Gestational Age at Birth and Outcomes after Neonatal Cardiac Surgery: An Analysis of the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database

Running title: Costello et al; Gestational Age and Cardiac Surgery

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Abstract

Background—Gestational age at birth is a potentially important modifiable risk factor in neonates with congenital heart disease. We evaluated the relationship between gestational age and outcomes in a multicenter cohort of neonates undergoing cardiac surgery, focusing on those born at early term (i.e., 37-38 weeks gestation).

Methods and Results—Neonates in the Society of Thoracic Surgeons Congenital Heart Surgery Database who underwent cardiac surgery from 2010-11 were included. Multivariable logistic regression was used to evaluate the association of gestational age at birth with in-hospital mortality, post-operative length of stay and complications, adjusting for other important patient characteristics. Of 4,784 included neonates (92 hospitals), 48% were born prior to 39 weeks gestation, including 31% at 37-38 weeks. Compared with a 39.5 week gestational age reference level, birth at 37 weeks gestational age was associated with higher in-hospital mortality, with an adjusted odds ratio (95% C.I.) of 1.34 (1.05-1.71, p=0.02). Complication rates were higher and postoperative length of stay was significantly prolonged for those born at 37 and 38 weeks gestation (adjusted p<0.01 for all). Late-preterm births (34-36 weeks gestation) also had greater mortality and postoperative length of stay (adjusted p≤0.003 for all).

Conclusions—Birth during the early term period of 37-38 weeks gestation is associated with worse outcomes following neonatal cardiac surgery. These data challenge the commonly held perception that delivery at any time during term gestation is equally safe and appropriate, and question the related practice of elective delivery of fetuses with complex congenital heart disease at early term.

Key words: heart defects, congenital; pediatrics; surgery; cardiopulmonary bypass, gestational age, prematurity
Introduction

Congenital heart defects are the most common birth anomalies, with moderate to severe variants occurring in approximately 6 per 1,000 live births.1 Patients with critical congenital heart disease, including a variety of anomalies characterized by ductal dependency of either systemic or pulmonary blood flow (including most single ventricle heart defects), typically undergo cardiac surgery during the first few days of life. In the United States alone, approximately 6,000 neonatal cardiac operations are performed annually. While outcomes have improved recently, certain lesions are still associated with average in-hospital mortality of 10-20% or more, and many survivors continue to experience significant morbidities and consume considerable healthcare resources.2,3 Thus, there is a need to examine potentially modifiable risk factors for poor outcomes.

Gestational age at birth is likely one such risk factor. Births occurring between 37 weeks 0 days and 41 weeks 6 days completed gestation are designated “term,” signifying a period traditionally perceived as a safe window for delivery.4 In neonates and young infants undergoing cardiac surgery, both prematurity and low birth weight are well-established risk factors for poor outcomes.5-7 Thus fetuses diagnosed prenatally with complex congenital heart disease are often scheduled for elective delivery once term gestation is reached. The majority of such births occur at early term (i.e., at 37-38 weeks gestational age), in the interest of facilitating care coordination at tertiary care centers.8-12

Recent investigations have explored the relationship between gestational age at term birth and outcome in babies with cardiac disease and have challenged the assumption that early term birth is optimal. However, these investigations have been limited by single center design13 and the use of administrative data.14 Thus, our understanding of the relationship between early term
birth and outcome in neonates with complex congenital heart disease is incomplete.

The purpose of the present study was to examine the association between early term birth and outcomes following neonatal heart surgery across a large multicenter cohort, using clinical registry data. Our primary outcome was in-hospital mortality. Post-operative length of stay and complications were examined as secondary outcomes.

Methods

Data source
The Society of Thoracic Surgeons Congenital Heart Surgery (STS-CHS) Database was used for this study. This database currently represents more than 85% of all pediatric heart centers in the United States. Perioperative, operative, and outcomes data are collected on all patients undergoing pediatric and congenital heart surgery at participating centers using standard definitions (STS Congenital Heart Surgery Database Data Specifications, Version 3.0, available at http://www.sts.org/node/518). The Duke Clinical Research Institute serves as the data warehouse and analytic center for all STS databases. This study was approved by the Duke University institutional review board with waiver of informed consent and by the STS-CHS Database Access and Publications Committee.

