The Differential Impact of Delivery Hospital on the Outcomes of Premature Infants

WHAT'S KNOWN ON THIS SUBJECT: Data suggest that delivery at high-volume, high-technology hospitals reduces neonatal mortality. No study has examined other complications or compared the effects in multiple states by using a study design to control for unmeasured differences in case mix.

WHAT THIS STUDY ADDS: The survival benefit to delivering at a high-level NICU between 1995 and 2005 is larger than previously reported and varies between states. The survival benefits affect both extremely and moderately preterm infants. Complication rates were similar between hospital types.

abstract

BACKGROUND: Because greater percentages of women deliver at hospitals without high-level NICUs, there is little information on the effect of delivery hospital on the outcomes of premature infants in the past 2 decades, or how these effects differ across states with different perinatal regionalization systems.

METHODS: A retrospective population-based cohort study was constructed of all hospital-based deliveries in Pennsylvania and California between 1995 and 2005 and Missouri between 1995 and 2003 with a gestational age between 23 and 37 weeks (N = 1 328 132). The effect of delivery at a high-level NICU on in-hospital death and 5 complications of premature birth was calculated by using an instrumental variables approach to control for measured and unmeasured differences between hospitals.

RESULTS: Infants who were delivered at a high-level NICU had significantly fewer in-hospital deaths in Pennsylvania (7.8 fewer deaths/1000 deliveries, 95% confidence interval [CI] 4.1–11.5), California (2.7 fewer deaths/1000 deliveries, 95% CI 0.9–4.5), and Missouri (12.6 fewer deaths/1000 deliveries, 95% CI 2.6–22.6). Deliveries at high-level NICUs had similar rates of most complications, with the exception of lower bronchopulmonary dysplasia rates at Missouri high-level NICUs (9.5 fewer cases/1000 deliveries, 95% CI 0.7–18.4) and higher infection rates at high-level NICUs in Pennsylvania and California. The association between delivery hospital, in-hospital mortality, and complications differed across the 3 states.

CONCLUSIONS: There is benefit to neonatal outcomes when high-risk infants are delivered at high-level NICUs that is larger than previously reported, although the effects differ between states, which may be attributable to different methods of regionalization. *Pediatrics* 2012;130:270–278

AUTHORS: Scott A. Lorch, MD, MSCE,[a,b,c] Michael Baiocchi, PhD,[d,e] Corinne E. Ahlberg, MS,[b] and Dylan S. Small, PhD[c,d]

[a]Department of Pediatrics, The Children's Hospital of Philadelphia and The University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; [b]Center for Outcomes Research, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [c]Senior Fellow, Leonard Davis Institute of Health Economics, and [d]Department of Statistics, The Wharton School, University of Pennsylvania, Philadelphia, Pennsylvania; and [e]Department of Statistics, Stanford University, Stanford, California

KEY WORDS

perinatal regionalization, premature infant, delivery hospital

ABBREVIATIONS

BPD—bronchopulmonary dysplasia
CI—confidence interval
ICD-9-CM—*International Classification of Diseases, Ninth Revision, Clinical Modification*
NEC—necrotizing enterocolitis
ROP—retinopathy of prematurity
RR—risk ratio

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Address correspondence to Scott A. Lorch, MD, MSCE, The Children's Hospital of Philadelphia, Center for Outcomes Research, 3535 Market St, Suite 1029, Philadelphia, PA 19104. E-mail: lorch@email.chop.edu

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Regionalization of health care may improve care by directing patients to facilities with the appropriate capabilities to manage a given type of illness.[1,2] The regional model of perinatal care began to weaken in many areas of the United States by the 1990s,[3–6] whereas several other countries attempted to increase regionalization with varying degrees of success.[7,8] Although studies using data from the early to mid-1990s suggest that delivery at a high-volume, high-technology hospital reduces neonatal mortality,[9–12] this issue is worth further examination. Besides mortality, there is little information on the effect of delivery hospital on other outcomes, such as complication rates.[13,14] Finally, there are no studies that compare the effects of delivery hospital on the outcomes of premature infants across states, even though state regionalization policies differ.[15]

The goals of this study, then, are to (1) obtain unbiased measurements of the impact on mortality of delivering at a high-volume, high-level NICU in comparison with other delivery hospitals in states with different systems of regionalization and different patient populations; and (2) examine common complications of premature birth. To best replicate a randomized controlled trial of this question, we will use an instrumental variables study design. This study design is new to the perinatal literature, but it has been used in other settings where policies direct patients to a particular site of care based on illness severity.[16–21]

METHODS

Study Design

Data Population and Sources

We obtained birth certificates from all deliveries occurring in Pennsylvania and California between January 1, 1995, and June 30, 2005 and Missouri between January 1, 1995, and December 31, 2003. Each state's department of health linked these birth certificates to death certificates by using name and date of birth and deidentified the records. More than 98% of these linked records were then matched to maternal and newborn hospital records by using previous methods.[10,22,23] More than 80% of the unmatched birth certificate records were missing hospital, suggesting a birth at home or a birthing center. The unmatched records had gestational age and racial/ethnic distributions similar to the matched records. The institutional review boards of The Children's Hospital of Philadelphia and the departments of health in California, Missouri, and Pennsylvania approved this study.

