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Original Article

Abnormal uterine artery Doppler velocimetry predicts adverse outcomes in patients with abnormal analytes

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ABSTRACT

Objectives: Our aim was to determine if uterine artery (UtA) Doppler studies would risk-stratify women with abnormal serum analytes on prenatal genetic screening into those at baseline and increased risk for preeclampsia and small-for-gestational age (SGA).
Study design: This retrospective cohort study examined outcomes of patients with ⩾one abnormal analyte (PAPP-A < 0.3, hCG > 3.0, AFP > 2.5, inhibin > 2.0, or unconjugated estriol < 0.3MoM). At approximately 24 weeks, we assessed UtA pulsatility index (PI).
Main outcome measures: Preeclampsia, preterm preeclampsia, SGA (birthweight (BW) <10%) and intrauterine growth restriction (IUGR) (BW < 3%).
Results: We identified 132 patients with ⩾one abnormal analyte, UtA Doppler screening, and delivery outcomes. Twenty-four (18%) had an elevated UtA PI (PI > 1.6); preeclampsia occurred in 16 (12%) and 26 (20%) delivered a SGA neonate. Abnormal UtA Doppler PI increased the likelihood of a composite outcome of preeclampsia or SGA from 27% to 71% (LR 6.48 (2.93, 14.30)); a negative UtA Doppler PI reduced the likelihood to 18% (LR 0.57 (0.42, 0.78)). Abnormal UtA Doppler PI increased the likelihood of a more severe composite outcome of preterm preeclampsia or IUGR from 11% to 39% (LR 5.49 (3.03, 9.97)); a negative UtA Doppler study reduced the likelihood to 4% (LR 0.35 (0.16, 0.80)).
Conclusions: In patients with abnormal serum analytes, abnormal UtA Doppler PI is significantly associated with preeclampsia or SGA and improves the prediction of these adverse outcomes by 9–15-fold. Providers can incorporate UtA Doppler PI into an abbreviated surveillance regimen; they can be reassured that a normal study markedly decreases the risk of a severe early adverse outcome.

Introduction

A recognized association exists between patients with abnormal serum analytes detected at the time of aneuploidy screening and adverse obstetrical outcomes such as preeclampsia (PET), and intrauterine growth restriction (IUGR). There is an even stronger correlation between these analytes and preterm PET (preterm preeclampsia with onset at less than 37 weeks) [1]. These patients deserve attention in their pregnancies in order to provide proper monitoring and detect impending adverse outcomes in a timely manner; however, no established guidelines exist for consistent management of this cohort [2].

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This is in part because previous research has demonstrated these analytes alone and in various combinations do not comprise a suitable screening test due to inadequate sensitivity and specificity [2–4].

There is utility in stratifying this intermediate-risk population into a group that would potentially benefit from intensive maternal and fetal surveillance and one for which routine prenatal care is sufficient.

Interrogating the utero-placental circulation is a biologically plausible approach for the prediction of PET and IUGR; increased uterine artery (UtA) Doppler resistance is associated with insufficient trophoblast invasion into the maternal spiral arteries, which is believed to be a contributing factor in placental dysfunction [5,6]. Other groups [7] have examined UtA Doppler indices and found that an elevated pulsatility index (PI) or notching in the waveform results in a 1.6-fold increased risk of PET and a 4.6-fold increased risk of IUGR. Abnormal first trimester analytes have been shown to be associated with pregnancy induced hypertension (OR = 4.56) and low birth weight (OR = 6.8) in those with an elevated UtA Doppler resistance index [8].

Given these findings, patients with abnormal serum analytes could reasonably be offered UtA Doppler evaluation in order to detect those at the highest risk of PET and IUGR. However, studies linking these modalities have been limited and inconclusive [9–11]. We hypothesized that, in a population of patients with abnormal aneuploidy screening analytes in either the first or second trimester, the addition of UtA Doppler screening will significantly improve the prediction of PET and IUGR, especially severe early-onset disease.