Study population
A variable specifying gestational age stratified by weeks was added to the STS-CHS Database on January 1st, 2010. Thus the potential study population eligible for inclusion consisted of 9,936 neonates from 101 STS-CHS centers who underwent a primary cardiovascular operation prior to 28 days of age from January 1st, 2010 through December 31st, 2011. We excluded 445 patients who underwent a non-cardiac primary operation. Given the significantly different operative risk
involved for various congenital heart detects, we excluded 109 patients whose operation could not be classified into one of the Society of Thoracic Surgeons–European Association for Cardiothoracic Surgery (STS-EACTS) Mortality Categories (category 1, lowest mortality risk; category 5, highest mortality risk). We also excluded patients undergoing isolated closure of patent ductus arteriosus (n = 1,702), or permanent/temporary pacemaker operation, and those in whom a patent ductus arteriosus operation or pacemaker was the primary procedure (n=93), in addition to those with missing data for key exposure and outcomes variables (n = 2,804, of which 2,012 were excluded for missing gestational age).

**Outcomes**

The primary outcome for this study was in-hospital mortality. Secondary outcomes included the occurrence of at least one of the following major complications: postoperative mechanical circulatory support, renal failure requiring dialysis, neurological deficit persisting at discharge, stroke, unplanned cardiac reoperation or interventional cardiovascular catheterization during the postoperative time period, and heart block requiring permanent pacemaker. We also assessed the occurrence of one or more of an inclusive list of complications coded in the STS-CHS database (STS Congenital Heart Surgery Database Data Specifications, Version 3.0, available at http://www.sts.org/node/518). Of note, complications occurring after discharge from the STS-CHS center are not captured in the database. Post-operative length-of-stay was also analyzed.

**Analysis**

Summary statistics were reported as count (percent) or median with 25th to 75th percentiles, as appropriate. The Wilcoxon-rank sum test was used to compare gestational age at birth for patients with and without a prenatal diagnosis of congenital heart disease. Since it is known that both treatment and outcomes may vary across centers, our analytic approach to evaluate the
relationship between gestational age and outcome was chosen specifically to account for confounding by center, and conditional logistic regression models stratified by center were used for our primary outcome variable. Results were adjusted for known factors associated with outcome in this population including STS-EACTS Mortality Category of the primary procedure, age and weight at surgery, gender, the presence of any STS pre-operative risk factor or any non-cardiac anatomic or genetic abnormality/syndrome. Both unadjusted and adjusted odds ratios and 95% confidence intervals are presented using models that account for center differences. In modeling the trend between event risk and gestational age, natural cubic spline transformation was applied to the gestational age variable in weeks, allowing the models to accommodate a non-linear relationship between the outcomes and gestational age. The knots (where the trend is allowed to change, subjecting to mathematical conditions ensuring smoothness) were chosen without knowledge of the clinical outcomes and based on the distribution of gestational age. The knots used in all models were 36.5, 38.5 and 40.5 weeks. We chose 39.5 weeks as the referent level of gestational age based on an empirical analysis of the study data and that available in prior studies. For the post-operative length-of-stay outcome, negative binomial models using the canonical log-link function were fitted with indicator variables for centers and other covariates as noted above, thereby generating estimated ratios of median postoperative length-of-stay between two gestational age values. To facilitate the interpretation of the ratios of length-of-stay, we calculated the extra days of stay associated with gestational age by multiplying the population median length-of-stay by (ratio -1).

We evaluated the missing data mechanism and determined that missing-at-random assumption was implausible for gestational age as the event of not having the variable recorded was likely associated with greater gestational age values even after conditioning on variables
collected by the STS-CHS database. In light of this, the multiple imputation approach was not adopted. We instead performed a complete case analysis because this approach is known to produce unbiased estimates under the assumption that the regression model is correctly specified and that missingness depends on covariates but not the outcomes.18

SAS/STAT® software version 9.2 (SAS Institute Inc., Cary, NC) and R version 2.14 (R Foundation for Statistical Computing, Vienna, Austria) were used to perform the analyses. A p-value <0.05 was considered statistically significant.

