Perinatal Regionalization for Very Low-Birth-Weight and Very Preterm Infants: A Meta-analysis

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REVIEW

Perinatal Regionalization for Very Low-Birth-Weight and Very Preterm Infants

A Meta-analysis

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Context For more than 30 years, guidelines for perinatal regionalization have recommended that very low-birth-weight (VLBW) infants be born at highly specialized hospitals, most commonly designated as level III hospitals. Despite these recommendations, some regions continue to have large percentages of VLBW infants born in lower-level hospitals.

Objective To evaluate published data on associations between hospital level at birth and neonatal or predischarge mortality for VLBW and very preterm (VPT) infants.

Data Sources Systematic search of published literature (1976–May 2010) in MEDLINE, CINAHL, EMBASE, and PubMed databases and manual searches of reference lists.

Study Selection and Data Extraction Forty-one publications met a priori inclusion criteria (randomized controlled trial, cohort, and case-control studies measuring neonatal or predischarge mortality among live-born infants ≤1500 g or ≤32 weeks' gestation delivered at a level III vs lower-level facility). Paired reviewers independently assessed publications for inclusion and extracted data using standardized forms. Discrepancies were decided by a third reviewer. Publications were reviewed for quality by 3 authors based on 2 content areas: adjustment for confounding and description of hospital levels. We calculated weighted, combined odds ratios (ORs) using a random-effects model and comparative unadjusted pooled mortality rates.

Data Synthesis We observed increased odds of death for VLBW infants (38% vs 23%; adjusted OR, 1.62; 95% confidence interval [CI], 1.44-1.83) and VPT infants (15% vs 17%; adjusted OR, 1.55; 95% CI, 1.21-1.98) born outside of level III hospitals. Consistent results were obtained when restricted to higher-quality evidence (mortality in VLBW infants, 36% vs 21%; adjusted OR, 1.60; 95% CI, 1.33-1.92 and in VPT infants, 7% vs 12%; adjusted OR, 1.42; 95% CI, 1.06-1.88) and infants weighing less than 1000 g (59% vs 32%; adjusted OR, 1.80; 95% CI, 1.31-2.46). No significant differences were found through subgroup analysis of study characteristics. Meta-regression by year of publication did not reveal a change over time (slope, 0.00; $P = .87$).

Conclusion For VLBW and VPT infants, birth outside of a level III hospital is significantly associated with increased likelihood of neonatal or predischarge death.

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THE CONCEPT OF ORGANIZING perinatal services within geographic regions emerged in the late 1960s as a way to maximize access to and capacity of neonatal intensive care units.[1] In 1976, the Committee on Perinatal Health and the March of Dimes issued *Toward Improving the Outcome of Pregnancy* (*TIOP*), which outlined a model for the regionalization of perinatal services to be implemented throughout the United States.[2] In the *TIOP* model, hospitals in a designated geographic region were categorized by the scope of perinatal service provided: level I hospitals provided basic, uncomplicated neonatal care; level II hospitals cared for moderately ill infants; and level III hospitals were those equipped to handle serious neonatal illnesses and abnormalities, including very low-birth-weight (VLBW) infants (<1500 g).[2] In the years that followed, systems of perinatal regionalization developed in most US states. Initially, these efforts were led largely by the voluntary efforts of health care professionals, and the system was widely credited with reducing neonatal and infant mortality rates.[3]

Despite the apparent success of perinatal regionalization, evidence began to surface in the late 1980s that these systems were beginning to weaken.[4] In 1993, the March of Dimes commissioned a second *TIOP*, which reaffirmed the importance of perinatal regionalization for both patient outcomes and cost-effective provision of care.[5] However, deregionalization continued, marked by an increase in VLBW infants being born outside of level III hospitals, as well as a proliferation of small neonatal intensive care units com-

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peting for market share in the same regions.[6-8]

The American Academy of Pediatrics issued expanded guidelines for organization of neonatal care in 2004, again emphasizing the importance of level III care for VLBW infants.[9] However, data from the Federal Maternal and Child Health Bureau show slow progress toward its goal of 90% of VLBW infants in each state being born in level III centers: preliminary 2008 data show that only 5 states have reached 90%, while 10 are below 70%.[10]

As policy makers prepare to again address perinatal regionalization with the publication of the 7th edition of *The Guidelines for Perinatal Care* (LuAnn Papile, MD, chair, Committee on Fetus and Newborn, American Academy of Pediatrics, written communication, April 12, 2010) and the commissioning of a third *TIOP* by the March of Dimes,[11] it is important to turn to the evidence: how important is level of care at birth to VLBW infant survival? This meta-analysis addresses more than 30 years of published data on the relationship between hospital level at birth and neonatal mortality and predischarge mortality for VLBW and very preterm (VPT) infants. It also explores differences in study methods and populations that may influence observed measures of effect and whether the available evidence has changed over time.

