GENETICS

Association of early-preterm birth with abnormal levels of routinely collected first- and second-trimester biomarkers

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OBJECTIVE: The purpose of this study was to examine the relationship between typically measured prenatal screening biomarkers and early-preterm birth in euploid pregnancies.

STUDY DESIGN: The study included 345 early-preterm cases (<30 weeks of gestation) and 1725 control subjects who were drawn from a population-based sample of California pregnancies who had both first- and second-trimester screening results. Logistic regression analyses were used to compare patterns of biomarkers in cases and control subjects and to develop predictive models. Replicability of the biomarker early-preterm relationships that was revealed by the models was evaluated by examination of the frequency and associated adjusted relative risks (RRs) for early-preterm birth and for preterm birth in general (<37 weeks of gestation) in pregnancies with identified abnormal markers compared with pregnancies without these markers in a subsequent independent California cohort of screened pregnancies (n = 76,588).

RESULTS: The final model for early-preterm birth included first-trimester pregnancy-associated plasma protein A in the ≤5th percentile, second-trimester alpha-fetoprotein in the ≥95th percentile, and second-trimester inhibin in the ≥95th percentile (odds ratios, 2.3–3.6). In general, pregnancies in the subsequent cohort with a biomarker pattern that were found to be associated with early-preterm delivery in the first sample were at an increased risk for early-preterm birth and preterm birth in general (<37 weeks of gestation; adjusted RR, 1.6–27.4). Pregnancies with ≥2 biomarker abnormalities were at particularly increased risk (adjusted RR, 3.6–27.4).

CONCLUSION: When considered across cohorts and in combination, abnormalities in routinely collected biomarkers reveal predictable risks for early-preterm birth.

Key words: biomarker, prenatal screening, preterm birth

Cite this article as: Jelliffe-Pawlowski LL, Shaw GM, Currier RJ, et al. Association of early-preterm birth with abnormal levels of routinely collected first- and second-trimester biomarkers. Am J Obstet Gynecol 2013;208:492.e1-11.

All biomarkers that are used in routine aneuploidy screening are directly or indirectly associated with placental function, pregnancy maintenance, and/or other processes that are tied closely to preterm birth (eg, parturition, placental and trophoblast function, inflammation, immune system function).[1-16] Thus, there is pathophysiologic evidence that supports the findings of a number of investigators who have reported an increased risk of preterm birth when ≥1 routinely collected screening markers are abnormally high and/or low (first-trimester nuchal translucency [NT], pregnancy-associated plasma protein-A [PAPP-A], and human chorionic gonadotropin [hCG], second-trimester alpha-fetoprotein [AFP], hCG, unconjugated estriol [uE3], and inhibin).[17-26] Despite these observations, the standard of care for pregnancies with abnormal biomarkers is uncertain.[25] One challenge in creating a set of standards is the absence of well-defined population-scale data that has investigated preterm delivery by important clinical subgroups (eg, early, spontaneous, medically indicated) in conjunction with biomarker patterns across trimesters.

Herein, we used data from the California Prenatal Screening Program[27,28] and the California Perinatal Quality Care Collaborative (CPQCC)[29] to investigate whether preterm birth (overall and by medically indicated and spontaneous labor subgroups) is associated with single and multiple biomarker abnormalities. Two independent population-scale sample sets of euploid singleton pregnancies were used: one population set was used to establish an association model, and one population set was used to determine whether the patterns could be recapitulated across cohorts.

Materials and Methods

Evaluation of early-preterm biomarker relationships was undertaken in 2 inde-

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Received Sept. 4, 2012; revised Dec. 12, 2012; accepted Feb. 4, 2013.

Funded in part by grants from the National Institutes of Health/National Heart, Lung and Blood Institute (RC2 HL101748) and the March of Dimes Prematurity Center, Stanford University School of Medicine, Stanford, CA.

The authors report no conflict of interest.

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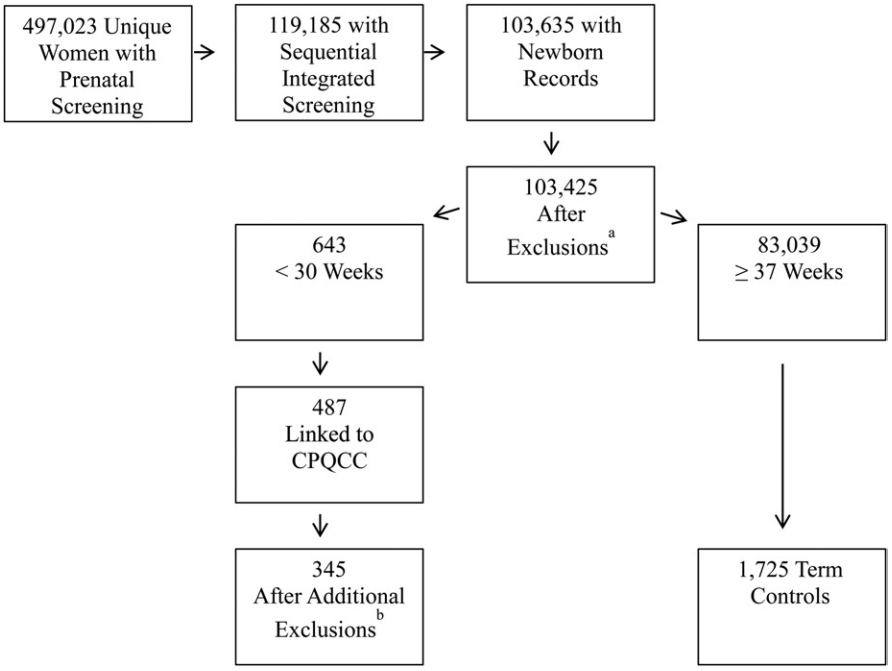
FIGURE 1
Selection of cases and control subjects for singleton pregnancies



