Pediatric Cardiovascular Morbidity of the Early Term Newborn

Gil Gutvirtz, MD[1], Tamar Wainstock, PhD[2], Eyal Sheiner, MD, PhD[1], Daniella Landau, MD[3], and Asnat Walfisch, MD[1]

Objective To determine whether early term delivery (at $37^{0/7}$-$38^{6/7}$ weeks of gestation) is associated with long-term pediatric cardiovascular morbidity of the offspring.

Study design A population-based cohort analysis was performed including all term deliveries occurring between 1991 and 2014 at a single tertiary medical center. Gestational age at delivery was subdivided into early term ($37^{0/7}$-$38^{6/7}$), full term ($39^{0/7}$-$40^{6/7}$), late term ($41^{0/7}$-$41^{6/7}$) and post term (≥$42^{0/7}$) delivery. Hospitalizations of children up to the age of 18 years involving cardiovascular morbidity were evaluated, including structural valvular disease, hypertension, arrhythmias, rheumatic fever, ischemic heart disease, pulmonary heart disease, perimyoendocarditis, congestive heart failure, and others. Kaplan-Meier survival curves were used to compare cumulative hospitalization incidence between groups. A multivariable Weibull parametric model was used to control for confounders.

Results During the study period, 223 242 term singleton deliveries met the inclusion criteria. Of them, 24% (n = 53 501) occurred at early term. Hospitalizations involving cardiovascular morbidity were significantly more common in children delivered at early term (0.7%) as compared with those born at full (0.6%), late (0.6%), or post term (0.5%; $P = .01$). The survival curve demonstrated a significantly higher cumulative incidence of cardiovascular-related hospitalizations in the early term group (log-rank $P < .001$). In the Weibull model, early term delivery was found to be an independent risk factor for cardiovascular-related hospitalization as compared with full term delivery (adjusted HR, 1.16; 95% CI, 1.01-1.32; $P = .02$).

Conclusion Early term delivery is independently associated with pediatric cardiovascular morbidity of the offspring as compared with offspring born at full term. *(J Pediatr 2017;■■:■■-■■).*

See editorial, p •••

Once considered a homogenous period for delivery with similar expected newborn outcomes, term delivery (defined as delivery between 37 and 42 completed weeks of gestation) is now being closely investigated for different short- and long-term outcomes among offspring according to its subcategories.

In 2005, the designation of "late preterm" infants for those born between 34 and 37 weeks of gestation instead of what was once referred to as "near term" emphasized that these infants may still experience morbidity and mortality traditionally related to prematurity. Later (in 2013), following the recommendations of the "Defining Term Pregnancy workgroup,"[1] the American College of Obstetrics and Gynecology published a new definition of term pregnancy subdividing it to 4 distinct periods: early (between $37^{0/7}$ and $38^{6/7}$ weeks), full (between $39^{0/7}$ and $40^{6/7}$ weeks), late (between $41^{0/7}$ and $41^{6/7}$ weeks), and post (≥$42^{0/7}$ weeks) term.[2] This change in definition was also made based on the realization that fetal maturation continues within term gestation and that early term infants might still be exposed to complications experienced at late preterm deliveries. Recent studies provide increasing evidence that perinatal outcomes of infants delivered at term differ within this 5-week period. The frequency of immediate neonatal adverse outcomes (mainly mortality and respiratory morbidity) seems to be U-shaped, with a nadir around 39-41 weeks of gestation (full term),[3,4] and higher rates observed at early term.

Studies on the long-term outcomes of early term born children previously focused either on respiratory morbidity (including abnormal lung functions,[5] asthma[6] and obstructive sleep apnea[7]) or on neurocognitive development, showing more attention deficit hyperactivity disorder in early term born children[8] and lower school performance and academic achievements.[9,10] The cardiovascular morbidity of early term born infants was not investigated previously. We sought to evaluate whether birth during this early period of term gestation impacts negatively on offspring, similar to the reported respiratory impact, and independent of other pregnancy characteristics, such as birthweight and placental disorders.

ICD-9	*International Classification of Disease, 9th edition*
LMP	Last menstrual period
SUMC	Soroka University Medical Center

From the [1]Department of Obstetrics and Gynecology, Soroka University Medical Center; [2]Department of Public Health, Faculty of Health Sciences; and [3]Department of Neonatology, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel

The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2017.09.060

Material and Methods

In this population-based retrospective cohort study, we included all singleton pregnancies of women who delivered at term between 1991 and 2014. The study was conducted at the Soroka University Medical Center (SUMC), the sole tertiary medical center in the Negev (southern Israel) and the largest birth center in the country. Thus, the study is based on nonselective population data.

The institutional review board approved the study that has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments (Helsinki Declaration 1975, revision 2013).