METHODS

Data Sources

We searched electronic databases (Ovid MEDLINE, CINAHL, EMBASE, and PubMed) and published reference lists to identify literature published between 1976, the year the first *TIOP* was released, and May 2010. Centers for Disease Control and Prevention (CDC) and Emory University reference librarians designed search strategies based on unique index terms (*infant, newborn*; *infant mortality*; *infant, low birth weight*; *perinatal care*; *intensive care, neonatal*; *pregnancy outcome*; *premature birth*; *patient admission/ or patient transfer*; *obstetrics and gynecology department, hospital*; *medical audit*; *health status disparities*; *quality of health care*; *hospital bed utilization/ or hospital utilization*; *patient transport*; *health care distribution/ or regionalization; health care quality*; *health services accessibility*) supplemented with key words (*perinatal regionalization*; *level*; *very low birth weight/VLBW*). Reference lists of obtained articles were manually searched for additional publications, and final results were reviewed by experts for completeness.

Study Selection

We reviewed titles and abstracts of search results to determine if the content was related to perinatal regionalization. Studies identified for potential inclusion were assessed by S.M.L. and W.D.B. using a priori inclusion criteria and standardized forms.

Inclusion criteria for study design were randomized controlled trial, prospective cohort, retrospective cohort, and case-control study designs. Criteria for study population included liveborn VLBW (≤1500 g) or VPT (≤32 weeks' gestation) infants born in or after 1976. For the measure of perinatal regionalization, studies had to include infant-level outcome data for births at level III facilities vs births at facilities with a lower designated level of care, regardless of subsequent transfer. Included outcome measures were neonatal mortality (death of liveborn infant between days 0 and 28) or predischarge/in-hospital mortality (death of continuously hospitalized infant before discharge).

We excluded publications that did not report numeric data in a format conducive to meta-analysis, including graphs without point estimates and rates without total population counts. Because of the length of time that had passed since publication of many of the articles, we did not contact authors for additional information. Publications in a language other than English could not be translated because of resource constraints and were excluded.

Data Extraction

Two reviewers (S.M.L. and a second coder) independently abstracted information from each included study. Discrepancies were decided by an independent third review (W.D.B. or L.B.). Reviewers were not blinded from publication details, but all used identical abstraction forms to collect data. Outcome data were abstracted as odds ratios (ORs), adjusted ORs, 95% confidence intervals (CIs), rates, adjusted rates, percentages, and counts. Additional information (study design, location, population-based data, data source, birth weight/gestational age range, hospital-level comparison, inclusion of infants <500 g, extent of adjustment for confounding, date of publication, and outcome variable), identified a priori, was extracted for use in subgroup analysis.

Quality Assessment

Each included publication was reviewed for quality independently by 3 authors according to 2 content areas: level of adjustment for confounding and description of level of care designations and/or hospital care capabilities. We placed publications in 1 of 3 quality categories:

- Insufficient quality: lack of appropriate adjustment for confounding factors; no hospital information or lack of clear description of the distinction between hospital levels
- Adequate quality: adjustment for a minimum of 2 potential confounding variables through statistical control or reporting of data in strata that could be combined using the meta-analysis software; some criteria for determining hospital levels but no clear descriptions of hospital capabilities
- High quality: thorough adjustment for confounding, including consideration of patient case mix appropriate to the population, perinatal risk factors, or infant illness severity; clear hospital-level definitions and descriptions of care capabilities

Publications were assigned to a quality category based on fulfillment of criteria in both content areas for that cat-

egory (ie, a study might have extensive adjustment for confounding but be limited to the adequate category because of limited reporting of hospital information).