The primary cohort for this study included infants with a gestational age between 23 and 37 weeks and a birth weight between 400 and 8000 g. A secondary cohort of infants with a birth weight between 500 and 1500 g was used to compare results with previous work.[12] Birth records were excluded if the birth weight was >5 SDs from the mean birth weight for the recorded gestational age in the cohort, because of potential recording errors in either variable.[24] Initially, we identified 1 362 782 birth records; 34 650 met the exclusion criteria, leaving 1 328 132 births in the final cohort.

Definition of Study Outcomes

The primary outcome for this study was in-hospital mortality, made up from 2 metrics: neonatal deaths, defined as death during the initial birth hospitalization; and fetal deaths with either a gestational age ≥23 weeks or a birth weight ≥400 g that met a previous definition of a potentially preventable fetal death by care delivered at the hospital, because management around the time of delivery could convert some neonatal deaths into fetal deaths.[10] We also examined 5 sets of complications of premature birth listed in Table 1.

Definition of Covariate Variables

We included specific covariate variables in our analysis based on their association with one or more study outcomes (Table 2). The covariates included gestational age; birth weight; maternal sociodemographic factors, such as race, age, education, and insurance status; maternal residential zip code sociodemographic information, such as the percentage of inhabitants living below the United States federal poverty line; maternal comorbid conditions; and 49 congenital anomalies grouped by affected organ system, each listed in Supplemental Technical Appendix 1.[10]

Hospital Definitions

Based on previous work,[9,10] a specialty hospital was defined as a level III facility that delivered a minimum of 50 very low birth weight infants, on average, per year. All levels of care were obtained from the American Academy of Pediatrics perinatal survey[25] and validated by using procedure codes from each hospital. The outcomes of infants were assigned to their delivery hospital, regardless of future transfers of care to other hospitals.[10,11] This method assesses the primary impact of perinatal regionalization, which is the antepartum transfer of the mother, and assigns credit to hospitals that appropriately transfer patients to higher-level hospitals.

Organization of Perinatal Systems

Each state has different perinatal policies. Pennsylvania and Missouri have no legislatively defined perinatal policies, including no certificate of need requirement to open a neonatal intensive care or obstetric unit[26] and no formal identification of a regional perinatal transport center. In Pennsylvania, 77% of the delivery hospitals have a level I NICU, and 21.2% of the NICUs have a level III designation. In Missouri, 86% of the delivery hospitals have a level I

TABLE 1 ICD-9CM Codes Used to Identify Complications of Premature Birth

Comorbid Condition	ICD-9-CM Code
BPD	770.7
Necrotizing enterocolitis (NEC)	777.5
Fungal sepsis	112.x, 771.7
Bacterial sepsis	038.x, 995.90-995.94, 041.x, 790.7
ROP	362.21
ROP surgery	14.2x, 14.34, 14.4x, 14.5x
Laparotomy	45.6x, 45.7x, 45.8, 45.9x, 46.0x, 46.1x, 46.2x, 46.3x, 46.4x, 46.5x, 46.8x, 54.1
Any IVH	431, 772.1, 772.1x

For each code, "x" represents any number at the digit location. IVH, intraventricular hemorrhage.

NICU, with 11.6% of the NICUs designated as a level III center. California has a legally codified regional perinatal system, with 23 designated regional perinatal centers, although there is a trend in California toward shifting the delivery of premature infants to lower-volume NICUs.[10] Only 60.4% of the delivery hospitals have a level I NICU, with a higher percentage of hospitals with a level III NICU (32.8%) compared with the other states.

Instrument and Study Design

Previous observational studies of perinatal regionalization adjusted for differences in observed case mix variables between high-level NICUs and other delivery hospitals, usually through regression analysis. However, these methods cannot adjust for unmeasured or unrecorded factors, such as the severity of a comorbid condition or laboratory results. This results in 2 potential problems. First, sicker patients tend to deliver at high-level NICUs at higher rates than their less sick counterparts. Second, low-level hospitals may appropriately transfer high-risk mothers to more capable hospitals, and thus only deliver a woman prematurely if there is an extreme emergency. In both cases, without detailed clinical data, it may be impossible to adequately measure these differences.