The primary exposure was early term delivery ($37^{0/7}$-$38^{6/7}$ weeks of gestation) as defined by American College of Obstetrics and Gynecology.[2] Gestational age was based on the best obstetrical estimate determined by providers and used for clinical decision making. The standard criteria used involved consideration of the clinical history and earliest ultrasound finding. If the last menstrual period (LMP) was certain and consistent with the ultrasound, dating was based on LMP. If the ultrasound examination was not consistent with the LMP, or the LMP was unknown, ultrasound data were used for determination of gestational age. We excluded multiple pregnancies, preterm deliveries (occurring before 37 completed weeks of gestation) or pregnancies with missing gestational age, perinatal mortality cases (intrauterine fetal death, intrapartum death, and postpartum death), and fetuses with congenital malformations.

A comparison was performed between children born at early term to those born later: at full term, late term, and post-term gestations. Outcomes assessed included adverse perinatal outcome (Apgar score and low birth weight) as well as hospitalizations of the offspring up to the age of 18 years owing to cardiovascular morbidity. A subanalysis using dummy variables was performed to compare full-term offspring with other gestational age study groups. We used the Cox regression model to account for duration of follow-up.

The cardiovascular morbidity diagnoses used were predefined by a set of *International Classification of Disease, 9th edition* (ICD-9) codes detailed in **Table I** (available at www.jpeds.com). Subcategories of cardiovascular morbidity included structural–valvular, hypertension, arrhythmia, rheumatic fever, ischemic heart disease, pulmonary heart disease, perimyoendocarditis, congestive heart failure, heart disease unspecified, and other. The group "other" is a group of diagnoses detailed in the supplement (**Table I**) that constitutes of the list of diagnoses not specified elsewhere in any of the other subgroups, mostly heart murmurs.

Follow-up was terminated if any of the following occurred: first hospitalization for any of the cardiovascular morbidities, hospitalization resulting in death unrelated to cardiovascular morbidity, or when the child reached 18 years of age.

Data were collected from 2 databases that were cross-linked and merged: the computerized hospitalization database of SUMC, and the computerized perinatal database of the obstetrics and gynecology department. The database of SUMC includes demographic information and ICD-9 codes for all medical diagnoses made during hospitalizations in any of the SUMC departments, including the pediatric division. The perinatal database consists of information recorded immediately after delivery by an obstetrician. Experienced medical secretaries routinely review the information before entering it into the database to ensure its maximal completeness and accuracy. Coding is performed after assessing medical prenatal care records as well as routine hospital documents.

Statistical Analyses

Statistical analysis was performed using the SPSS package 23rd edition (IBM/SPSS, Chicago, Illinois) as well as the STATA software 12th edition (StataCorp LLC, College Station, Texas). Categorical data are shown in counts and rates and the differences were assessed by χ^2 for general associations. An ANOVA test was used for comparison of continuous variables with normal distribution. Kaplan–Meier survival curves were used to compare cumulative hospitalization incidences over time among the 4 study groups. Only the first admission with any cardiac-related condition for a given individual was included in the survival analysis. The differences between the 4 curves (according to the different gestational ages) were assessed using the log-rank test.

A multivariable Weibull parametric survival analysis was performed to adjust for duration of follow-up. In this analysis, mothers in the cohort were entered as clusters and the dependence among the siblings was accounted for. The model was constructed to establish an independent association between gestational age at birth and future cumulative cardiovascular hospitalization incidence among the offspring while adjusting for confounding and clinically significant variables, including maternal age, birthweight, maternal hypertensive disorders of pregnancy (chronic hypertension, gestational hypertension, or preeclampsia with or without severe features), maternal diabetes (pregestational and gestational), induction of labor, and mode of delivery. The variables used in the Weibull model were coded as follows: maternal age and birthweight are continuous, and hypertensive disorders, diabetes, induction of labor, and mode of delivery (vaginal or cesarean) are dichotomous. Deliveries occurring at full term (ie, $39^{0/7}$-$40^{6/7}$ weeks) were considered as the reference values. All analyses were 2-sided; $P < .05$ was considered significant.

Results

During the study period, 223 242 deliveries meeting the inclusion criteria occurred at SUMC, of which 53 501 (24%) were early term, 122 602 at full term (54.9%), 37 919 late term (17%), and 9220 at post term (4.1%) gestation. **Table II** summarizes maternal characteristics and immediate perinatal outcomes for the different gestational age groups. Mothers in the early term group were more likely to be diagnosed with hypertensive disorders of pregnancy (chronic hypertension, gestational hypertension, or preeclampsia with or without severe features)

FLA 5.5.0 DTD ■ YMPD9487_proof ■ November 9, 2017