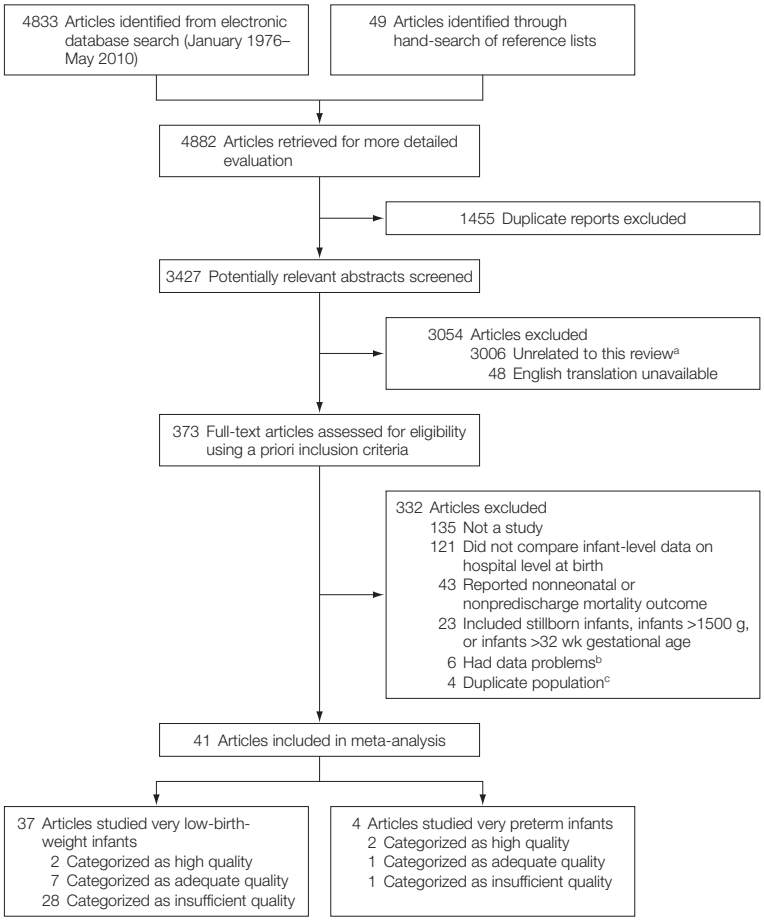
Statistical Analysis

Analysis was conducted using Comprehensive Meta-analysis software.[12] A random-effects model was chosen because it provides a more conservative estimate of variance between studies. Combined effect measures, weighted by population size, were calculated using the natural logarithm of the OR or adjusted OR and corresponding weight for each study. Results are reported as ORs and 95% CIs. Odds ratios calculated from adequate- and high-quality studies are based on risk-adjusted data. Unadjusted pooled incidence rates were calculated from reported birth and death counts at compared hospital levels. Four studies[13-16] did not provide level-specific death/birth counts and are excluded from these estimates.

Publication bias was assessed using the Egger test of the intercept[17] and by inspection of a funnel plot. The 1-study-removed method of sensitivity analysis was used to determine the robustness of individual studies. To assess shifts in the published evidence over time, a meta-regression test was run by plotting the weighted log OR for each study by year of publication. Heterogeneity of effects among studies was assessed using the Q statistic (approximate χ^2 distribution with degrees of freedom equal to the number of studies minus 1). The Qb statistic (approximate χ^2 distribution with degrees of freedom equal to the number of subgroup comparison levels minus 1) was calculated as an indicator of between-group differences in subgroup analysis. Statistical significance was determined by 2-sided $P<.05$.

To meet the assumption of independence of effect size, we included 1 point estimate of effect from each study. If studies compared outcomes of infants at more than 2 hospital levels, the highest reported level of hospital being compared with level III care was chosen as a more conservative measure of effect (ie, level II vs III chosen over level I vs III). If studies reported data for multiple subgroups of birth weight or gestational age, the widest range of birth weights or gestational weeks within the inclusion criteria was included. We combined data presented in nonoverlapping birth weight strata (eg, 500-999 g and 1000-1500 g) using the Comprehensive Meta-analysis software to create 1 point estimate. We identified 3 sets of publications that used data from the same population.[18-24] In each instance, we included only the study with the higher quality rating.[18,22,24] Populations defined by birth weight were not considered synonymous with those defined by gestational age and were analyzed separately.

