Association between Off-Peak Hour Birth and Neonatal Morbidity and Mortality among Very Low Birth Weight Infants

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Objective To assess the independent association between overnight or "off-peak" hour delivery and 3 neonatal morbidities strongly associated with childhood neurocognitive impairment.

Study design Retrospective population based cohort study of all infants with birth weights of 500-1499 g born without severe congenital anomalies in California or Pennsylvania between 2002 and 2009. Off-peak hour delivery was defined as birth between 12:00 a.m. and 6:59 a.m. The study outcomes were death; bronchopulmonary dysplasia, retinopathy of prematurity, and severe (grade 3 or 4) intraventricular hemorrhage among survivors; the composite of each morbidity or mortality; and the composite of death or 1 or more of the evaluated morbidities.

Results Of 47 617 evaluated infants, 9317 (19.6%) were born during off-peak hours. The frequencies of all study outcomes were higher among infants born during off-peak compared with peak hours. After adjusting for maternal, infant, and hospital characteristics, off-peak hour delivery was associated with increased odds of severe intraventricular hemorrhage among survivors (OR 1.39, 95% CI 1.23-1.57) and the composite outcomes of death or severe intraventricular hemorrhage (OR 1.16, 95% CI 1.07-1.25) and death or major morbidity (OR 1.08, 95% CI 1.02-1.15). There was no evidence of subgroup effects based on delivery mode, birth hospital neonatal intensive care level or annual very low birth weight infant delivery volume, or weekday vs weekend off-peak hour delivery for any study outcome.

Conclusions Very low birth weight infants born between midnight and 7:00 a.m. are at increased risk for severe intraventricular hemorrhage and death or major neonatal morbidity. *(J Pediatr 2017;186:41-8).*

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Approximately 20% of all births in the US occur between midnight and 7 a.m.[1] Several epidemiological studies raised concern that delivery during overnight or "off-peak" hours may increase mortality risk among preterm infants.[2-6] Recent data, largely from tertiary academic centers, suggest that this increased risk is due to differences in case-mix or illness severity among infants born during the day compared with overnight.[7-9] Whether this is also true in a broader, population-based cohort of preterm infants is uncertain. Moreover, there is limited data on the association between off-peak hour delivery and neonatal morbidities that are predictive of childhood neurodevelopmental impairment. Evaluation of these outcomes is essential to assess the true adverse effects association with off-peak hour delivery.

The objectives of the present study were to compare the risks for death, severe intraventricular hemorrhage, bronchopulmonary dysplasia, and retinopathy of prematurity among very low birth weight (VLBW; birth weight <1500 g) infants born during off-peak vs peak hours in California and Pennsylvania. We used hierarchical regression modeling and mediation analysis to quantify the relative importance of maternal, neonatal, and hospital level factors on any observed differences in outcome risk.

Methods

We conducted a retrospective, population-based cohort study of all infants with birth weights between 500 and 1499 g and born without severe congenital anomalies between January 1, 2002, and December 31, 2009 in California and Pennsylvania. Each state's department of health linked infant birth and death certificates using name and date of birth and deidentified the records. Greater than 98% of these records were then matched to maternal and newborn hospital discharge records using previously described methods.[10-12] More

BPD	Bronchopulmonary dysplasia
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
IVH	Intraventricular hemorrhage
NICU	Neonatal intensive care unit
ROP	Retinopathy of prematurity
VLBW	Very low birth weight

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than 80% of the unmatched birth certificates were missing a hospital identifier, suggesting these infants were delivered at home or at a birthing center. The gestational ages and racial/ethnic distributions were similar between the matched and unmatched records. We excluded records with birth weights greater than 5 SDs from the mean birth weight for the recorded gestational age because of potential recording errors in either variable.[13] Infants born less than 500 g were also excluded to reduce bias secondary to potential variability in resuscitation strategies among infants born at the limits of viability. The institutional review boards at The Children's Hospital of Philadelphia and the departments of health in California and Pennsylvania approved this study.

