr Res 2020;87:95-103.

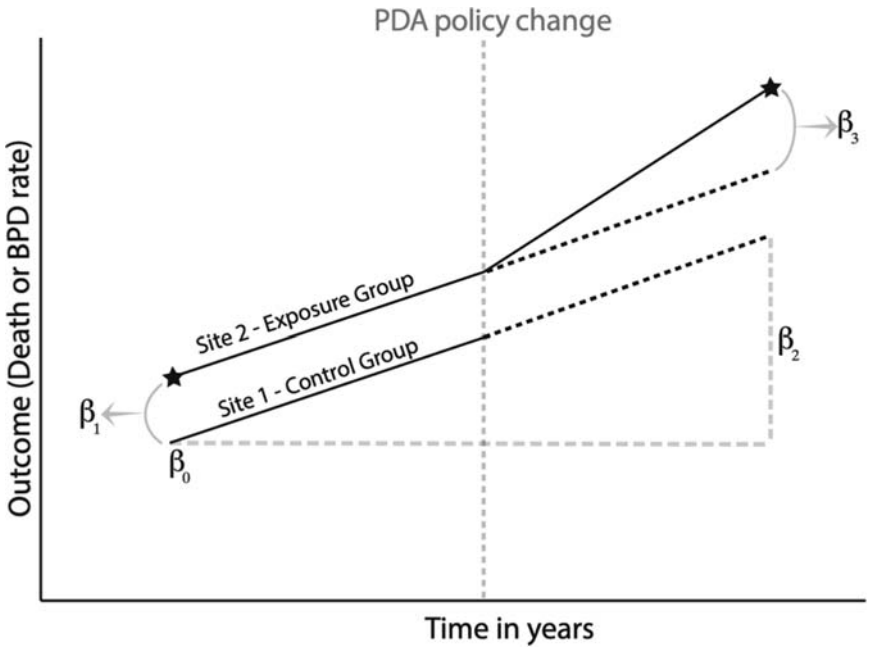

Figure 1. DID design models the outcome for the exposure to the change in practice, the epochs and the interaction between both using a regression analysis. Yi (the probability of the outcome for subject i, here death or BPD) = $\beta 0 + \beta 1$*[Site of exposure] + $\beta 2$*[epoch pre or post-policy adoption] + $\beta 3$*[Site*epoch] + ε (robust standard errors). Where $\beta 0$ is the incidence of the outcome before the intervention at site 1 (control); $\beta 1$ is the difference in the outcome incidence among those exposed to site 2 (*exposure to the change in practice*) compared with site 1 (*control*) in the prepolicy adoption epoch; $\beta 2$ is the difference in the outcome incidence in the epoch following the adoption of the policy compared with the epoch prior at site 1 (*control*); $\beta 3$ is the DID estimator and represents the change in the outcome incidence in the epoch following the adoption of the policy that is specific to site 2 controlling for shared temporal changes and fixed effects.

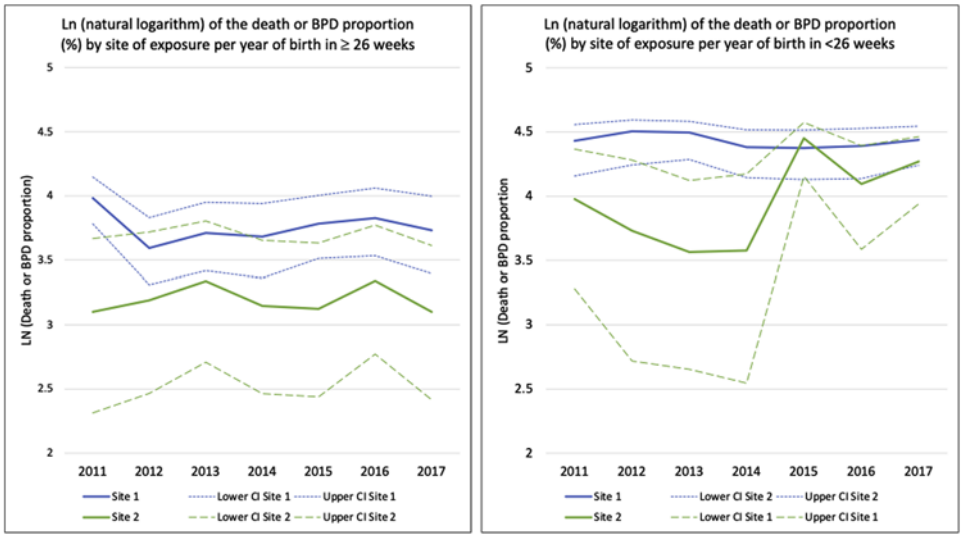

Figure 3. Graphic presentation of the natural logarithm of the proportion of the primary outcome of death or BPD per year of birth and by site (*site 1 control, blue; site 2, exposure to the change in practice, green*). The 95% CIs for each trend is represented with corresponding dash lines. The parallel assumption prior to policy in September 2013 at site 2 was verified visually. The natural log of the proportion of the primary outcome increased at site 2 after adoption of the policy. Lines were obtained joining yearly values.