Figure 1. Selection of Publications



[a] Because of the broad search strategy, many records on neonatal care and general hospital organization were returned but were unrelated to this review.
[b] For example, data graphed but point estimates not given, rates given without group N.
[c] There were 3 sets of studies (7 studies total[18-24]) that based data on the same or partially overlapping infant populations. One study was included from each set (3 studies[18,22,24]), leaving 4 excluded.[19,21-23]

RESULTS

Results of the publication search and selection are presented in FIGURE 1. A list of excluded publications with justifications for their exclusion is available from the authors.

Change in Published Evidence Over Time

The lack of significant slope (0.000; $P=.87$) indicates that available evidence on the association between level of hospital for VLBW infants at

birth and neonatal or predischarge mortality has not shifted over time (FIGURE 2).

VLBW Publications

Thirty-seven publications reporting infant populations by birth weight met all criteria for inclusion before quality category assessment.[13-16,18,22,25-55] Study details are presented in the eTable (available online at http://www.jama.com). The number of VLBW infants included in studies ranged from 29 to 27 191 and together form a population of 104 944 VLBW infants. Twenty-two studies were conducted in the United States; the remaining 15 were in Canada, Ghana, Israel, Australia, and Europe. Year of publication ranged from 1979 to 2008, with 1 study published in the 1970s, 16 in the 1980s, 5 in the 1990s, and 15 since 2000. The combined estimate of effect of VLBW studies indicated a 62% increase in odds of neonatal/predischarge mortality for infants born in non–level III hospitals compared with those born in level III hospitals (38% vs 23%; adjusted OR, 1.62; 95% CI, 1.44-1.83). Statistical heterogeneity was present ($Q=153.14$; $P<.001$).

Adequate- and High-Quality Evidence

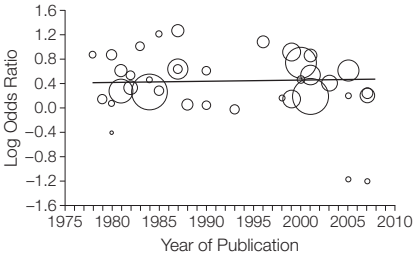
Nine publications were considered to be of sufficient quality for in-depth analysis (adequate- and high-quality categories; FIGURE 3).* When restricted to only adequate- and high-quality evidence (n=46 318 infants), a 60% increase in the odds of neonatal and/or predischarge mortality was estimated for VLBW infants born at non–level III hospitals (36% vs 21%; adjusted OR, 1.60; 95% CI, 1.33-1.92). Statistical heterogeneity persisted ($Q=39.11$; $P<.001$).

Extremely Low-Birth-Weight Subset

To explore the possibility of differences in effect of hospital level at birth for the smallest VLBW infants, data from 5 studies[16,18,29,32,37] that reported birth weight–stratified data or that restricted study population to extremely low-birth-weight (≤1000 g) infants were combined (n=13 093). Extremely low-birth-weight infants born in non–level III hospitals had an

*References 13, 15, 16, 18, 22, 29, 32, 37, 50.

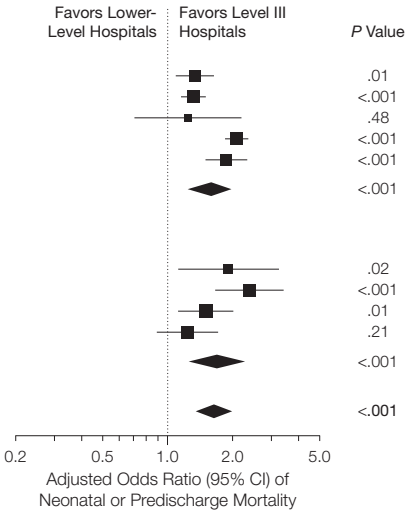
Figure 2. Meta-regression of Association Between Hospital Level of Birth and Neonatal/Predischarge Mortality by Year of Publication



Each circle in the plot represents a study, and the circumference of each circle is proportional to study population size. These data represent change in published evidence over time, not actual outcome measures at a given time. Because each study includes its own unique range of birth dates (eTable), calculation of change by infant birth date was not possible.

