Influence of interpregnancy interval on neonatal morbidity

Emily A. DeFranco, DO, MS; Laura M. Seske, MD; James M. Greenberg, MD; Louis J. Muglia, MD, PhD

OBJECTIVE: We sought to assess the influence of birth spacing on neonatal morbidity, stratified by gestational age at birth.

STUDY DESIGN: This was a population-based retrospective cohort study using Ohio birth records, 2006 through 2011. We compared various interpregnancy interval (IPI) lengths in multiparous mothers with the rate and risk of adverse newborn outcomes. The frequency of neonatal intensive care unit admission or neonatal transport to a tertiary care facility was calculated for births occurring after IPI lengths: <6, 6 to <12, 12 to <24, 24 to <60, and ≥60 months, and stratified by week of gestational age. Neonatal morbidity risk was calculated for each IPI compared to 12 to <24 months (referent), and adjusted for the concomitant influences gestational age at birth, maternal race, age, and prior preterm birth.

RESULTS: We analyzed 395,146 birth outcomes of singleton nonanomalous neonates born to multiparous mothers. The frequency and adjusted odds of neonatal morbidity were lowest following IPI of 12 to <24 months (4.1%) compared to short IPIs of <6 months (5.7%; adjusted odds ratio [adjOR], 1.40; 95% confidence interval [CI], 1.32–1.49) and 6 to <12 months (4.7%; adjOR, 1.19; 95% CI, 1.13–1.25), and long IPIs 24 to <60 months (4.6%; adjOR, 1.12; 95% CI, 1.08–1.17) and ≥60 months (5.8%; adjOR, 1.34; 95% CI, 1.28–1.40), despite adjustment for important confounding factors including gestational age at birth. The lowest frequency of adverse neonatal outcomes occurred at 40-41 weeks for all IPI groups. The frequency of other individual immediate newborn morbidities were also increased following short and long IPIs compared to birth following a 12- to <24-month IPI.

CONCLUSION: IPI length is a significant contributor to neonatal morbidity, independent of gestational age at birth. Counseling women to plan an optimal amount of time between pregnancies is important for newborn health.

Key words: birth spacing, birth timing, interpregnancy interval, neonatal morbidity

Cite this article as: DeFranco EA, Seske LM, Greenberg JM, et al. Influence of interpregnancy interval on neonatal morbidity. Am J Obstet Gynecol 2015;212:386.e1-9.

Many years of research have shown that both short and long interpregnancy intervals (IPIs) are associated with adverse outcomes, such as birth defects, preterm birth, low birthweight, and maternal morbidity.[1,2] These complications are likely a result of a multifactorial effect. Several postulated mechanisms contributing to these adverse outcomes include folate depletion, continued presence of inflammatory response markers, maternal anemia, and

EDITORS' ★ CHOICE

hormonal dysregulation, which occur in late pregnancy and postpartum periods.[3-5] A recent study from India and Pakistan demonstrated that both young maternal age and short IPIs increased the risk for infant mortality.[6] An IPI of 18 to <24 months has been postulated to have the lowest maternal and feto-infant risks.[7] Congenital anomalies are typically seen with shorter and longer IPIs. Neural tube defects are commonly reported in shorter IPIs, likely due to the folate depletion theory.[8] Cleft palate has been reported in longer (>60 month) IPIs.[9] Shorter IPIs increase the odds for neonatal mortality, even after adjusting for factors such as small for gestational age, low birthweight, and other variables.[10] Management recommendations for short IPI have included ultrasound assessments for fetal anomalies and growth, biophysical profile assessment

From the Center for Prevention of Preterm Birth, Perinatal Institute (all authors), and Division of Neonatology, Department of Pediatrics (Drs Seske, Greenberg, and Muglia), Cincinnati Children's Hospital Medical Center, and Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology (Drs DeFranco and Muglia), and Department of Pediatrics (Drs Greenberg and Muglia), University of Cincinnati College of Medicine, Cincinnati, OH.

Received July 30, 2014; revised Oct. 19, 2014; accepted Nov. 11, 2014.

Financial support was provided by the Perinatal Institute, Cincinnati Children's Hospital Medical Center, and March of Dimes grant number 22-FY14-470.

The authors report no conflict of interest.

All analyses, interpretations, and conclusions derived from the data source and included in this article are those of the authors and not necessarily those of the Ohio Department of Health.

Presented in oral format at the 81st annual meeting of the Central Association of Obstetricians and Gynecologists, Albuquerque, NM, Oct. 8-11, 2014.

Corresponding author: Emily A. DeFranco, DO, MS. emily.defranco@uc.edu

0002-9378/free • http://dx.doi.org/10.1016/j.ajog.2014.11.017

of fetal well-being, and cervical length assessment to determine risk for preterm labor.[11] Appropriate birth spacing remains a public health concern and should be addressed by health care providers as a means to reduce infant mortality.