Methods

This retrospective study was conducted at the University of California San Diego (UCSD) Placental Function Clinic (PLC) from 2010 to 2013 and was approved by the UCSD Human Research Protection Program prior to initiation. Patients from the greater San Diego area were referred to the PLC if they had either (1) an abnormally low (less than 0.3 multiples of the median (MoM)) PAPP-A in the first trimester of pregnancy (measured at 10 + 0 to 13 + 6 weeks gestational age (GA) as per the California Prenatal Screening Program), or (2) elevated alpha-feto protein (AFP) greater than 2.5 MoM, human chorionic gonadotropin (hCG) greater than 3.0 MoM, inhibin (Inh) greater than 2.0 MoM, or low estriol (uE3) less than 0.3 MoM at the time of second-trimester quad screening (measured at 15 + 0 to 20 + 0 weeks GA also per California protocol). Cutoffs for these analytes for admission to PLC were selected considering the prevalence of adverse outcomes based on a recent meta-analysis [12].

Patients were initially evaluated at the PLC for risk assessment at 24 + 0 weeks GA (±2 weeks), where a sonographer (licensed by ARDMS in Obstetrics & Gynecology Ultrasound) performed an ultrasound examination to determine fetal biometry, placental characteristics (size, homogeneity, grading), amniotic fluid index, transvaginal cervical length, and Doppler indices (umbilical artery, middle cerebral artery, UtA, and ductus venosus). Results were interpreted by one of the two senior authors (DAW or LCL). Doppler velocity waveforms were obtained from a transabdominal approach per protocol [13] using a General Electric (GE Healthcare, Bedford, United Kingdom) Voluson E8 machine and a 4C (1.0–5.0 MHz) transducer with Version 12.0.0 software.

Patients were eligible for this study if they had one or more abnormal analytes on either first or second trimester screening and UtA Doppler waveform assessment. Patients were excluded from analysis if they did not deliver within the UCSD hospital system, as outcomes for patients delivering at outside facilities could not be reliably obtained.

Maternal records were reviewed for demographic information, number and type of abnormal analytes, and mode of delivery. The predictors of adverse outcomes, UtA Doppler indices (PI and presence of notching), were recorded. A UtA Doppler study was defined as abnormal if: (1) there was an elevated PI $\geqslant$ 1.6 MoM either (above the 95th percentile) unilaterally or bilaterally; or (2) if there was notching, defined as a 20% drop in the UtA waveform in early diastole compared to late diastole, unilaterally or bilaterally.

In order to establish baseline risks of adverse outcomes at our institution, we abstracted the medical record of an equal number of control patients who had *normal* analytes during the same time course as our study. No control patients with abnormal analytes and UtA testing were available for analysis.

For all patients (cases and controls), the delivery record and discharge summary were examined to determine obstetrical outcomes, including: (1) GA at delivery; (2) birthweight (BW), with infants designated as small for gestational age (SGA) if BW was less than the 10th percentile, or as IUGR if BW was less than the 3rd percentile; and (3) PET as defined by two abnormal blood pressure measurements ($\geq$140 mm Hg systolic or >90 mm Hg diastolic or higher), occurring more than 6 h apart and less than 1 week apart, after 20 weeks GA in a woman with previously normal blood pressure, AND proteinuria of 0.3 mg or greater on a 24-h urine specimen, or 1+ or greater dipstick [14].

Our primary outcome was the association of abnormal UtA Doppler indices with a composite outcome of severe preterm PET or IUGR at less than 37 weeks. Secondary outcomes included the association with PET, SGA, or IUGR at term or before 37 weeks. We tested this association and report odds ratios, likelihood ratios, and posttest probabilities. No analysis was performed on patients with normal analytes except calculations of proportions of adverse outcomes. Statistical analysis was performed using SPSS (Version 20, SPSS Inc, Chicago, IL). Student's *T*-test was utilized for comparison of continuous variables, and chi-squared and Fisher exact tests for categorical variables as appropriate. Odds ratios were calculated with simple logistic regression.

Results

During the three year study period, 342 total women were enrolled in the UCSD PLC with 1 or more abnormal