Figure 3. Meta-analysis Results of Adequate- and High-Quality Publications on Very Low-Birth-Weight (VLBW) Infants, Stratified by Level of Adjustment for Confounding

Source	Level Comparison	Deaths/Live Births, No. Lower Levels	Deaths/Live Births, No. Level III	Adjusted Odds Ratio (95% CI)	Z Value	*P* Value
Adjustment for Confounding: Case Mix						
Paneth et al,[50] 1982	II vs III	602/1083	423/869	1.32 (1.08-1.62)	2.68	.01
Gortmaker et al,[37] 1985[a]	I and II vs III	708/2717	508/2382	1.30 (1.14-1.48)	3.95	<.001
Sanderson et al,[18] 2000	II + vs III	15/88	292/2038	1.23 (0.70-2.17)	0.71	.48
Bode et al,[32] 2001[b]	II vs III	929/2266	2517/14 479	2.06 (1.82-2.33)	11.39	<.001
Kamath et al,[16] 2008	I and II vs III	757	1459	1.85 (2.31-1.22)	5.44	<.001
Combined estimate[c] Test for heterogeneity: $Q=31.56$; $P<.001$		2254/6154	3740/19 768	1.56 (1.22-1.98)	3.61	<.001
Adjustment for Confounding: Extensive						
Verloove-Vanhorick et al,[22] 1988	II vs III	83/359	125/482	1.90 (1.11-3.24)	2.36	.02
Cifuentes et al,[13] 2002	II vs III	1414	2472	2.37 (1.65-3.40)	4.68	<.001
Bacak et al,[29] 2005	I and II vs III	232/545	570/1127	1.50 (1.11-2.02)	2.66	.01
Howell et al,[15] 2008	I and II vs III/IV	1626/11 781		1.23 (0.89-1.70)	1.25	.21
Combined estimate[c] Test for heterogeneity: $Q=7.60$; $P=.06$		315/904	695/1609	1.66 (1.24-2.23)	3.42	<.001
Overall: all adequate- and high-quality VLBW studies[c] Test for heterogeneity: $Q=39$; $P<.001$		2569/7058	4435/21 377	1.60 (1.33-1.92)	4.96	<.001



Case mix indicates adjustment for demographic and/or socioeconomic status variables; extensive indicates adjustment for case mix plus maternal/perinatal risk factors and infant illness severity. CI indicates confidence interval. Size of data markers indicates size of study population.
[a] Included data are for urban populations and combine reported black/white race strata and birth weight strata (750-1000 g and 1001-1500 g).
[b] Included data combine reported birth date interval strata (1980-1984, 1985-1989, and 1990-1994) and birth weight strata (500-1000 g and 1001-1500 g).
[c] Raw death counts are not reported in Cifuentes et al[13] and Kamath et al[16] and are not stratified by hospital level in Howell et al.[15] These studies are not included in combined death/birth counts.

estimated 80% increase in odds of neonatal and/or predischarge mortality compared with those born at level III hospitals (59% vs 32%; adjusted OR, 1.80; 95% CI, 1.31-2.46) (FIGURE 4). Statistical heterogeneity was present (Q=28.40; P<.001).

VPT Studies

An additional 4 publications reporting infant populations by gestational age met criteria for inclusion (n=9300 infants)[24,56-58] (eTable). The weighted, combined data from these studies indicated that VPT infants born in lower-level hospitals have a 55% increase in odds of neonatal/predischarge mortality compared with those born in level III facilities (15% vs 17%; adjusted OR, 1.55; 95% CI, 1.21-1.98). Restricting to the 3 studies rated as adequate- and high-quality[24,56,58] (n=6100 infants) reduced the estimate to a 42% increased odds of mortality (7% vs 12%; adjusted OR, 1.42; 95% CI, 1.06-1.88). No evidence of heterogeneity was found in either the full sample (Q=3.81; P=.28) or the subset of adequate-/high-quality studies (Q=2.31; P=.31) (FIGURE 5).

Subgroup Analyses

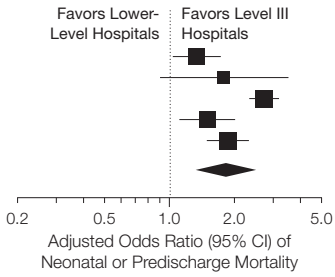
Subgroup analyses were performed separately on the full sample of 37 VLBW studies, 4 VPT studies, and subsets of adequate- and high-quality evidence and ELBW infants. No significant between-group differences were found based on study design, use of population-based or non–population-based data, data source, US or non-US location, outcome variable, birth weight range, inclusion of infants smaller than 500 g, or extent of control for confounding (P>.05 for all).