Results

Study Population

The study population included 4,784 neonates who underwent cardiac operations at 92 institutions. Preoperative characteristics and operative variables are displayed in Table 1. The median gestational age at birth was 39 weeks (25th to 75th percentile, 37-39 weeks). Median gestational age in those with a prenatal diagnosis of congenital heart disease was 38 weeks (25th to 75th percentile, 37-39 weeks) and in those without a prenatal diagnosis was 39 weeks (25th to 75th percentile, 37-40 weeks; p=<0.001). Of note, 48% of study patients were born prior to 39 weeks gestation, including 31% at 37-38 weeks gestation. Age at surgery was similar for patients born at 39-40 weeks gestational age when compared to patients born at 37-38 weeks (median, 7 days; 25th to 75 percentile, 4 to 12 days for both groups). Patients born at earlier gestational ages underwent surgery at progressively older ages (median age at surgery, 8 days for 34-36 weeks and 13 days for ≤34 weeks). Given the small number of study patients born at the extremes of gestational age (n = 154 patients born ≤33 weeks gestational age at birth; n = 14 patients born ≥42 weeks gestational age), the analyses, tables and figures presented below pertain to patients
born between 34-41 weeks gestational age.

**In-hospital Mortality**

Overall in-hospital mortality was 9.9% (474 of 4,784). Unadjusted mortality rates by week of gestational age at birth are shown in Table 2. In-hospital mortality was 7.3% at 39-40 weeks, 9.0% at 38 weeks, and 13.2% at 37 weeks. Adjusted mortality data are shown in Table 2 and Figure 1. When compared to the 39.5 week referent level, adjusted odds of mortality were significantly higher for patients born at 37 weeks gestation. Birth during the late preterm period of 34-36 weeks gestation also had greater adjusted mortality. Adjusted mortality data stratified by cardiopulmonary bypass vs. non-cardiopulmonary bypass cases, and by lower complexity (STS-EACTS category 1-3) vs. higher complexity (STS-EACTS category 4-5) operations may be found in Supplemental Table 1. The patterns of adjusted odds of mortality for these subsets were directionally similar to those of the overall study cohort, although not statistically significant for patients born at early term (37-38 weeks gestational age) when compared to the 39.5 week referent group. Division of the cohort into smaller subsets (e.g., on-pump and off-pump operations) likely results in the analyses being underpowered to detect differences in adjusted mortality for the patient subgroups born at early term.

**Post-operative Complications**

Of 4,784 study patients, at least one postoperative complication occurred in 67.9% (n=3,247), and at least one major postoperative complication occurred in 19.0% (n=911). When compared to a 39.5 week referent level, patients born at 37 and 38 weeks gestation had greater adjusted odds of developing one or more postoperative complications of any type, and those born at 37 weeks had greater adjusted odds of developing one or more major postoperative complications (Table 3).
Postoperative Length of Stay

The median postoperative hospital length of stay for all study patients was 16 days (25th to 75th percentile, 9 – 34 days). When compared to a 39.5 week referent level, patients born at 34 to 38 weeks gestation had longer adjusted duration of postoperative length of stay (Figure 2).

Differences in estimated extra days of postoperative hospitalization and ratios of medians of postoperative length of stay between gestational age groups are shown in Table 4. Of the 4,310 patients who survived to hospital discharge, those born at 39-40 weeks were less likely to be discharged to another acute or chronic care center (4.0%) compared to those born at 37-38 weeks (5.5%), 34-36 weeks (6.4%), or less than 34 weeks (18.9%; 3 degree-of-freedom chi-squared test p-value, <0.001). This observation likely has differential influence on length of stay data and capture of complications.

Discussion

In neonates undergoing cardiac surgery, we found that outcomes were worse in patients born during the early term period of 37-38 weeks completed gestation. When compared to a 39.5 week referent group, risk adjusted in-hospital mortality was significantly higher for patients born at 37 weeks gestation. Early term neonates also had higher rates of post-operative complications and prolonged length of stay. Consistent with prior studies, we also found that birth during the late preterm period of 34-36 weeks gestation was associated with worse outcomes.

