OBSTETRICS

Predicting gestational age using neonatal metabolic markers

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BACKGROUND: Accurate gestational age estimation is extremely important for clinical care decisions of the newborn as well as for perinatal health research. Although prenatal ultrasound dating is one of the most accurate methods for estimating gestational age, it is not feasible in all settings. Identifying novel and accurate methods for gestational age estimation at birth is important, particularly for surveillance of preterm birth rates in areas without routine ultrasound dating.

OBJECTIVE: We hypothesized that metabolic and endocrine markers captured by routine newborn screening could improve gestational age estimation in the absence of prenatal ultrasound technology.

STUDY DESIGN: This is a retrospective analysis of 230,013 newborn metabolic screening records collected by the Iowa Newborn Screening Program between 2004 and 2009. The data were randomly split into a model-building dataset (n = 153,342) and a model-testing dataset (n = 76,671). We performed multiple linear regression modeling with gestational age, in weeks, as the outcome measure. We examined 44 metabolites, including biomarkers of amino acid and fatty acid metabolism, thyroid-stimulating hormone, and 17-hydroxyprogesterone. The coefficient of determination (R^2) and the root-mean-square error were used to evaluate models in the model-building dataset that were then tested in the model-testing dataset.

RESULTS: The newborn metabolic regression model consisted of 88 parameters, including the intercept, 37 metabolite measures, 29 squared metabolite measures, and 21 cubed metabolite measures. This model explained 52.8% of the variation in gestational age in the model-testing dataset. Gestational age was predicted within 1 week for 78% of the individuals and within 2 weeks of gestation for 95% of the individuals. This model yielded an area under the curve of 0.899 (95% confidence interval 0.895−0.903) in differentiating those born preterm (<37 weeks) from those born term (≥37 weeks). In the subset of infants born small-for-gestational age, the average difference between gestational ages predicted by the newborn metabolic model and the recorded gestational age was 1.5 weeks. In contrast, the average difference between gestational ages predicted by the model including only newborn weight and the recorded gestational age was 1.9 weeks. The estimated prevalence of preterm birth <37 weeks' gestation in the subset of infants that were small for gestational age was 18.79% when the model including only newborn weight was used, over twice that of the actual prevalence of 9.20%. The newborn metabolic model underestimated the preterm birth prevalence at 6.94% but was closer to the prevalence based on the recorded gestational age than the model including only newborn weight.

CONCLUSIONS: The newborn metabolic profile, as derived from routine newborn screening markers, is an accurate method for estimating gestational age. In small-for-gestational age neonates, the newborn metabolic model predicts gestational age to a better degree than newborn weight alone. Newborn metabolic screening is a potentially effective method for population surveillance of preterm birth in the absence of prenatal ultrasound measurements or newborn weight.

Key words: fetal growth, neonatal metabolism, preterm birth

Accurate estimation of gestational age is important for perinatal care and research. Clinically, predicting gestational age during pregnancy is important for determining the treatment and management of pregnancies that may end in preterm birth (<37 weeks' completed gestation). Preterm birth is the leading cause of child death, ahead of infectious disease, worldwide with the greatest rates in low-resource regions such as West Africa.[1] Population estimates of gestational age are extremely important for determining the burden of preterm birth and small-for-gestational age, particularly in low-resource settings.[1] Accurate gestational age estimates are necessary for identifying the causes and risk factors for preterm birth and small-for-gestational age as well as evaluating interventions that may be used to prevent these conditions in the future. Identifying areas with greater-than-average preterm and small-for-gestational age rates can aid health professionals in targeting interventions where they would have the largest impact.

There are several methods commonly used for estimating gestational age during pregnancy. One such method, ultrasound dating, is based on estimating gestational age by measuring the size of the fetus in early pregnancy. Another commonly used method, particularly in areas without access to ultrasound technologies, is estimating gestational length based on a woman's last menstrual period. Last menstrual period often is inferior to ultrasound dating, because it relies on a woman remembering the date of her last menstrual cycle.[2-4] Although ultrasound dating is becoming increasingly common in the United States, it is not currently practical in most developing regions of the world or for women receiving little or no prenatal care. Gestational age dating by fetal ultrasound also is not robust for neonates who are small or large for their gestational age.[5,6]

For underdeveloped areas in which women do not have access to prenatal care, gestational age can be estimated after birth. Dubowitz or Ballard examinations estimate gestational age by the use of standardized scoring systems based on physical and neuromuscular characteristics of the newborn infant.[7,8] Gestational age estimates based on either the Dubowitz or Ballard criteria are less precise than obstetric

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estimates.[9,10] In fact, neonatal-derived gestational age estimates most often overestimate the number of infants born less than 40 weeks' gestation while underestimating the number of infants born at or greater than 40 weeks' gestation.[9,10] Birthweight also can be used to estimate gestational age but is limited in the same way as neonatal examinations and is not robust in small- or large-for-gestational age infants.[11]