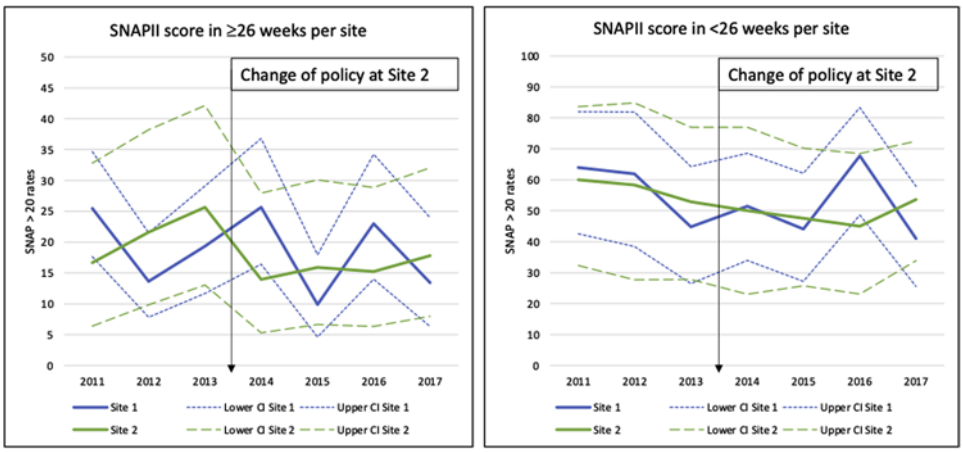

Figure 4. Site 1 (*control, blue*), site 2 (*exposure to the change in practice, green*). The 95% CI for each trend is represented with corresponding dash lines. The proportion of those with a Score for Neonatal Acute Physiology, Version II (SNAP-2) score above 20 were similar between the 2 sites and did not change significantly after the adoption of the policy at site 2. Lines were obtained joining yearly averages. In total, 908 newborns were in the category 26-29 weeks, whereas 341 newborns were <26 weeks.

Table I. Population by gestational age at birth by site and epoch

	Epoch 1 (2011-2013)		Epoch 2 (2014-2017)	
Gestational age, wk	Site 1, n (%) n = 383	Site 2, n (%) n = 156	Site 1, n (%) n = 449	Site 2, n (%) n = 261
23	9 (2.0)	7 (2.7)	18 (4.0)	14 (5.4)
24	21 (5.5)	15 (9.6)	66 (14.7)	39 (14.9)
25	45 (11.7)	22 (14.1)	55 (12.2)	30 (11.5)
26	58 (15.1)	19 (12.2)	61 (20.9)	47 (10.3)
27	81 (21.1)	25 (16.0)	71 (15.8)	32 (12.3)
28	75 (19.6)	41 (26.3)	84 (18.7)	51 (19.5)
29	94 (24.5)	27 (17.3)	94 (20.9)	48 (18.4)

Distribution of estimated gestational age in weeks of birth per epoch and site. There has been an absolute increase in the number of premature newborns admitted to each unit. The distribution of these age groups remained the same in both units. $P = .45$ for comparisons between % differences of 2 epochs

Table IV. DID linear regression model using the placebo (SNAP-II score) as the outcome

<26 wk	Point estimate (β)	95% CI	*P* value
Intercept	0.56	0.45-0.67	<.001
Site	0.01	−0.18 to 0.19	.93
Epoch	−0.06	−0.20 to 0.08	.43
Interaction term	0.001	−0.23 to 0.23	1.00
≥26 wk	**Point estimate (β)**	**95% CI**	***P* value**
Intercept	0.19	0.15-0.24	<.001
Site	0.02	−0.07 to 0.11	.64
Epoch	−0.02	−0.08 to 0.04	.58
Interaction term	−0.04	−0.15 to 0.07	.47

SNAP-II score, Score for Neonatal Acute Physiology, Version II.
DID regression with the placebo (in our case the proportion of SNAP-II score >20) as the outcome modeled for the exposure to site, epoch (2011-2013 vs 2014-2017) and interaction between site and epoch. The interaction term between epoch and site exposure is not, as expected significantly associated with the placebo outcome and, as such, the policy at site 2 did not "impact" the distribution of SNAP-II scores.