Prematurity was formally defined in the 1960s by an American Academy of Pediatrics committee as birth prior to 37 weeks completed gestation.19 It has long been known that premature neonates, including those with heart defects, are at risk for adverse outcomes.7 When compared to term babies with congenital heart disease, those born prematurely have an
approximately 2-fold greater risk of in-hospital mortality. The findings reported in our study and others suggest that gestational age, when analyzed as an ordinal variable, may provide more granularity and additional inferences relative to analyses based on a binary determination of prematurity.

Two prior studies have examined the association between gestational age at term and outcomes in patients with heart disease. In an investigation of 971 neonates with critical congenital heart disease, those born at 37 to 38 weeks gestation had 2.3-fold greater adjusted odds of in-hospital mortality when compared to a referent group born at 39 to 40 weeks. That study involved robust risk adjustment, but was limited by its single center design and failure to account for any post-natal deaths that occurred prior to interhospital transfer to the study center.

In a study examining National Health Statistics linked birth-death files of 14.9 million infants born in the United States, the infant mortality rate attributable to congenital heart disease increased in a linear fashion with decreasing gestational age prior to 39 weeks. That study captured all postnatal mortalities regardless of referral to a tertiary care center, but risk adjustment was limited by the use of an administrative dataset. The design of the present study overcame several of these limitations. The multicenter cohort of patients captured by the STS-CHS Database makes our findings highly generalizable, and the use of rich clinical registry data allowed more comprehensive risk-adjustment. Importantly, we were able to adjust for weight at the time of surgery, a potential source of confounding when assessing the relationship between gestational age and outcomes.

Our findings are consistent with those reported in recent observational studies involving babies without cardiac or other birth defects. In such patients, a “U-shaped” relationship exists between gestational age at term birth and outcomes, with a nadir for adverse results at 39-40
weeks. In these studies, seemingly healthy babies born at early term have consistently higher rates of mortality, neonatal intensive care admission, and other morbidities commonly associated with prematurity. Although our study and those noted above were not designed to establish causality, maturational differences in multiple organ systems are likely contributory to the adverse outcomes experience by patients born at early term. When compared to babies without birth defects who undergo elective delivery at 39 to 40 weeks gestation, those born at early term are much more likely to require mechanical ventilation, to have respiratory distress syndrome requiring surfactant, to develop hypoglycemia, and to develop sepsis. Subtle but important developmental changes in the respiratory system occur in late gestation, including pathways critical to nitric oxide and surfactant production and fetal lung fluid clearance. Incomplete maturation of energy stores, enzyme function and immunity may also be causal in the observed outcomes.

A number of studies have identified an association between a prenatal diagnosis of congenital heart disease and earlier delivery. This finding may be explained in part by the fact that mothers expecting a fetus with congenital heart disease often undergo frequent fetal monitoring in late gestation, such as serial fetal non-stress tests and biophysical profiles, with the potential that the results of such testing are false positives far more often than true positives. Physician and maternal anxiety could also be a factor. Further study of the relationship between prenatal diagnosis and earlier delivery is warranted.

When considering our findings and the cumulative body of literature examining the relationship between gestational age and outcomes in neonates with or without cardiac disease, the “take home message” is consistent and clear. Delivery at 39-40 weeks gestation is associated with the lowest rates of early morbidity and mortality. Some evidence suggests that
neurodevelopmental outcomes may also be more favorable in infants born at 39-40 weeks gestational age who undergo cardiac surgery.\textsuperscript{31} There are several important inferences from these data. The relatively common practice of scheduled, elective delivery of neonates with a prenatal diagnosis of congenital heart disease at 37 to 38 weeks gestation requires re-evaluation. In selected cases, there may be compelling fetal or maternal indications for earlier delivery (e.g., hydrops fetalis, preeclampsia). However, our data and others suggest that scheduling the elective delivery of a fetus with congenital heart disease prior to 39 weeks gestational age should generally be avoided. Such scheduled deliveries are often motivated by a desire to achieve a “controlled” birth near a congenital heart center. The perceived convenience of having a set delivery date for the parents, extended families and the multiple clinician subspecialists involved in the care of these neonates may be contributory. It is important to recognize that the elimination of elective early term deliveries could potentially lead to the spontaneous delivery of more babies with critical congenital heart disease at hospitals remotely located from a congenital heart center. This issue could be largely overcome by anticipatory relocation of the expectant mother closer to the pediatric heart center during late gestation to await the onset of labor.