A potential source of heterogeneity was identified in subgroups based on level of adjustment for confounding. Studies that controlled more extensively (adjusting for maternal/perinatal risk factors and/or infant illness severity)[13,15,16,22,29] did not show significant evidence of heterogeneity (n=5 studies; Q=7.60; P=.06) (Figure 3).

Although the between-group differences were not statistically significant, 2 patterns were observed in the adequate- and high-quality studies; combined ORs were higher when studies had more extensive adjustment for confounding and when studies measured the outcome as predischarge mortality as opposed to measuring neonatal mortality (TABLE).

Figure 4. Meta-analysis Results of Adequate- and High-Quality Publications on Extremely Low-Birth-Weight Infants

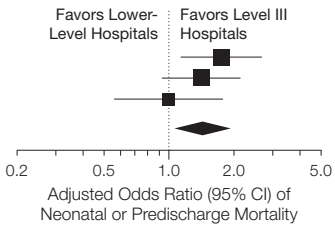
Source	Level Comparison	Deaths/Live Births, No. Lower Levels	Deaths/Live Births, No. Level III	Adjusted Odds Ratio (95% CI)	Z Value	P Value
Gortmaker et al,[37] 1985[a]	I and II vs III	245/442	249/515	1.33 (1.08-1.72)	2.19	.03
Sanderson et al,[18] 2000[b]	II + vs III	15/36	249/869	1.78 (0.90-3.51)	1.66	.10
Bode et al,[32] 2001[c]	II vs III	763/1100	1696/6243	2.71 (2.32-3.18)	12.44	<.001
Bacak et al,[29] 2005	I and II vs III	232/545	570/1127	1.50 (1.11-2.02)	2.66	.01
Kamath et al,[16] 2008	I and II vs III	757	1459	1.85 (1.43-2.31)	5.44	<.001
Overall		1255/2123	2764/8754	1.80 (1.31-2.46)	3.66	<.001
Test for heterogeneity: Q=28.40; P<.001[d]						



CI indicates confidence interval. Size of data markers indicates size of study population.
[a] Included data are for urban populations and combine reported black/white race strata.
[b] Included data combine reported birth weight strata (500-749 g and 750-1000 g).
[c] Included data combine reported birth date interval strata (1980-1984, 1985-1989, and 1990-1994).
[d] The study by Kamath et al[16] does not report raw death count data and is not included in combined death/birth counts.

Figure 5. Meta-analysis Results of Adequate- and High-Quality Publications on Very Preterm Infants

Source	Level Comparison	Deaths/Live Births, No. Lower Levels	Deaths/Live Births, No. Level III	Adjusted Odds Ratio (95% CI)	Z value	P Value
Lee et al,[24] 2003[a]	Outborn vs inborn	89/508	274/2454	1.75 (1.14-2.68)	2.56	.01
Johansson et al,[56] 2004	II vs III	136/1320	131/924	1.41 (0.98-2.13)	1.63	.10
Palmer et al,[58] 2005	Outborn vs inborn	15/148	88/746	1.00 (0.56-1.78)	0.00	>.99
Overall		240/1976	493/4124	1.42 (1.06-1.88)	2.38	.02
Test for heterogeneity: Q=2.31; P=.31						



CI indicates confidence interval. Size of data markers indicates size of study population. Inborn infants are those born in a level III hospital; outborn infants are those born in a lower-level hospital then transferred to a level III hospital.
[a] Included data combine reported gestational age strata (<26 weeks, 27-29 weeks, and 30-31 weeks).

Publication Bias and Sensitivity Analysis

No evidence of publication bias was found in the VLBW studies (Egger test of the intercept, $P = .83$) (eFigure). There was borderline evidence of publication bias ($P = .05$) for the VPT studies. One-study-removed sensitivity analysis did not reveal any study to have a more significant effect on combined estimates than any other.