TABLE 2 Demographics of Patients Delivering at High-level and Other Delivery Hospitals, Pennsylvania, California, and Missouri, 1995–2005

	Pennsylvania			California			Missouri		
	High-level NICU	Other Delivery Hospital	Δ/SD[a]	High-level NICU	Other Delivery Hospital	Δ/SD[a]	High-level NICU	Other Delivery Hospital	Δ/SD[a]
Differential travel time, min	6.97	21.81	−0.84	3.41	14.55	−0.59	15.04	40.15	−0.60
Birth weight, g	2474	2725	−0.34	2527	2804	−0.33	2657	2873	−0.29
Gestational age, wk	34.7	35.7	−0.39	35.3	35.6	−0.17	34.8	35.4	−0.24
Race									
White	64.50%	77.90%	−0.29	63.52%	65.24%	−0.04	77.88%	75.61%	0.05
Black	22.20%	9.30%	0.35	9.29%	5.84%	0.13	18.61%	21.88%	−0.08
Asian	1.30%	1.10%	0.02	9.70%	9.00%	0.02	2.16%	1.68%	0.04
Other	3.00%	3.40%	−0.02	15.74%	18.40%	−0.07	0.72%	0.68%	0.00
Insurance status									
FFS	19.50%	22.80%	−0.08	2.94%	5.26%	−0.12	27.96%	27.98%	0.00
HMO	37.80%	34.60%	0.07	49.08%	39.01%	0.20	28.86%	21.13%	0.18
Public	31.80%	29.70%	0.05	44.20%	50.83%	−0.13	37.17%	41.63%	−0.09
Other	9.40%	10.50%	−0.04	0.87%	1.13%	−0.03	2.71%	6.48%	−0.17
Uninsured	1.20%	1.70%	−0.04	2.89%	3.72%	−0.05	3.04%	2.60%	0.03
Singleton birth	80.60%	86.50%	−0.16	88.23%	91.94%	−0.12	85.70%	90.98%	−0.17
SGA	16.90%	15.20%	0.05	11.39%	8.69%	0.09	14.14%	10.92%	0.10
Maternal comorbid conditions and complications of pregnancy									
Comorbid conditions									
Chronic HTN	2.00%	1.17%	0.07	1.17%	0.75%	0.04	1.81%	1.22%	0.05
Gestational diabetes	5.49%	4.85%	0.03	6.18%	4.74%	0.06	5.08%	4.05%	0.05
Diabetes mellitus	2.13%	1.40%	0.05	1.50%	0.78%	0.07	1.72%	1.12%	0.05
Renal disease	0.33%	0.24%	0.02	0.18%	0.14%	0.01	0.32%	0.20%	0.03
Congenital heart disease	0.16%	0.05%	0.03	0.06%	0.03%	0.01	0.08%	0.05%	0.01
Complications of pregnancy									
Preterm labor	48.65%	39.79%	0.18	30.34%	21.29%	0.21	37.58%	26.50%	0.24
PIH	12.14%	8.25%	0.13	7.83%	5.58%	0.08	10.16%	8.33%	0.06
PROM	20.85%	14.86%	0.16	11.14%	8.98%	0.06	16.45%	10.45%	0.18
Oligohydramnios	4.61%	3.02%	0.08	3.87%	2.26%	0.09	5.69%	3.43%	0.11
Disorders of placentation	6.57%	4.57%	0.09	4.57%	3.42%	0.05	5.69%	3.91%	0.09

FFS, fee for service; HMO, health maintenance organization; SGA, small for gestational age; HTN, hypertension; PIH, pregnancy-induced hypertension; PROM, premature rupture of membranes.

[a] Δ/SD is the standardized difference between the high-level NICU and other delivery hospital groups for a specific variable, defined as (difference in means between 2 groups of patients) ÷ (SD of entire cohort). A value <0.20 is considered adequate balance between groups.

To address both of these potential issues, our study uses a matched-pair instrumental variables design, referred to as "near-far matching."[27] An instrument is a variable that encourages patients to deliver at a particular hospital, in essentially a randomized fashion. A strong and valid instrument varies where a mother delivers, while controlling for both measured and unmeasured differences in case mix between types of hospitals, similar to a randomized study. Our instrument is the difference in travel times from the mother's residential zip code to the nearest high-level NICU and the mother's residence to the nearest other delivery hospital. We calculated travel times by using ArcView software (ESRI, Inc) as in previous work.[28] Women with lower differential travel times lived in residential zip codes that were closer to a high-level NICU. Differential travel time satisfies the 3 characteristics of an instrument[29]: (i) Association with treatment: previous studies suggest that women tend to deliver at hospitals near their residential zip code[30,31]; (ii) Independence from unmeasured confounding: women do not expect to have a premature delivery, and, conditional on measured socioeconomic variables, women do not choose where to live based on distance to a high-level NICU; (iii) No direct effect: the marginal travel time to either facility should not directly affect outcomes.[30,31]