Further evaluation of such strategies is necessary. The information provided by this study and others may also be useful for counseling parents and referring clinicians. Finally, when conducting outcomes research, the analysis of gestational age as a continuous or ordinal variable may be more powerful and clinically relevant when compared to the binary variable of prematurity.

**Limitations**

The strengths of this study lie in the multicenter patient population, which makes the findings highly generalizable. Limitations of this study are primarily related to the nature of the STS-CHS
database. Importantly, obstetrical factors that may have influenced the timing of birth such as the onset of natural labor, scheduled elective delivery, or the existence of maternal or fetal indications for delivery, were not available in the database. Similarly, perinatal details such as method of delivery (vaginal versus cesarean) and cord blood gases were not available. It is thus possible that confounding by factors related to fetal well-being in utero may have influenced the observed outcomes. However, prior studies have found that elective deliveries are commonly scheduled at early term for fetuses with complex congenital heart disease, and our collective experience indicates that the medical indications cited for some unscheduled early term deliveries are rather “soft.” As would be expected, the rates of non-cardiac risk factors, including chromosomal anomalies/syndromes and non-cardiac congenital anatomic abnormalities, were slightly higher in the late pre-term and early term patient groups (data not shown). However, the multivariable models were adjusted for these and other preoperative risk factors. This study was not designed to determine the ideal timing of cardiac surgery for neonates born at earlier gestational ages. For such patients, it is unknown whether a strategy of early surgery is superior to a strategy of medical management and nutritional support while awaiting growth and maturity. However, our analysis was adjusted for age at surgery, and thus our results are independent of any associations related to this variable. The STS-CHS database also does not include fetuses that die in-utero or any postnatal deaths that occur prior to a cardiac surgical procedure at an STS center. Finally, the database primarily captures complications specific to congenital heart surgery and not those medical complications more generally associated with prematurity. The observation that complication rates did not progressively increase with earlier gestational age at birth is counterintuitive but is likely explained by both this issue as well as other aspects of the study design. Premature neonates with complex cardiac defects who
underwent preoperative medical management for more than 28 days prior to surgery were excluded from this study based on non-neonatal age at surgery. Additionally, postoperative complications occurring after transfer to another institution from the center where the cardiac operation was performed were not captured in the STS-CHS Database, and such transfers were more common in patients born at earlier gestational ages.

Conclusions

In neonates who undergo cardiac surgery, optimal early outcomes are associated with delivery at 39-40 weeks gestation. These data challenge the commonly held perception that delivery at any time during term gestation is equally safe and appropriate, and question the related practice of elective delivery of fetuses with complex congenital heart disease at early term. In the absence of fetal or maternal indications for earlier delivery, the potential advantages and risks of scheduling the elective delivery of fetuses with congenital heart disease prior to 39 weeks gestation should be carefully considered. Further study of interventions designed to optimize timing of delivery is also needed in order to evaluate whether such initiatives are associated with improved outcomes.

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Conflict of Interest Disclosures: None.

References:


13. Costello JM, Polito A, Brown DW, McElrath TF, Graham DA, Thiagarajan RR, Bacha EA,


Table 1. Preoperative characteristics and operative variables for 4,784 study patients.