The study exposure was delivery during "off-peak" hours defined as birth between 12:00 a.m. and 6:59 a.m. "Peak-hour" births were those that occurred at all other times of the day. We a priori selected this 7-hour overnight period because it is similar to the off-peak periods used in several other studies on this topic and because 7:00 a.m. is a common time that overnight physician and nurse staffing shifts conclude.[2,5,9,14,15] The study outcomes were death; severe (grade 3 or 4) intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP) among infants who survived to discharge; the individual composites of death or severe IVH, BPD, and ROP; and death or major morbidity, which included 1 or more of the evaluated morbidities.

The clinical and sociodemographic data used in this analysis were obtained from infant birth and death certificates and the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis and procedure codes present in the maternal and infant hospital discharge records (**Table I**; available at www.jpeds.com). The death outcome includes neonatal deaths that occurred before neonatal intensive care unit (NICU) discharge and in-hospital fetal deaths with a gestational age ≥23 weeks gestation or a birth weight ≥500 g that met a previous definition of a potentially preventable fetal death.[11] We included these fetal deaths to reduce bias against hospitals with high-level obstetrical services capable of rapid cesarean deliveries that resulted in live births that may have otherwise died in utero.[11,16] Birth hospital NICU level was defined based on the 2004 American Academy of Pediatrics report on levels of neonatal care and was retrospectively applied to deliveries that occurred before 2004 to maintain consistency over the study period.[17]

Statistical Analyses

Infant, maternal, and hospital characteristics were summarized with standard descriptive statistics and compared between the infants born during peak and off-peak hours. The proportions of infants born via cesarean and vaginal delivery were calculated for each hour of the day (number of deliveries per hour divided by the total sample size) and reported graphically.

Hourly adjusted delivery rates were also determined to account for maternal and infant factors that may affect the choice of delivery mode. The adjusted rates were calculated using logistic regression and marginal standardization, with delivery mode as the dependent variable and all maternal, infant (excluding gestational age), and birth hospital characteristics listed in **Table II** as independent variables.[18]

We used hierarchical logistic regression to explore the potential association between off-peak hour delivery and the study outcomes. In each model, the outcome of interest was defined as the dependent variable. The first regression model included the year and state of birth only, to account for potential differences across the 2 geographic regions and change in outcome incidence over time. The following prespecified groups of independent covariates were then sequentially added based on the order that they occur during pregnancy: maternal sociodemographic characteristics, chronic comorbidities, and complications of pregnancy (model 2); infant demographic factors present at birth (model 3); and birth hospital characteristics (model 4). This approach to model development permits the mediation analysis described below. Gestational age was not used in the models because of missing data for 6% of the cohort. We used a robust variance estimator for cluster-correlated data in each of the above models to account for possible within-hospital outcome correlation.[19,20]

We performed subgroup analyses to assess for potential differences in the association between off-peak delivery and the study outcomes based on the following 5 covariates: delivery mode, birth hospital NICU level, birth hospital annual volume of VLBW infant deliveries, and 2 definitions of weekday vs weekend off-peak hour delivery (birth between 12:00 a.m. and 6:59 a.m. on Saturday, Sunday, and Monday and birth between 12:00 a.m. and 6:59 a.m. on Sunday and Monday only). Subgroup effects were assessed by adding an interaction term between the dichotomous off-peak hour delivery variable and the subgroup variable to the full regression model (model 4) described above. To account for multiple comparisons, a P value of ≤.0013 was used to identify a statistically significant subgroup effect.[21]

In a secondary analysis, we calculated the risk-aORs for developing the study outcomes based on delivery during each hour of the day. The full regression model (model 4) was used in this analysis. Births between 10:00 a.m. and 10:59 a.m. were used as the reference because more infants were born during this period than any other hour throughout the day.

Finally, we assessed for mediation of the association between off-peak hour delivery and the study outcomes by the evaluated maternal, infant, and hospital level factors. Mediation analysis divides the association between an exposure and an outcome (total effect) into the proportion of the association attributable to the study exposure itself (direct and/or residual effects) and the proportion of the association attributable to mediating factors (indirect effects). (**Figure 1**; available at www.jpeds.com) In the present analysis, the direct or residual effect indicates the proportion of the association between off-peak hour delivery and the study outcomes not accounted for by the evaluated maternal, infant, and hospital level factors. Observed residual effect may be due to unmeasured mediation by the evaluated factors. It may also result, at least in part, from hospital structural factors (ie, capabilities of hospital professionals, staff, and the overall health care delivery system) that