Prediction of preterm birth in symptomatic women using decision tree modeling for biomarkers

Jacquelyn L. Hill, MSc; M. Karen Campbell, PhD; Guang Yong Zou, PhD; John R. G. Challis, PhD; Gregor Reid, PhD; Hiroshi Chisaka, MD; Alan D. Bocking, MD

OBJECTIVE: The objective of the study was to use recursive partitioning (RP) to identify gestational age–specific and threshold values for infectious and endocrine biomarkers of imminent delivery.

STUDY DESIGN: RP was developed using a previously collected data set and then applied to a prospectively collected cohort of women in threatened preterm labor. Predictors of preterm birth were considered, including white blood cell count (WBC), corticotrophin-releasing hormone (CRH), cortisol, and maternal age.

RESULTS: At 22-27 weeks' gestation, WBC of greater than 12,000/mL was the most accurate predictor of delivery within 48 hours; at 28-31 weeks' gestation, CRH of greater than 684 pg/mL was the most accurate predictor; and at 32-26 weeks' gestation, CRH and maternal age were the most important variables.

CONCLUSIONS: These results indicate that maternal WBC greater than 12,000/mL prior to 28 weeks' gestation and CRH beyond 28 weeks are the most accurate biomarkers in predicting preterm birth within 48 hours. RP assists in establishing clinically relevant and gestational age–specific threshold levels for these variables.

Key words: corticotrophin-releasing hormone, infection, preterm labor, recursive partitioning

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Preterm birth continues to be a major challenge in obstetrics,[1] and there are few methods available to reliably predict true preterm labor in women who present with symptoms of labor. Currently transcervical ultrasound measurements and/or cervicovaginal fetal fibronectin levels are the most commonly used diagnostic tools.[2] These techniques both have high negative predictive values but relatively low positive predictive values. Consequently, many women and their fetuses are exposed unnecessarily to tocolytic drugs and corticosteroids and are admitted to hospital. These admissions and treatments create emotional and financial stress on the mother and family as well as significant financial costs to society. We and others have previously shown that maternal corticotropin-releasing hormone (CRH) levels are higher in symptomatic women who give birth within 48 hours, compared with those who do not.[3,4]

Our previous prospective study involving 218 symptomatic women showed that, at different gestational ages, different factors were associated with preterm birth within 48 hours.[5] White blood cell count (WBC), a marker of subclinical infection, was the only variable shown to be predictive at 22-27 weeks, supporting previously published work suggestive of the gestational age dependence (particularly less than 32 weeks) of the relationship between markers of infection and preterm birth.[6-8] Beyond 28 weeks' gestation, CRH and adrenocorticotropic hormone were predictors of birth within 48 hours, indicating an early activation of the fetal hypothalamic-pituitary-adrenal axis. Additionally, at 32-36 weeks' gestation, demographic and lifestyle variables were significantly associated with preterm birth.

For the purposes of clinical decision making, it is useful to identify threshold levels of biomarkers, above which preterm birth is probable. Recursive partitioning (RP) to produce decision trees[9,10] has been increasingly utilized to identify accurate biomarker cutpoints for obstetrical conditions including preterm birth.[11-13] Prediction rules derived from decision tree analysis and based on critical thresholds of variables are simpler and more clinically applicable than the results of more conventional analyses. For example, logistic regressions (LR) can treat predictive variables as continuous or categorical and can estimate effects with statistical accuracy, but the interpretation of parameters are more abstract and do not as readily provide decision-making thresholds. However, RP analysis has limitations, including the potential for spurious findings because the findings are highly depen-

From the Departments of Epidemiology and Biostatistics (Ms Hill and Drs Campbell and Zou), Obstetrics and Gynaecology (Dr Campbell), Surgery and Immunology, and Microbiology, and the Canadian R&D Centre for Probiotics, Lawson Health Research Institute (Dr Reid), the University of Western Ontario, London, and the Departments of Physiology and Obstetrics & Gynaecology, University of Toronto, Toronto (Drs Challis, Chisaka, and Bocking), ON, Canada, and the Tohoku University Graduate School of Medicine, Sendai, Japan (Dr Chisaka).

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dent on the data set used in the analysis.[14] We know of no previous reports describing the use of classification trees to predict preterm birth among symptomatic women with the biomarkers of interest in this study.

The objectives of this study were: (1) to explore, by RP, the relationship of gestational age–specific endocrine, infection, and other variables with delivery within 48 hours using our previously published data,[5] (2) to compare results derived by LR and RP; and (3) in a new prospective cohort of symptomatic pregnant women, to apply the threshold values for infectious and endocrine biomarkers developed in the previous cohort using RP. We were also interested in the potential utility of assessment of cervicovaginal fetal fibronectin measurements, in these women because at the time of this study, there was minimal information regarding its predictive value for preterm birth in symptomatic women.