<table>
<thead>
<tr>
<th>Preoperative characteristics</th>
<th>Male gender</th>
<th>Prenatal diagnosis of congenital heart disease (n = 4,699)</th>
<th>Age at surgery (days)</th>
<th>Weight at surgery (kilograms)</th>
<th>Weight at surgery &lt;2.5 kilograms</th>
<th>Any STS preoperative risk factor</th>
<th>Any non-cardiac anatomical or chromosomal abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2,848 (60%)</td>
<td>2,207 (46%)</td>
<td>7 (5 - 12)</td>
<td>3.2 (2.8 - 3.5)</td>
<td>621 (13%)</td>
<td>2,067 (43%)</td>
<td>956 (20%)</td>
</tr>
</tbody>
</table>

Operative variables

<table>
<thead>
<tr>
<th>STS-EACTS level</th>
<th>Any STS preoperative risk factor</th>
<th>Cardiopulmonary bypass use</th>
<th>Cardiopulmonary bypass time (minutes; n = 3,319)</th>
<th>Aortic cross clamp time (minutes; n = 3,309)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2,067 (43%)</td>
<td>2,124 (44%)</td>
<td>132 (89 - 175)</td>
<td>62 (37 - 90)</td>
</tr>
<tr>
<td>2</td>
<td>2,067 (43%)</td>
<td>728 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>698 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>2,124 (44%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>1,066 (21%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are reported as median (25%-75%) or count (%).

STS-EACTS, Society of Thoracic Surgeons–European Association for Cardiothoracic Surgery.

Table 2. Unadjusted and adjusted in-hospital mortality by week of gestation at birth.

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Number of patients</th>
<th>Observed mortality % (95% CI)</th>
<th>Unadjusted OR (95% CI)</th>
<th>P-value</th>
<th>Adjusted OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>132</td>
<td>15.2 (9.5, 22.4)</td>
<td>2.81 (2.11, 3.73)</td>
<td>&lt;0.001</td>
<td>1.83 (1.26, 2.66)</td>
<td>0.002</td>
</tr>
<tr>
<td>35</td>
<td>177</td>
<td>15.3 (10.3, 21.4)</td>
<td>2.50 (1.92, 3.25)</td>
<td>&lt;0.001</td>
<td>1.70 (1.22, 2.37)</td>
<td>0.002</td>
</tr>
<tr>
<td>36</td>
<td>357</td>
<td>16.2 (12.6, 20.5)</td>
<td>2.15 (1.70, 2.71)</td>
<td>&lt;0.001</td>
<td>1.53 (1.15, 2.03)</td>
<td>0.003</td>
</tr>
<tr>
<td>37</td>
<td>524</td>
<td>13.2 (10.4, 16.4)</td>
<td>1.79 (1.44, 2.22)</td>
<td>&lt;0.001</td>
<td>1.34 (1.05, 1.71)</td>
<td>0.02</td>
</tr>
<tr>
<td>38</td>
<td>949</td>
<td>9.0 (7.2, 11.0)</td>
<td>1.43 (1.16, 1.76)</td>
<td>&lt;0.001</td>
<td>1.16 (0.93, 1.45)</td>
<td>0.19</td>
</tr>
<tr>
<td>39.5</td>
<td>2321</td>
<td>7.3 (6.3, 8.4)</td>
<td>Reference level</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>41</td>
<td>156</td>
<td>7.7 (4.0, 13.1)</td>
<td>0.99 (0.73, 1.36)</td>
<td>0.96</td>
<td>1.18 (0.86, 1.62)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio. Unadjusted values were estimated by models that included a center variable but did not include other patient level risk factors.

*Exact binomial confidence intervals.
Table 3. Data for complications by week of gestational age at birth.

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Observed complication rate (95% CI)</th>
<th>Unadjusted OR (95% CI)</th>
<th>P-value</th>
<th>Adjusted OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>56.1 (47.2, 64.7)</td>
<td>1.13 (0.92, 1.40)</td>
<td>0.24</td>
<td>1.10 (0.88, 1.39)</td>
<td>0.40</td>
</tr>
<tr>
<td>35</td>
<td>65.5 (58.0, 72.5)</td>
<td>1.17 (0.97, 1.42)</td>
<td>0.10</td>
<td>1.13 (0.92, 1.38)</td>
<td>0.24</td>
</tr>
<tr>
<td>36</td>
<td>64.1 (58.9, 69.1)</td>
<td>1.24 (1.05, 1.45)</td>
<td>0.01</td>
<td>1.17 (0.99, 1.39)</td>
<td>0.07</td>
</tr>
<tr>
<td>37</td>
<td>64.1 (59.8, 68.2)</td>
<td>1.32 (1.14, 1.53)</td>
<td>&lt;0.001</td>
<td>1.23 (1.06, 1.43)</td>
<td>0.007</td>
</tr>
<tr>
<td>38</td>
<td>63.0 (59.9, 66.1)</td>
<td>1.34 (1.17, 1.54)</td>
<td>&lt;0.001</td>
<td>1.24 (1.08, 1.43)</td>
<td>0.003</td>
</tr>
<tr>
<td>39.5</td>
<td>58.3 (56.3, 60.4)</td>
<td>Reference level</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>41</td>
<td>60.3 (52.1, 68.0)</td>
<td>1.00 (0.76, 1.31)</td>
<td>0.99</td>
<td>1.05 (0.81, 1.37)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