Table. Subgroup Analysis Patterns[a]

Variable	Adequate-/High-Quality VLBW (≤1500 g) Studies (n = 9)		Adequate-/High-Quality VPT (≤32 wk Gestation) Studies (n = 3)	
	No. of Studies	OR (95% CI)	No. of Studies	OR (95% CI)
Level of adjustment for confounding				
Case mix[b]	5[16,18,32,37,50]	1.56 (1.22-1.98)	1[58]	1.00 (0.56-1.78)
Extensive[c]	4[13,15,22,29]	1.66 (1.24-2.23)	2[24,56]	1.56 (1.16-2.11)
Outcome measurement				
Neonatal mortality	7[15,16,18,29,32,37,50]	1.51 (1.24-1.83)	2[56,58]	1.25 (0.90-1.76)
Predischarge mortality	2[13,22]	2.21 (1.64-2.98)	1[24]	1.75 (1.14-2.68)

Abbreviations: CI, confidence interval; OR, odds ratio; VLBW, very low-birth-weight; VPT, very preterm.
[a] All between-group differences were insignificant as measured by the *Qb* statistic (all $P < .001$).
[b] Case mix indicates adjustment for demographic and/or socioeconomic status variables.
[c] Extensive indicates adjustment for case mix plus maternal/perinatal risk factors and infant illness severity.

COMMENT

This is the first publication, to our knowledge, to analyze more than 30 years of published data on this key premise of perinatal regionalization: access to risk-appropriate perinatal care improves infant mortality outcomes in VLBW and VPT deliveries. Birth weight–specific neonatal or predischarge mortality rate calculated by hospital level at birth is the most widely used indicator in assessing and comparing outcomes within perinatal care systems.

Much has changed in the field of neonatology since the introduction of perinatal regionalization.[59] The introduction of surfactant therapy in the late 1980s and antenatal steroids in the mid-1990s has improved outcomes for VLBW infants,[60,61] the supply of neonatologists has increased,[62] and analytical capacity in epidemiology has increased.[63] Dissemination of these advancements to lower-level hospitals, following initial introduction at level III centers, may be contributing to improvements in infant survival at all levels. Because studies use wide-ranging and overlapping birth date ranges, we could not cumulatively measure change in the association between hospital level of birth and infant outcomes at specific time points, but the meta-regression test based on year of publication shows that the body of evidence available to policy makers and stakeholders has remained consistent over time.

Our *Q* statistics indicated heterogeneity of effects among the full sample of VLBW publications, suggesting that more variation existed between studies than would be expected by chance. Restricting the sample to studies that adjusted for perinatal risk factors and/or infant illness severity eliminated significant statistical heterogeneity, implying that a possible source of variation in studies is distribution of the highest-need infants. Studies of VPT infants were free from statistical heterogeneity, suggesting a more homogeneous population. Heterogeneity in exposure is common when analyzing epidemiological evidence,[64] and variations in hospital level definitions and perinatal systems[65] are likely a source of variation among these studies. However, we were unable to explore this because hospital information was insufficiently reported in most studies. The magnitude of combined effects remained remarkably consistent across subsets of studies with and without statistical heterogeneity, indicating that the variation did not change the overall conclusion: there is an increase in odds of death for VLBW and VPT infants born at non–level III facilities. We have chosen to report all combined outcomes using a random-effects model, which assumes variability, and to limit extrapolation of the data.

Publications in the past decade have trended toward measurement by gestational age in addition to birth weight. Although birth weight is an easier and more accurate measurement to obtain than estimates of gestational age, the latter is a better indicator of physiologic maturity and is key in an obstetrician's decision-making process in a threatened preterm delivery.[60] Our analysis did not show a marked difference in combined outcomes between VLBW and VPT studies.

Observed patterns of higher odds of death when measured by predischarge mortality as opposed to neonatal mortality may indicate that VLBW infants born at level II hospitals may survive beyond the first 28 days, but proportionately fewer survive to discharge compared with those born at level III facilities. Shifts in the time of death among VLBW births, from early neonatal to postneonatal deaths, were observed in the 1990s.[60,66]

We included studies from countries other than the United States, despite the possibility of variation due to differences in underlying health infrastructures. Results of subgroup analysis indicated no significant difference between US and non-US studies. Additionally, some non-US studies use American Academy of Pediatrics guidelines[22] or levels of care that mirror those outlined in *TIOP*,[24] suggesting similar organization of care and increasing comparability. The exclusion of non-English studies may limit the number of non-US studies in our analysis and is a potential source of bias in our study selection. Lack of inclusion of unpublished data is a potential source of bias; however, given the large volume of published work, we think it unlikely that either would have altered our results.