To ensure that patients with higher and lower values of the instrument are comparable, we matched patients on 59 measured covariates while maximizing the difference in the instrument. This design parallels a matched-pair randomized controlled trial of patients encouraged to deliver at a high-level NICU versus patients not encouraged to deliver at a high-level NICU. By including both an instrumental variables approach and this matched-pairs design, we improved the equality of the 2 study groups, which improved the accuracy of the results (Supplemental Technical Appendix 2).[27]

Data Analysis

We first assessed the strength of the instrument. A strong instrument would find that women living closer to high-level NICUs would deliver at high-level NICUs at higher rates than women living further away. We then assessed the validity of the instrument and the matched pairs by calculating the standardized difference of each measured covariate. A valid instrument should distribute measured covariates equally across both the quartiles of the instrument and the matched pairs. A value <0.20 for the standardized difference is considered adequate balance.[32,33] For the instrument, this statistic equals (largest pairwise difference in means across quartiles of the instrument) ÷ (SD of entire prematch cohort). For the matched pairs, this statistic equals (difference in means between matched patients) ÷ (SD of entire prematch cohort).

Three analyses will be presented. First, we present a naïve analysis by using unadjusted differences in each of the 9 outcome measures between patients delivering at a high-level NICU and other delivery hospitals. Second, we present the appropriate analysis that controls for measured and unmeasured differences by using a matched-pairs instrumental variables analysis. Finally, as a secondary analysis, we present results after controlling for measured differences in case mix with a matched-paired propensity score analysis, to allow the comparison of our results with previous work. Risk differences and risk ratios are presented for each analysis. Confidence intervals for risk differences were calculated by standard inversion of a pivot-based test of the null, at an α-error rate of .05.[30] Confidence intervals for risk ratios were calculated by using bootstrap methods. All data are presented separately by state and for the 2 infant cohorts.

RESULTS

Women who delivered at a high-level NICU were more likely to have either a preexisting comorbid condition, such as diabetes mellitus, or a complication of pregnancy, such as preterm labor (Table 2). Infants delivered at high-level NICUs had a younger gestational age.

Strength and Validity of Instrument

The instrument was strong. In Pennsylvania, 79.8% of the pregnancies in the first quartile of the instrument delivered at a high-level NICU, compared with 23.9% in the fourth quartile (Supplemental Results Appendix 1). Similar instrument strengths were seen in California (79.6% vs 38.3%, respectively) and Missouri (55.7% vs 10.1%, respectively). In all 3 states, women in the middle 2 quartiles delivered at high-level NICUs at rates between the 2 extremes. The analysis also balanced all measured covariates between those patients encouraged to deliver at a high-level NICU versus patients not encouraged to deliver at a high-level NICU (Table 3). There were differences between states in the prevalence of complications of pregnancy, such as preterm labor, and in the racial/ethnic distributions of the mothers.

Primary Cohort: 23 to 37 Weeks' Gestation

Association of Delivery Hospital and Mortality

In the unadjusted analysis, delivering at a high-level NICU was associated with higher mortality rates in all 3 states (Table 4). After adjusting for both measured and unmeasured case mix differences between hospital types, delivering at a high-level NICU was associated with

TABLE 3 Improved Balance of Measured Covariates Between High-level NICUs and Other Delivery Hospitals After Use of Instrument and Matching, Pennsylvania, California, and Missouri, 1995–2005