Our study examines a population-based cohort of births in Ohio with the immediate outcomes data of transfer to neonatal intensive care unit (NICU) or tertiary care center as markers of aggregate neonatal morbidity, as an indication of illness, based on live birth records, stratified by IPI. Adjustment for maternal age, race, and gestational age at birth was performed to quantify the independent effect of IPI on newborn outcomes.

Materials and Methods

The protocol for this study was approved, and a deidentified data set was provided by the Ohio Department of Health. This study was exempt from review by the institutional review board at the University of Cincinnati, Cincinnati, OH.

We performed a population-based retrospective cohort study including all births that occurred in the state of Ohio during a 6-year period, 2006 through 2011, using Ohio live birth records which were recorded on the US Standard Certificate of Live Birth, 2003 version. Our analyses were limited to singleton births between 20-42 weeks of gestation to multiparous mothers with a recorded IPI, N = 395,146. We excluded births complicated by major congenital anomalies.

The exposure of interest, IPI, was defined as time from the most recent prior birth to the subsequent conception of the index birth. The date of prior birth is recorded in the US birth certificate, which was used for data analyzed in this study. The variable "interval" is calculated as the amount of time in months from the prior birth to the current birth. We created the variable "interpregnancy interval" by converting the gestational age of the current (index) birth into months and subtracting it from the interbirth "interval" variable. We stratified IPI into time periods divided into 6-month intervals. We then analyzed the frequency of adverse outcomes in numerous strata of IPI lengths and identified the 12- to <18-month and 18- to <24-month groups to have similarly low risks and therefore combined them into 1 referent group. The following IPI lengths were ultimately categorized for the purposes of this study: 0 to <6, 6 to <12, 12 to <24, 24 to <60, and ≥60 months. The IPI category associated with the lowest rate of adverse outcome (12 to <24 months) was used as the referent group for comparisons.

The primary outcome for this study was neonatal morbidity. Because only immediate newborn outcomes occurring within the first 24-48 hours after birth are documented in the birth record, we defined neonatal morbidity as admission to a NICU or transfer of the neonate to a tertiary care facility as a marker of newborn illness. We chose NICU admission as an outcome because it is an indicator of newborn illness at any gestational age, whether preterm, term, or postterm birth. We added transport of the newborn to a tertiary care facility to the composite variable of neonatal morbidity to account for sick babies born at hospitals in Ohio without a NICU. The National Vital Statistics System in the United States defines the variable for NICU admission on the birth certificate as "admission into a facility or unit staffed and equipped to provide continuous mechanical ventilator support for a newborn" and the variable for neonatal transport as "transfer of the infant within 24 hours after delivery."[12] The variable "gest_comb," combined estimate of gestational age, which takes into account a combination of last menstrual period, ultrasound, and clinical dating—as is commonly defined in clinical practice—was also used in this study. Fetal growth restriction (FGR) was defined as birthweight less than the 5th and 10th percentile for gestational age.[13]

We conducted a population-based retrospective cohort study to measure the effect of IPI on adverse newborn outcomes. We first compared differences in baseline maternal demographic, behavioral, socioeconomic, prenatal, and delivery characteristics among births within the 5 IPI categories. The frequency of composite and individual neonatal morbidities were calculated and compared for births following various IPI lengths, and then further stratified by weeks of gestational age from 32-42 weeks. Analyses were not stratified at earlier weeks of gestation because nearly all neonates would be expected to be admitted to NICU at <32 weeks of gestational age. Crude risk was calculated comparing births following short and long IPI lengths compared to the referent IPI of 12 to <24 months. Multivariate logistic regression was then used to estimate the risk of IPI on composite morbidity after accounting for the coexisting influences of gestational age at birth, maternal race, age, and prior preterm birth. A full model of potential confounders was initially constructed choosing baseline factors with significant differences noted in univariate comparisons and those with biologic plausibility. Stepwise backward selection yielded a final parsimonious model including statistically influential and biologically plausible covariates. The adjusted odds ratios (adjOR) were then demonstrated in sequential models to show the relative influence of each final covariate on the primary outcome. Significant differences were defined as comparisons with probability value of < .05 and 95% confidence interval (CI) not inclusive of the null value of 1.0. Statistical analyses were performed using STATA Release 12 software (StataCorp, College Station, TX).

Results

The total number of nonanomalous live births in Ohio during the study period was 892,733. We excluded multiple gestations (n = 32,282), births <20 weeks (n = 565) and >44 weeks (n = 39), and births to women with missing age (n = 566) or erroneous appearing maternal age ≥55 years (n = 11). Analyses were