The quality of reviewed studies was limited by inadequate definitions of hospital levels or inadequate descriptions of hospital capabilities, perhaps reflecting a lack of clearly defined systems in many states.[65] The measures of effect calculated from this body of evidence combine data from non–level III hospitals, providing an estimate for "highest level of care" vs "lower levels of care," the basic concept of perinatal regionalization. However, when attempting to compare combined outcomes at specific lower levels, such as II+ vs III, interhospital variation in capabilities[67-69] is of greater concern. Failure to report hospital-level definitions and/or capabilities not only leaves the intervention undefined, it limits the ability of stakeholders to relate the research to other perinatal systems and translate it into practice.

Studies varied in adjustment for confounding factors. Because of analytical limitations in earlier decades, such adjustment was not expected. However, it must now be considered essential because it is known that VLBW infants present with differing levels of illness severity and other variables that may affect potential for survival regardless of hospital of birth.[29] There is also a risk of bias due to selective transfer of infants with the highest chance of survival[60] and possible increased baseline risk in level III hospital populations due to prenatal referral for known complications.[70] Identifying uniform standards by which to evaluate control of confounding across studies is difficult. Sources of confounding can vary by population or be difficult to measure, such as parental wishes for aggressive resuscitation.[25] Studies can weaken effect estimates by controlling for variables like necrotizing enterocolitis, which is linked to management of the infant[71] and thus in the pathway of effect between birth and death. Future research must ensure that adjustment for confounding is both thorough and appropriate to achieve accurate effect estimates.

The included literature is limited by the lack of consideration of obstetric capability at hospitals. *Toward Improving the Outcome of Pregnancy* included obstetric care as well as neonatal care in its original guidelines[2] but it is the latter that has come to be synonymous with perinatal regionalization. Although level III facilities provide high-level maternal-fetal as well as neonatal services, disproportionate capabilities do exist at level II facilities,[72] and few studies adjust for differences in obstetric expertise.

Although hospital level at birth and neonatal or predischarge mortality have been used consistently in the past 30 years to evaluate perinatal regionalization, there are several variations on this association. The inclusion of fetal death may offer important insight into the effect of level of obstetric care[73] as well as reduce bias due to differences in assessments of viability and resuscitation protocols.[74] Other studies show that the effect of hospital level at birth is modified by the hospital's volume of VLBW deliveries.[15,73] And as VLBW infant survival rates increase, neonatal and predischarge mortality may no longer be sensitive enough measures; research that examines long-term morbidity may be more important.[20,75] It is also notable that studies in this analysis evaluate infants born at lower-level hospitals regardless of subsequent transfer to a higher-level hospital for care. A study measuring VPT infant survival based on the level of hospital where an infant received its first 48 consecutive hours of care reported an OR of 7.9 (95% CI, 2.2, 29.1) for mortality at level I and II facilities.[76] Understanding the effect of deregionalization also requires assessing outcomes when non–level III hospitals do not transfer VLBW/VPT infants after birth.

This review addresses outcomes of a single high-risk infant group and does not evaluate maternal outcomes or the other improvements in care systems that perinatal regionalization was designed to foster, such as cost-effectiveness through centralization of expensive technologies and development of expertise through the concentration of relatively rare cases at a few locations. Deregionalization and the long-term consequences of inefficient use of health care resources may affect families and children in more ways than can be evaluated here.

CONCLUSION

The results of this review confirm a primary premise on which perinatal regionalization systems are based: high-risk infants have higher mortality rates when born outside hospitals with the most specialized levels of care. Although they represent less than 2% of US births, 55% of infant deaths occur among VLBW infants.[77] Strengthening perinatal regionalization systems in states with high percentages of VLBW and VPT infants born outside of level III centers could potentially save thousands of infant lives every year.

Future research should use appropriate risk adjustment and thorough reporting of hospital-level information. Further exploration of the effect of hospital volume, obstetrical level, infants that remain for care at lower-level hospitals after birth, and additional outcome measures such as long-term infant morbidity and fetal and maternal mortality will add to the understanding of this important intervention.

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Study concept and design: Lasswell, Barfield, Rochat, Blackmon.
Acquisition of data: Lasswell, Barfield.
Analysis and interpretation of data: Lasswell, Barfield, Blackmon.
Drafting of the manuscript: Lasswell, Barfield, Blackmon.
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We try often, though we fall back often. A brave delight, fit for freedom's athletes, fills these arenas, and fully satisfies, out of the action in them, irrespective of success.

—Walt Whitman (1819-1892)