	Pennsylvania			California			Missouri		
	High-level NICU	Other Delivery Hospital	Δ/SD[a]	High-level NICU	Other Delivery Hospital	Δ/SD[a]	High-level NICU	Other Delivery Hospital	Δ/SD[a]
Birth weight, g	2598	2597	0.00	2849	2849	0.00	2818	2817	0.00
Gestational age, wk	35.2	35.2	0.00	35.2	35.2	0.00	35.2	35.2	0.00
Race									
White	85.0%	85.9%	−0.02	68.4%	71.9%	−0.07	91.6%	91.7%	0.00
Black	5.1%	4.7%	0.01	5.9%	5.8%	0.01	7.3%	7.3%	0.00
Asian	1.1%	0.4%	0.06	8.0%	6.8%	0.04	0.6%	0.5%	0.01
Other	2.3%	1.3%	0.05	16.5%	13.9%	0.06	0.4%	0.4%	0.00
Insurance status									
FFS	23.9%	25.1%	−0.03	3.3%	5.4%	−0.09	27.8%	25.6%	0.05
HMO	37.0%	30.9%	0.13	45.7%	44.2%	0.03	21.1%	19.7%	0.03
Public	28.7%	33.4%	−0.10	47.2%	45.6%	0.03	45.5%	49.1%	−0.07
Other	9.1%	9.0%	0.00	0.9%	1.5%	−0.06	3.3%	3.6%	−0.01
Uninsured	1.0%	1.2%	−0.01	3.0%	3.3%	−0.02	2.3%	2.0%	0.01
Singleton birth	84.4%	83.9%	0.01	89.7%	88.9%	0.03	90.6%	90.1%	0.02
SGA	16.0%	16.4%	−0.01	10.7%	10.9%	−0.01	11.9%	11.7%	0.01
Maternal comorbid conditions and complications of pregnancy									
Comorbid conditions									
Chronic HTN	1.1%	1.2%	0.00	0.9%	1.0%	−0.01	1.0%	1.0%	0.00
Gestational diabetes	4.7%	4.7%	0.00	5.2%	5.3%	0.00	3.8%	3.4%	0.02
Diabetes mellitus	1.4%	1.8%	−0.03	1.0%	1.1%	0.00	1.0%	1.1%	−0.01
Renal disease	0.2%	0.3%	−0.01	0.1%	0.2%	−0.01	0.2%	0.2%	−0.01
Congenital heart disease	0.1%	0.1%	0.00	0.0%	0.1%	−0.01	0.1%	0.0%	0.01
Complications of pregnancy									
Preterm labor	45.2%	45.2%	0.00	28.7%	28.4%	0.01	30.0%	29.9%	0.00
PIH	9.7%	10.4%	−0.03	6.6%	7.6%	−0.04	8.0%	8.3%	−0.01
PROM	18.3%	17.7%	0.02	10.2%	11.4%	−0.04	11.5%	11.6%	0.00
Oligohydramnios	3.3%	3.1%	0.01	3.0%	2.9%	0.00	3.8%	3.5%	0.01
Disorders of placentation	4.2%	5.0%	−0.03	3.7%	4.2%	−0.03	3.2%	3.7%	−0.02

FFS, fee for service; HMO, health maintenance organization; SGA, small for gestational age; HTN, hypertension; PIH, pregnancy-induced hypertension; PROM, premature rupture of membranes.

[a] Δ/SD is the standardized difference between the high-level NICU and other delivery hospital groups for a specific variable, defined as (difference in means between 2 groups of patients) ÷ (SD of entire cohort). A value <0.20 is considered adequate balance between groups.

lower in-hospital mortality rates (Table 5). The risk differences ranged from 2.7 fewer deaths/1000 deliveries in California (95% confidence interval [CI] 0.9–4.5) to 12.6 fewer deaths/1000 deliveries in Missouri (95% CI 2.6–22.6). The risk ratios for in-hospital mortality at high-level NICUs ranged from 0.35 in Pennsylvania to 0.82 in California. Pennsylvania and Missouri showed a 2-fold reduction in neonatal mortality rates with delivery at a high-level NICU, whereas California showed a reduction in the rate of preventable fetal deaths.

Association of Delivery Hospital and Neonatal Complications

In unadjusted analyses, there were higher rates of all studied complications at high-level NICUs regardless of state. After accounting for case mix differences, few of these differences remained (Table 5). Delivering at a high-level NICU in Missouri was associated with lower rates of bronchopulmonary dysplasia (9.5 fewer cases/1000 deliveries, 95% CI 0.7–18.4), whereas Pennsylvania and California showed smaller, statistically nonsignificant changes. Rates of other complications were similar between the high-level NICU and other delivery hospital group, with the exception of infection rates, where the risk difference decreased from 5 to 45 extra infections at high-level NICUs/1000 deliveries in unadjusted analyses to 0 to 14 cases/1000 deliveries in adjusted analysis. The risk difference and risk ratios for most complications showed variation between states.

Secondary Cohort: 500 to 1500 g Birth Weight

Similar results were found when we analyzed the 500- to 1500-g cohort separately. Delivering at a high-level NICU was associated with lower mortality rates in all 3 states (Table 6). Complication rates were similar, in general, between the 2 types of NICUs, except that, as with the 23- to 37-week cohort, rates of bronchopulmonary dysplasia (BPD) were lower in Missouri high-level NICU hospitals, and rates of bacterial sepsis were higher in Pennsylvania high-level NICUs. The relative risk for the improvement in mortality

TABLE 4 Unadjusted Rates of Mortality and Complications at High-level NICUs and Other Delivery Hospitals, Pennsylvania, California, and Missouri 1995–2005