Materials and Methods

This study was approved by the University of Western Ontario Review Board for Research Involving Human Subjects. Briefly, RP was developed using a previously collected data set and then applied to a prospectively collected cohort termed validation study.

Derivation data and analysis

Data for 201 of the 218 women in our earlier study[5], excluding 17 for missing data, were partitioned with respect to preterm birth within 48 hours of admission or not, by the algorithm of Atkinson and Therneau,[15,16] implemented in S Plus 6.1 (Seattle, WA). The resulting classification tree graphically summarizes the predictors, in order of their discriminating power relative to each other.[17,18] The method also selects the optimum threshold level for each predictor. The highest-risk subgroups are easily identified in the tree by the combinations of predictors.[11] Analysis assigned equal misclassification costs for false positives as for false negatives and used the Gini index for splitting nodes.

For all 3 gestational age categories, the following predictor variables were considered: WBC, cortisol, cervical dilatation 2-4 cm, CRH, multiparous, smoker, maternal age, contractions at admission, and cervical effacement of at least 50%. Maternal age, endocrine variables, and WBC were continuous scale variables, whereas cervical dilatation, parity, smoking, contractions, and cervical effacement were binary variables.

In addition to developing the RP algorithm, for 32-36 weeks' gestation only, sample size permitted the further evaluation of the use of these cutpoints in a LR analysis.

Validation data

Two hundred seven women with singleton pregnancies, who presented with threatened preterm labor to St Joseph's Health Care London, a tertiary perinatal center in London, Canada, from April 1999 to July 2002, were recruited to the study after obtaining informed consent. Sample size was based on our previous study with an anticipated birth rate within 48 hours of presentation of 30%. Exclusions were multifetal gestations, fetal anomalies, maternal diabetes mellitus, abruptio placenta, preeclampsia, intrauterine growth restriction, cervical dilatation greater than 4 cm, ruptured membranes, and clinical signs of infection (WBC greater than 18,000/mL).

A sterile speculum examination was performed in all women prior to digital examination and cervicovaginal swabs were taken to determine the presence of bacterial vaginosis (BV) by Nugent scoring.[19] In women who were eligible, cervicovaginal swabs were taken for determination of fetal fibronectin levels using a Dacron swab. Swabs were immediately placed in buffer provided by the manufacturer (Adeza Biomedical Corp, Sunnyvale, CA). Measurements were made using a commercially available enzyme-linked immunosorbent assay (Adeza Biomedical Corp). Results were considered positive at 50 ng/mL or greater.[20]

Maternal blood samples were obtained at the time of recruitment, and WBC was determined from whole blood before centrifugation to collect plasma. Aliquots of plasma were immediately frozen and stored at -80°C for later determination of CRH and cortisol by radioimmunoassay.[4] Intra- and interassay coefficients of variation for CRH previously measured were 12% and 6.5%, respectively. Interassay coefficients of variation for cortisol measurements were approximately 11%. CRH and cortisol values were normalized using gestational age appropriate norms from an earlier study of subjects who gave birth at term[4] using the Standardization Procedure of SAS (version 8.02, Cary, NC). Gestational age was determined by a combination of last menstrual period and early ultrasound examination.

Results

Derivation study

Using the derivation data at 22-27 weeks' gestational age, RP analysis indicated that WBC was the most accurate predictor of preterm delivery within 48 hours (Figure 1). A threshold of the 48th percentile of these data (12,000/mL) was important and, for those with WBC 12,000/mL or greater, further differentiation was provided by the next most accurate predictor, cortisol 55th percentile or greater (202 ng/mL). Fourteen women at this gestational age exceeded both thresholds and, of these, 10 (71%) delivered within 48 hours. In contrast, none of the 21 women with WBC less than 12,000/mL delivered within 48 hours. Competitive variables for the first predictive split in the tree, in lieu of WBC, were cortisol and cervical dilatation. At higher levels of WBC, competitive variables for the second split, in lieu of cortisol, were maternal age and WBC (at a different cutpoint).

For women of 28-31 weeks' gestational age, CRH was the most accurate predictor of birth within 48 hours. Of 8 women exceeding the CRH threshold of the 83rd percentile (684 pg/mL), 5 (63%) gave birth within 48 hours as compared with 4 of the 43 (9%) of women with CRH less than 684 pg/mL (Figure 2). Competitive variables, in lieu of CRH, were WBC, cortisol, cervical effacement, and maternal age.

For gestational ages 32-36 weeks (Figure 3), CRH was the most predictive variable with a first split at a threshold