**Major Complication**

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Observed complication rate (95% CI)</th>
<th>Unadjusted OR (95% CI)</th>
<th>P-value</th>
<th>Adjusted OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>18.9 (12.6, 26.7)</td>
<td>1.29 (1.01, 1.65)</td>
<td>0.04</td>
<td>1.21 (0.92, 1.60)</td>
<td>0.18</td>
</tr>
<tr>
<td>35</td>
<td>21.5 (15.7, 28.3)</td>
<td>1.32 (1.05, 1.64)</td>
<td>0.02</td>
<td>1.23 (0.96, 1.58)</td>
<td>0.10</td>
</tr>
<tr>
<td>36</td>
<td>21.0 (16.9, 25.6)</td>
<td>1.33 (1.09, 1.61)</td>
<td>0.004</td>
<td>1.23 (0.99, 1.52)</td>
<td>0.06</td>
</tr>
<tr>
<td>37</td>
<td>24.4 (20.8, 28.3)</td>
<td>1.32 (1.11, 1.58)</td>
<td>0.002</td>
<td>1.21 (1.00, 1.46)</td>
<td>0.049</td>
</tr>
<tr>
<td>38</td>
<td>19.3 (16.8, 21.9)</td>
<td>1.27 (1.07, 1.50)</td>
<td>0.007</td>
<td>1.16 (0.97, 1.38)</td>
<td>0.11</td>
</tr>
<tr>
<td>39.5</td>
<td>17.6 (16.1, 19.2)</td>
<td>Reference level</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>41</td>
<td>17.3 (11.7, 24.2)</td>
<td>0.73 (0.51, 1.04)</td>
<td>0.08</td>
<td>0.76 (0.53, 1.10)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio. Unadjusted values were estimated by models that included a center variable but did not include other patient level risk factors.

*Exact binomial confidence intervals.
Table 4. Unadjusted postoperative days, estimated extra postoperative days and ratios of medians of postoperative days of hospitalization by week of gestation at birth.

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Observed postoperative LOS in days*</th>
<th>Unadjusted extra days† (95% CI)</th>
<th>Unadjusted Ratio (95% CI)</th>
<th>P-value</th>
<th>Adjusted extra days† (95% CI)</th>
<th>Adjusted ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>19.0 (10.0, 42.5)</td>
<td>7.7 (5.7, 9.8)</td>
<td>1.48 (1.36, 1.61)</td>
<td>&lt;0.001</td>
<td>6.1 (4.4, 8.0)</td>
<td>1.38 (1.27, 1.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>35</td>
<td>24.0 (12.0, 44.0)</td>
<td>6.2 (4.6, 8.0)</td>
<td>1.39 (1.29, 1.50)</td>
<td>&lt;0.001</td>
<td>4.8 (3.4, 6.4)</td>
<td>1.30 (1.21, 1.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>36</td>
<td>18.0 (10.0, 37.0)</td>
<td>5.0 (3.7, 6.4)</td>
<td>1.31 (1.23, 1.40)</td>
<td>&lt;0.001</td>
<td>3.7 (2.5, 4.9)</td>
<td>1.23 (1.16, 1.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>37</td>
<td>18.5 (10.0, 35.0)</td>
<td>3.9 (2.8, 5.1)</td>
<td>1.24 (1.18, 1.32)</td>
<td>&lt;0.001</td>
<td>2.6 (1.7, 3.6)</td>
<td>1.16 (1.10, 1.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>38</td>
<td>18.0 (9.0, 35.0)</td>
<td>2.7 (1.7, 3.7)</td>
<td>1.17 (1.11, 1.23)</td>
<td>&lt;0.001</td>
<td>1.6 (0.7, 2.5)</td>
<td>1.10 (1.05, 1.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>39.5</td>
<td>15.0 (8.0, 29.0)</td>
<td>Reference level</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>41</td>
<td>13.5 (8.0, 25.3)</td>
<td>-0.9 (-2.3, 0.5)</td>
<td>0.94 (0.86, 1.03)</td>
<td>0.20</td>
<td>-0.2 (-1.5, 1.2)</td>
<td>0.99 (0.91, 1.08)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