Gestational age is correlated strongly with many developmental and metabolic processes and is a strong predictor of neonatal outcome.[12] Several studies have demonstrated altered maternal and cord blood amino acid and fatty acid metabolites in pregnancies that end in preterm birth or the birth of a low birthweight or small for gestational age neonate.[13-15] In addition, there are distinct urinary metabolic patterns in preterm neonates compared with their term counterparts.[16] We and others have shown that metabolites related to amino acid and fatty acid metabolism measured 24−72 hours after birth are vastly different among very preterm (<32 weeks), moderately preterm (32−36), and term (≥37 weeks) neonates.[17,18] Newborn metabolic screening via the use of tandem mass spectrometry has long been recognized as a critical public health initiative to identify mostly treatable but individually rare inborn errors of metabolism.[19] Newborn metabolic screening captures data from a variety of biomarkers, including amino acids, free carnitine, and acylcarnitines. We hypothesized that metabolic and endocrine markers captured by routine neonatal screening could improve gestational age estimation in the absence of prenatal ultrasound technology. This technique would have practical application for surveillance of preterm birth at a population level when prenatal care is limited.

Materials and Methods

Study population

We performed a retrospective analysis of 238,315 newborn metabolic screening records collected by the Iowa Newborn Screening Program between 2004 and 2009. Forty-four metabolites were measured on all subjects during the entire study period, including 2 enzymes (biotinidase and galactose-1-phosphate uridyl transferase), 2 hormones (thyroid-stimulating hormone [TSH] and 17-hydroxyprogesterone [17-OHP]), 9 amino acids, 30 acylcarnitines, and free carnitine (C0) (Supplementary Table 1). Blood spot specimens were collected, dried, and handled as part of routine clinical care according to the Clinical Laboratory Standards Institute guidelines.[20] At the time of neonatal screening, the health care provider records the gestational age in weeks, the sex of the infant, current weight in grams, if the infant is currently on total parenteral nutrition, and age of the newborn in hours. This information is included with each newborn screening specimen. Data such as delivery mode or maternal characteristics were not available. The method of gestational dating, ie, last menstrual period or fetal ultrasound, is provider dependent and is not distinguished on the newborn screen record. All specimens were analyzed as part of the Iowa Newborn Screening Program by the State Hygienic Laboratory in Ankeny, Iowa. Screening procedures in Iowa are based on previously established methodology.[18,19]

The State Hygienic Laboratory identified multiple gestations by examining birth date, gestational age, mother's first name, and facility identification number. The data were deidentified by the State Hygienic Laboratory and provided for use in this study. Approval for use of the deidentified data was obtained from the Iowa Department of Public Health and a waiver of consent from the Institutional Review Board at the University of Iowa (IRB#200908793).

Only initial newborn screening specimens, not repeats, were included in the analysis. We excluded screening records with missing gestational age data (n = 5749) or those with a recorded gestational age day outside the range of 20−45 completed weeks (n = 108). Records for specimens that were rejected by the screening laboratory as being of poor quality (n = 2445) were excluded from analysis. The remaining dataset consisted of 230,013 neonatal metabolic screening records. To determine the final performance of the predictive model, the data were randomly split into a model-building dataset (n = 153,342) and a model-testing dataset (n = 76,671). The predictive model was created using the model-building dataset and the performance of this model was then evaluated in the model-testing dataset.

Statistical analysis

Univariate analysis was performed with each metabolite and gestational age. Linearity between gestational age and single metabolite levels was inspected visually by plots of the residuals vs the predicted values. To address nonlinearity between each metabolite and gestational age, squared terms and then the cubed terms were included for each model. We performed multiple linear regression modeling with gestational age, in weeks, as the outcome measure, using metabolites that were significant in the univariate analysis. The regression was estimated by the use of ordinary least squares. In the model-building dataset, all metabolites significant at $P < .01$ from the univariate models were included in the initial model, and significant terms ($P < .05$) were retained for subsequent modeling. Squared and cubed terms of significant metabolites were included successively in the model after which nonsignificant ($P > .05$) terms were removed. Cubic terms were examined only when squared terms were significant.

Next, within the model-building dataset, we determined whether the final selected model was robust in the presence of covariates that could affect the prediction of gestational age by the metabolic panel. These covariates included the child's sex, age at time of sample collection (in hours, month, and year of sample collection), neonatal weight at time of screening in grams, weight for gestational age categorized as small-for-gestational age (<10th percentile for each gestational age week), large-for-gestational age (>90th percentile for each gestational age week), and average-for-gestational age and multiple gestation. Residuals vs the predicted values were inspected visually for the relationship between gestational age