	Pennsylvania		California		Missouri	
	RD[a]	RR[b]	RD[a]	RR[b]	RD[a]	RR[b]
In-hospital death	11.4	1.99	6.9	1.50	7.3	1.43
Neonatal death	9.5	1.93	7.3	1.77	8.0	1.59
Preventable fetal death	1.9	2.40	−0.4	0.92	−0.6	0.82
BPD	18.6	3.83	8.5	2.55	8.2	1.68
NEC	6.3	2.98	4.1	2.82	6.1	3.10
Fungal sepsis	7.7	2.97	3.9	2.22	7.6	2.04
Bacterial sepsis	24.8	1.94	18.7	1.85	47.7	2.92
ROP	7.7	3.28	14.4	3.96	22.3	3.16
Surgery for ROP	1.2	3.79	2.4	4.78	2.4	2.27
Laparotomy	1.8	1.97	2.2	2.03	4.0	2.44
Any IVH	19.2	3.47	10.9	3.34	13.6	2.18

RD, risk difference.

[a] RD between groups. A positive RD indicates a higher rate at high-level NICUs compared with other delivery hospitals. A negative RD indicates a lower rate at high-level NICUs compared with other delivery hospitals.

[b] A RR >1 indicates a higher rate at high-level NICUs compared with other delivery hospitals. A RR <1 indicates a lower rate at high-level NICUs compared with other delivery hospitals.

in the 500- to 1500-g cohort was somewhat smaller for each state in comparison with the 23- to 37-week cohort.

Secondary Analysis

In the propensity score analysis (Supplemental Results Appendix 2), which accounts for measured differences in case mix between the hospitals, neonatal mortality rates at both types of hospitals were statistically similar in Missouri (relative risk [RR] 1.01, 95% CI 0.92–1.01), Pennsylvania (RR 0.95, 95% CI 0.85–1.05), and California (RR 0.96, 95% CI 0.93–1.01). As with the unadjusted analyses, there were higher rates of all studied complications at high-level NICUs regardless of state in the propensity score analysis. For both cohorts, the results showed no difference over the 11 years of the study.

DISCUSSION

Determining the true impact of a policy intervention such as perinatal regionalization is critical to accurately weighing the benefits and costs of the intervention. In perinatal regionalization, specialty hospitals usually treat sicker patients in ways that may not be measurable.[4] Also, perinatal policies may vary between geographic areas.[15] Regardless of geographic region, our study suggests that there is a continued survival benefit to delivering premature infants at high-level NICUs that is much larger than the effect shown in previous studies. These effects differ

TABLE 5 Adjusted Difference in Mortality and Complications of Prematurity for Infants Between 23 and 37 Weeks' Gestation Delivering at a High-level NICU Compared With Other Delivery Hospitals, Pennsylvania, California, and Missouri 1995–2005

Outcome	Statistic	Pennsylvania	California	Missouri
Mortality measures				
All hospital death	RD per 1000 deliveries[a]	−7.8 (−11.5 to −4.1)[b]	−2.7 (−4.5 to −0.9)[b]	−12.6 (−22.6 to −2.6)[b]
	RR[c]	0.35 (0.09–0.61)[b]	0.82 (0.70–0.94)[b]	0.50 (0.26–0.82)[b]
Neonatal death	RD per 1000 deliveries	−7.2 (−10.7 to −3.7)[b]	−0.5 (−2.0 to 1.0)	−8.4 (−17.5 to 0.7)
	RR	0.27 (0–0.59)[b]	0.94 (0.79–1.07)	0.56 (0.27–1.07)
Preventable fetal death	RD per 1000 deliveries	−0.6 (−2.0 to 0.8)	−2.2 (−3.1 to −1.2)[b]	−4.2 (−9.1 to 0.7)
	RR	0.72 (0.22–1.46)	0.60 (0.48–0.74)[b]	0.32 (0–1.30)
Complication measures				
BPD	RD per 1000 deliveries	0 (−3.5 to 3.6)	1.0 (−0.3 to 2.4)	−9.5 (−18.4 to −0.7)[b]
	RR	1.02 (0–2.53)	1.21 (0.96–1.53)	0.05 (0–1.00)[b]
NEC	RD per 1000 deliveries	1.6 (−0.9 to 4.1)	1.7 (0.7–2.6)[b]	−4.5 (−9.8 to 0.7)
	RR	—[d]	1.98 (1.46–3.04)[b]	0.28 (0–1.20)
Fungal sepsis	RD per 1000 deliveries	4.9 (2.3–7.6)[b]	0.7 (−0.4 to 1.8)	3.2 (−4.3 to 10.7)
	RR	3.67 (1.88–11.6)[b]	1.28 (0.95–1.87)	1.67 (0–17.7)
Bacterial sepsis	RD per 1000 deliveries	10.1 (4.6–15.6)[b]	15.9 (13.4–18.3)[b]	10.6 (−4.4 to 25.7)
	RR	2.37 (1.50–4.51)[b]	1.92 (1.69–2.05)[b]	1.29 (0.92–2.02)
ROP	RD per 1000 deliveries	−0.7 (−3.2 to 1.9)	3.0 (1.6–4.4)[b]	3.5 (−5.6 to 12.7)
	RR	0.38 (0–6.34)	2.52 (1.52–3.33)[b]	1.31 (0.60–3.52)
Surgery for ROP	RD per 1000 deliveries	−1.1 (−2.3 to 0)[b]	1.6 (0.9–2.3)	1.3 (−2.8 to 5.3)
	RR	—[d]	—[d]	—[d]
Laparotomy	RD per 1000 deliveries	−0.6 (−2.3 to 1)	−1.3 (−2.1 to −0.4)[b]	0 (−4.6 to 4.6)
	RR	—[d]	0.16 (0–0.70)[b]	1.00 (0–11.5)
Any IVH	RD per 1000 deliveries	−0.8 (−4.6 to 3.1)	1.1 (−0.3 to 2.6)	−4.9 (−14.0 to 4.3)
	RR	—[d]	—[d]	—[d]