CI, confidence interval. Unadjusted values were estimated by models that included a center variable but did not include other patient level risk factors.

*Data reported as median (interquartile range).

†Unadjusted extra days were calculated by multiplying the population median postoperative length of stay (16 days) by the ratio of medians-1.
Figure Legends:

Figure 1. Estimated adjusted odds ratios for in-hospital mortality by week of gestational age at birth (reference: 39.5 weeks) and piecewise 95% confidence intervals (shaded area).

Figure 2. Estimated adjusted ratios of medians of post-operative length-of-stay (reference: 39.5 weeks) and piecewise 95% confidence intervals (shaded area).
Gestational Age at Birth and Outcomes after Neonatal Cardiac Surgery: An Analysis of the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database
John M. Costello, Sara K. Pasquali, Jeffrey P. Jacobs, Xia He, Kevin D. Hill, David S. Cooper, Carl L. Backer and Marshall L. Jacobs

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Supplemental Table S-1. Adjusted odds of in-hospital mortality by week of gestation at birth, stratified by cardiopulmonary bypass vs. non-cardiopulmonary bypass cases, and by lower complexity (STS-EACTS 1-3) vs. higher complexity (STS-EACTS 4-5) operations.

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Overall</th>
<th>CPB</th>
<th>Non-CPB</th>
<th>STS-EACTS 1-3</th>
<th>STS-EACTS 4-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw mortality rate</td>
<td>9.9% (474/4784)</td>
<td>10.8% (363/3348)</td>
<td>7.7% (111/1436)</td>
<td>4.4% (72/1654)</td>
<td>12.8% (402/3130)</td>
</tr>
<tr>
<td>34</td>
<td>1.83 (1.26, 2.66)</td>
<td>0.002</td>
<td>1.63 (1.08, 2.46)</td>
<td>0.02</td>
<td>2.19 (1.02, 4.67)</td>
</tr>
<tr>
<td>35</td>
<td>1.70 (1.22, 2.37)</td>
<td>0.002</td>
<td>1.52 (1.05, 2.19)</td>
<td>0.03</td>
<td>1.91 (0.96, 3.79)</td>
</tr>
<tr>
<td>36</td>
<td>1.53 (1.15, 2.03)</td>
<td>0.003</td>
<td>1.40 (1.02, 1.92)</td>
<td>0.04</td>
<td>1.57 (0.85, 2.91)</td>
</tr>
<tr>
<td>37</td>
<td>1.34 (1.05, 1.71)</td>
<td>0.019</td>
<td>1.29 (0.97, 1.71)</td>
<td>0.08</td>
<td>1.22 (0.67, 2.22)</td>
</tr>
<tr>
<td>38</td>
<td>1.16 (0.93, 1.45)</td>
<td>0.19</td>
<td>1.17 (0.89, 1.53)</td>
<td>0.25</td>
<td>0.97 (0.55, 1.72)</td>
</tr>
<tr>
<td>39.5</td>
<td>Referent level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>1.18 (0.86, 1.62)</td>
<td>0.32</td>
<td>0.96 (0.63, 1.47)</td>
<td>0.87</td>
<td>2.39 (0.90, 6.32)</td>
</tr>
</tbody>
</table>

CPB, cardiopulmonary bypass; CI, confidence interval; OR, odds ratio; STS-EACTS, Society of Thoracic Surgeons-European Association of Cardiovascular Surgeons.