UC San Diego

UC San Diego Previously Published Works

Title

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

Permalink

<https://escholarship.org/uc/item/767907hk>

Journal

Pregnancy hypertension, 4(4)

ISSN

2210-7789

Authors

Roeder, Hilary A
Dejbakhsh, Sheila Z
Parast, Mana M
et al.

Publication Date

2014-10-01

DOI

10.1016/j.preghy.2014.10.001

Peer reviewed

Contents lists available at ScienceDirect

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

journal homepage: www.elsevier.com/locate/preghy

Original Article

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

Hilary A. Roeder^{a,*}, Sheila Z. Dejbakhsh^b, Mana M. Parast^c, Louise C. Laurent^{a,1}, Douglas A. Woelkers^{a,1}

^a UC San Diego Health System, Department of Reproductive Medicine, 200 W. Arbor Drive – MC 8433, San Diego, CA 92103, USA

^b UCLA Medical Center, Department of Obstetrics and Gynecology, 757 Westwood Plaza, Room B711, Los Angeles, CA 90095, USA

^c UC San Diego Health System, Department of Pathology, Sanford Consortium for Regenerative Medicine, University of California San Diego, 9500 Gilman Drive, MC 0695, La Jolla, CA 92093-0695, USA

ARTICLE INFO

Article history:

Received 8 October 2014

Accepted 9 October 2014

Available online 30 October 2014

Keywords:

Uterine artery Doppler
Abnormal analytes
Risk stratification
Preeclampsia
Growth restriction
Preterm delivery

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 $\geq$ one abnormal analyte (PAPP-A < 0.3 , hCG > 3.0 , AFP > 2.5 , inhibin > 2.0 , or unconjugated estriol < 0.3 MoM). 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 $\geq$ 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.

© 2014 International Society for the Study of Hypertension in Pregnancy Published by Elsevier B.V. All rights reserved.

Introduction

A recognized association exists between patients with abnormal serum analytes detected at the time of aneu-

ploidy 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].

* Corresponding author. Tel.: +1 (619) 543 6906; fax: +1 (619) 543 3703.

E-mail address: haroeder@ucsd.edu (H.A. Roeder).

¹ Denotes co-senior authorship.

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 ≥ 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 (≥ 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

first or second trimester maternal serum analyte(s). Ten women did not have UtA Doppler studies performed, and 200 women delivered at an outside medical facility. Included in our analysis were $N = 132$ eligible patients who delivered at UCSD Hospital. In this cohort, the mean GA at delivery was 37.8 ± 3.3 weeks (minimum 25 weeks, maximum 41.6 weeks), and 34 (25.8%) delivered at <37 weeks GA, and 14 (10.6%) of patients delivered at <34 weeks GA. Sixteen (12%) had PET and 8 (6%) had preterm PET. Twenty-six (19.7%) had SGA and 10 (7.6%) had preterm SGA.

In a separate cohort of $N = 132$ patients with normal analytes, the mean (SD) GA at delivery was 39.1 ± 2.1 weeks (minimum 26 + 2 and maximum 42 + 0 weeks), 12 (9%) delivered at <37 weeks GA, and 3 (2.2%) delivered at <34 weeks GA. Six (4.5%) developed PET with no cases of preterm PET. Five (3.8%) had SGA, with one of the SGA fetuses (0.7%) born preterm.

Table 1 displays the baseline demographics for the study population. The mean age was 32.2 ± 5.3 years, and median BMI was 24.2 kg/m^2 ; 53.8% ($n = 71$) were nulliparous, 43.9% ($n = 58$) white, and 53.0% ($n = 70$) delivered vaginally. In comparing baseline demographics for women with normal vs. abnormal UtA Doppler studies, there were no significant differences between the groups by age, parity, BMI, ethnicity, or mode of delivery. In this study population, 74.2% ($n = 98$) had 1 abnormal analyte, 22.7% ($n = 30$) had 2 abnormal analytes, and 3% ($n = 4$) had 3 or more abnormal analytes. All patients had at least 1 abnormal analyte; the percentage of patients with each specific analyte abnormality is specified in Table 1. There were 44 patients (33.9%) who screened positive for Down syndrome (either with first trimester, second trimester, or sequential screening) and 17 patients (12.9%) who screened positive for open neural tube defects with an AFP ≥ 2.5 MoM. At the time of delivery, no infants were

diagnosed with Down syndrome or an open neural tube defect.