All values in parentheses indicate 95% confidence intervals for a given statistic.

[a] RD between groups. A positive RD indicates a higher rate at high-level NICUs compared with other delivery hospitals. A negative RD indicates a lower rate at high-level NICUs compared with other delivery hospitals.

[b] All results statistically significant at a $P < .05$ level.

[c] A RR >1 indicates a higher rate at high-level NICUs compared with other delivery hospitals. A RR <1 indicates a lower rate at high-level NICUs compared with other delivery hospitals.

[d] RR calculations were unstable because of the limited number of events occurring at other delivery hospitals or at high-level NICUs.

TABLE 6 Adjusted Difference in mortality and complications of prematurity for infants between 500 and 1500 g birth weight delivering at a high-level NICU compared with other delivery hospitals, Pennsylvania, California, and Missouri 1995–2005

Outcome	Statistic	Pennsylvania	California	Missouri
Mortality measures				
All hospital death	RD per 100 deliveries[a]	−5.7 (−11.0 to −0.4)[b]	−5.3 (−8.5 to −2.0)[b]	−0.4 (−10.7 to 9.8)
	RR[c]	0.68 (0.44–0.96)[b]	0.77 (0.66–0.91)[b]	0.98 (0.60–1.76)
Neonatal death	RD per 100 deliveries	−5.9 (−11.0 to −0.8)[b]	−2.6 (−5.6 to 0.4)	0.5 (−9.2 to 10.1)
	RR	0.63 (0.40–0.94)[b]	0.85 (0.71–1.04)	1.03 (0.61–2.06)
Preventable fetal death	RD per 100 deliveries	0.2 (−1.7 to 2.1)	−2.7 (−4.4 to −0.9)[b]	−0.9 (−5.7 to 3.9)
	RR	1.13 (0.27–5.40)	0.56 (0.38–0.78)[b]	0.75 (0–8.0)
Complication measures				
BPD	RD per 100 deliveries	4.0 (−2.6 to 10.5)	3.5 (0.2–6.8)	−21.9 (−32.9 to −10.9)[b]
	RR	1.22 (0.88–1.70)	1.33 (1.03–1.81)	0.29 (0.12–0.52)[b]
NEC	RD per 100 deliveries	3.9 (0.1–7.6)b	0.7 (−1.4 to 2.7)	−2.1 (−8.0 to 3.8)
	RR	—[d]	1.12 (0.79–1.67)	0.78 (0.32–1.67)
Fungal sepsis	RD per 100 deliveries	0.7 (−2.1 to 3.5)	−2.1 (−4.1 to 0)[b]	−4.1 (−11.3 to 3.0)
	RR	1.47 (0–27.1)	0.52 (0.22–0.96)[b]	0.51 (0.07–2.06)
Bacterial sepsis	RD per 100 deliveries	13.6 (7.1–20.9)[b]	−1.7 (−5.5 to 2.1)	−8.1 (−20.1 to 3.8)
	RR	2.64 (1.65–6.03)[b]	0.93 (0.79–1.11)	0.79 (0.56–1.13)
ROP	RD per 100 deliveries	−1.4 (−5.9 to 3.1)	12.0 (8.4–15.5)[b]	−6.2 (−17.8 to 5.4)
	RR	0.68 (0–3.67)	2.46 (1.82–3.67)[b]	0.84 (0.60–1.19)
Surgery for ROP	RD per 100 deliveries	1.1 (−1.1 to 3.3)	3.5 (1.8–5.1)[b]	−3.9 (−9.4 to 1.7)
	RR	—[d]	—[d]	0.50 (0.08–1.47)
Laparotomy	RD per 100 deliveries	0 (−2.2 to 2.2)	−1.5 (−3 to 0)	−1.6 (−6. to 2.7)
	RR	1 (0–8.0)	0.65 (0.39–1.06)	0.63 (0–2.75)
Any IVH	RD per 100 deliveries	12.5 (6.5–18.5)	3.0 (0–6.1)	−7.8 (−18.3 to 2.5)
	RR	—[d]	—[d]	—[d]

All values in parentheses indicate 95% confidence intervals for a given statistic.