[a]Exclusions, which were based on screening and registry data and included 197 mother-infant pairs with chromosomal defects, 10 pairs with neural tube defects, 1093 pairs with a stated history of smoking, and 715 pairs with diabetes mellitus; [b]Additional exclusions based on California Perinatal Quality Care Collaborative (*CPQCC*)/neonatal intensive care unit data included 55 mother-infant pairs with other critical birth defects, 55 additional pairs with reported diabetes mellitus during or before pregnancy, 13 additional pregnancies with reports of smoking, 10 pregnancies with preeclampsia, and 9 pregnancies with oligo- or polyhydramnios.

Jelliffe-Pawlowski. Early-preterm birth and screening markers. Am J Obstet Gynecol 2013.

pendent datasets; one set was used for model building (the "training" study set), and one set was used for model testing (the "testing" study set). The training study set included 345 early-preterm singleton cases (<30 weeks of gestation) and 1725 term singleton pregnancies (control subjects) with expected dates of delivery in September 2009 through December 2010. These cases and control subjects were drawn from 497,023 unique women who were participants in the California Prenatal Screening Program during this same time period. Cases and control subjects were restricted to pregnancies with ultrasound dating, maternal age between 12 and 60 years, no missing information on race/ethnicity, and sequential integrated screening results (that is, pregnancies with first-trimester NT, PAPP-A, and hCG measurements and second-trimester measures of AFP, hCG, uE3, and inhibin; n = 119,185). Cases and control subjects were also restricted to pregnancies with a linked newborn screening record (indicating a live birth between 20 and 44 completed weeks of gestation) without any history of diabetes mellitus or smoking and without chromosomal or neural tube defects in registries that are maintained by the Genetic Disease Screening Program.[30] We identified 643 case pregnancies that had resulted in early-preterm birth between 22 weeks 0 days and 29 weeks 6 days of gestation and 83,039 control pregnancies with births ≥37 completed weeks of gestation. The final case determination was made after linkage of the case group to the CPQCC dataset.[29] The CPQCC database stores clinical data on >90% of all neonates who receive neonatal intensive care in California. All newborn infants with a gestational age between 22 weeks 0 days and 29 weeks 6 days qualify for inclusion in the CPQCC, regardless of department of care within partner hospitals. This set of early-preterm pregnancies was ideal for more intensive analyses because of the availability of extensive data on pregnancies. The CPQCC dataset was used to make additional exclusions from the early-preterm case grouping (Figure 1). The final case-control set included the 345 cases after CPQCC linkage and exclusions and 1725 control subjects who were selected randomly from the available 83,309 term pregnancies at a ratio of 5 control subjects for each case.

First-trimester PAPP-A and total hCG were measured in serum samples that had been drawn between 10 weeks 0 days and 13 weeks 6 days of gestation. Second-trimester AFP, hCG, uE3, and inhibin were measured in serum samples that were drawn between 15 weeks 0 days and 20 weeks 0 days of gestation. NT measurements were done between 11 weeks 2 days and 14 weeks, 2 days of gestation by practitioners who were credentialed by the Nuchal Translucency Quality Review Program[31] or Fetal Medicine Foundation.[28,32] All serum samples were sent to 1 of 7 regional laboratories in California for testing with fully automated equipment (Auto DELFIA; Perkin Elmer Life Sciences, Waltham, MA). As part of routine prenatal screening, all biomarker levels were converted to biomarker multiples of the medians (MoM) to adjust for gestational age with log-linear or nonlinear regression methods, as appropriate; median analyte values were regressed against gestational age and were adjusted for maternal weight (as a proxy for blood volume) and self-reported race/ethnicity

Our analyses used logistic regression to calculate odds ratios (ORs). We estimated the odds that were associated with specific maternal characteristics in 3 early-preterm case groups (spontaneous labor, medically indicated, and combined groupings) compared with those in the term control grouping. Preterm groupings were based on information from the CPQCC. Mater-