At the time of the first study ultrasound, the median [IQR] GA was 24.4 [24.0, 25.2] weeks. Thirty-two women had abnormal UtA Doppler studies; there were 11 women with bilateral notching, 13 with unilateral notching, and 24 with unilateral or bilateral elevated PI ≥ 1.6 (Table 2).

Data were analyzed to determine which component of the abnormal UtA Doppler study contributed the most to adverse outcomes. Any abnormal UtA Doppler (any notching or PI ≥ 1.6) was associated with increased odds of having an adverse pregnancy outcome, but PI ≥ 1.6 was most strongly associated with PET or SGA; notching was found to be a weaker predictor (Table 3). Given that the adverse cases detected with notching were also detected by an elevated PI, notching was dropped from the models. Henceforth this paper reports abnormal UtA Doppler indices defined as an abnormal unilateral or bilateral PI. An alternate analysis for both notching and abnormal PI is reported in the supplemental data online section.

There was a significant association between abnormal UtA Doppler PI and PET and SGA at all GA. Abnormal UtA Doppler PI also had a relationship approaching significance with IUGR (Table 4).

Using simple logistic regression calculations, the odds of preterm delivery, PET, preterm PET, SGA, and preterm SGA were significantly increased in those with abnormal UtA Doppler vs. normal UtA Doppler (Table 4). In particular, abnormal UtA Doppler PI was associated with a 17.7-fold increased odds of preterm PET ($p = 0.004$).

The utility of abnormal UtA PI as a screening test is shown in Table 5; sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are reported for each adverse outcome. Most notably, the NPV of normal uterine artery Doppler velocimetry with respect to preterm PET is 98%. In other words, it was highly likely that an individual with normal UtA Doppler would not develop preterm PET. Moreover, the sensitivity of UtA Doppler for detecting preterm PET is higher than any other outcome.

The normal and abnormal UtA Doppler indices were also used to calculate the odds ratios and likelihood ratios (Table 6) for various permutations of composite outcomes. Abnormal UtA Doppler PI increased the likelihood of a composite outcome of PET or SGA from 27% to 71%; a negative UtA Doppler PI reduced the likelihood to 18%.

Table 1
Study population demographics. Mean (SD), median [IQR] or frequency (percent).

Age (years)	32.2 (5.3)
Parity	
Nulliparous	71 (53.8%)
Multiparous	61 (46.2)
BMI (kg/m^2)	24.2 [22.1,27.8]
Ethnicity	
White	58 (43.9%)
Hispanic	52 (39.4%)
Black	2 (1.5%)
Other	20 (15.2%)
Prior preeclampsia	6 (4.5%)
Chronic hypertension	13 (9.8%)
Prior IUGR	3 (2.3%)
Pregestational diabetes	3 (2.3%)
Abnormal analyte	
PAPP-A ≤ 0.3 MoM	33 (25.0%)
AFP ≥ 2.5 MoM	17 (12.9%)
Estriol ≤ 0.3 MoM	3 (2.3%)
hCG ≥ 3.0 MoM	30 (22.7%)
Inhibin ≥ 2.0 MoM	90 (68.1%)

IQR, interquartile range; BMI, body mass index; IUGR, intrauterine growth restriction; PAPP-A, pregnancy-associated plasma protein A; AFP, alpha-fetoprotein; hCG, human chorionic gonadotropin.

Table 2
Ultrasound findings at the time of first study.