[a] A positive RD indicates a higher rate at high-level NICUs compared with other delivery hospitals. A negative RD indicates a lower rate at high-level NICUs compared with other delivery hospitals.

[b] All results statistically significant at a $P < .05$ level.

[c] A RR >1 indicates a higher rate at high-level NICUs compared with other delivery hospitals. A RR <1 indicates a lower rate at high-level NICUs compared with other delivery hospitals.

[d] RR calculations were unstable because of the limited number of events occurring at other delivery hospitals or at high-level NICUs.

across the 3 states. The largest benefit in mortality was found in the cohort that included both very low birth weight infants and moderately preterm infants, suggesting that choice of delivery hospital may influence the outcomes of all preterm infants, not just the extremely premature infant.

Studies use an instrumental variables approach when patients with certain characteristics are more likely to receive a given treatment.[16–21] With this approach we found statistically significant results that were much larger than shown in previous studies.[4–6,9–11,34–37] This difference may arise because, as more infants are delivered at lower-volume, lower-level NICUs, gestational age and maternal indications for premature delivery cannot adequately control for the differences in case mix between types of NICUs. Increased access to clinical information, such as data available in electronic health records, would be 1 solution to obtain more accurate estimates of the impact of health policies.

The strongest effect of delivery hospital was seen in the improvement in mortality rates. The 100% to 300% higher risk-adjusted mortality rates at hospitals without a high-level NICU suggest that the delivery, resuscitation, and initial management of a premature infant is highly important to the infant's survival. The use of these therapies varies between hospitals.[38] Our work also examined the association between delivery hospital and neonatal complication rates. After adjusting for differences in case mix, rates of important complications, such as BPD, necrotizing enterocolitis (NEC), and retinopathy of prematurity (ROP),[39] were statistically similar in the 2 hospitals. This similarity occurred despite lower mortality rates at high-level NICUs, which should increase the rate of these complications that are diagnosed several weeks or months after birth.

Our study also suggests that the association between delivery hospital and neonatal outcomes differs between states. Although our study design may adjust for unmeasured differences in case mix between types of hospitals, systematic differences between states still exist, including the characteristics of women delivering in various types of hospitals in each state. Additionally, differences in regionalization legislation or financial incentives to hospitals may change which hospitals build a low- or high-level NICU.[2,15] For example, California has stronger regionalization legislation, which reduced the number of level I delivery hospitals in comparison with other states. Thus, the "other delivery hospital" group is made up of

hospitals with different characteristics in California in comparison with the other states. Each of these factors could contribute to the state differences observed in this study.

One complication that remains elevated at high-level NICUs in all 3 states was bacterial infections. Studies suggest that organizational factors of the NICU, such as increased patient-nurse ratios and fewer sinks, are associated with higher infection rates.[40,41] Although increased volume was not associated with increased infections in those studies, high-level NICUs may also have periods of crowding or increased occupancy, which are also associated with higher infection rates.[42–45] In contrast, recent data from multiple NICUs in New York City suggests that infection rates could be lower in high-level NICUs with the use of standardized guidelines.[46] Determining hospital characteristics and policies associated with lower infection rates is important to optimize the care of premature infants.

There are several limitations to this study. We used *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes to detect complications of pregnancy and of premature birth. Thus, there may be some heterogeneity in how different hospitals code for these conditions. We included 2 surgical conditions, which should be coded more accurately than medical diagnoses,[47] and found similar patterns to the medical complications. There are no codes for the administration of surfactant or antenatal corticosteroids in our dataset, so the impact of these therapies on individual patients could not be measured. The instrumental variables approach cannot estimate what would happen to those women who, because of preexisting maternal or fetal conditions, would always deliver at a high-level NICU. Given the specialized conditions of these pregnancies, the effect on mortality is likely larger than we have reported.

In conclusion, our work suggests that the survival benefit to delivering at a high-level NICU between 1995 and 2005 is larger than previously reported and appears to benefit both extremely preterm and moderately preterm infants. Complication rates were similar between hospital types. These benefits vary between states, suggesting that the effect of delivery hospital may depend on the organization of perinatal services or the types of populations served. Assessments of perinatal policies that only use variables available in administrative databases may not adequately adjust for actual case mix differences between hospitals.

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