Median [IQR] GA (weeks)	24.4 [24.0–25.2]
n (percent) with SGA (EFW ≤ 10 th %)	12 (9.1)
n (percent) with IUGR (EFW ≤ 3 rd %)	4 (3.0)
n (percent) with abnormal UtA Doppler	
Mean PI ≥ 1.6	16 (12.1)
Any PI ≥ 1.6	24 (18.2)
Bilateral notching	11 (8.3)
Any notching	24 (18.2)
Any abnormal finding above	32 (24.2)

IQR, interquartile range; GA, gestational age; SGA, small for gestational age; EFW, estimated fetal weight; IUGR, intrauterine growth restriction; UtA, uterine artery; PI, pulsatility index.

Table 3

UtA Doppler and pregnancy outcome.

	Prevalence		Pregnancy outcome n (%)			
	#	%	Adverse	Normal	p-value	OR
Normal Doppler ^a	100	75.8	31	69	<i>p</i> = 0.002	0.27 (0.12, 0.62)
Any Abnormal Doppler	32	24.2	20	12	<i>p</i> = 0.002	3.71 (1.61, 8.52)
Any notching	24	18.2	14	10	<i>p</i> = 0.032	2.69 (1.09, 6.63)
Any PI ≥ 1.6	24	18.2	20	4	<i>p</i> < 0.001	12.42 (3.93, 39.29)

^a Normal Doppler: no notching, PI < 1.6; UtA, uterine artery; PI, pulsatility index Significance *p* < 0.05.**Table 4**

UtA Doppler and adverse pregnancy outcomes n(%).

	Overall Number	Normal UtA <i>n</i> = 108	Abnormal UtA ^a <i>N</i> = 24	OR (95% CI)	<i>p</i> -value ^b
Preterm delivery	34 (26)	20 (18.5)	14 (58.3)	6.20 (2.35, 16.33)	<i>p</i> = 0.001
PET	16 (12)	8 (7.4)	8 (33.3)	6.25 (2.05, 19.02)	<i>p</i> = 0.001
PET < 37	8 (6)	2 (1.9)	6 (25.0)	17.67 (3.30, 94.46)	<i>p</i> = 0.001
SGA	26 (20)	15 (13.9)	11 (45.8)	5.25 (1.99, 13.85)	<i>p</i> = 0.001
SGA < 37	12 (9)	5 (4.6)	5 (20.8)	5.42 (1.43, 20.55)	<i>p</i> = 0.013
IUGR	13 (10)	7 (6.5)	6 (25.0)	4.81 (1.45, 15.97)	<i>p</i> = 0.01
IUGR < 37	6 (6)	3 (2.8)	3 (12.5)	5.00 (0.94, 26.49)	<i>p</i> = 0.059

UtA, uterine artery; PET, preeclampsia; PET < 37, preterm preeclampsia; SGA, small for gestational age; SGA < 37, preterm small for gestational age less than 37 weeks gestation; IUGR, intrauterine growth restriction; IUGR < 37, preterm intrauterine growth restriction less than 37 weeks gestation.

^a Abnormal UtA means abnormal PI only.^b Simple logistic regression, Significance *p* < 0.05;**Table 5**

Screening performance of abnormal Doppler. Sensitivity, specificity, PPV NPV.

	Normal UtA <i>n</i> = 108	Abnormal UtA ^a <i>N</i> = 24	Screening performance of abnormal Doppler			
			Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
PET	8 (7.4)	8 (33.3)	50.0 (24.7, 75.3)	86.2 (78.6, 91.9)	33.3 (15.6, 55.3)	92.6 (85.9, 96.7)
PET < 37	2 (1.9)	6 (25.0)	75.0 (34.9, 96.8)	85.5 (78.0, 91.2)	25.0 (9.8, 46.7)	98.1 (93.5, 99.8)
SGA	15 (13.9)	11 (45.8)	42.3 (23.4, 63.1)	87.7 (79.9, 93.3)	45.8 (25.6, 67.2)	86.1 (78.1, 92.0)
IUGR	7 (6.5)	6 (25.0)	46.2 (19.2, 74.9)	84.9 (77.2, 90.8)	25.0 (9.77, 46.7)	93.5 (87.1, 97.4)
Preterm delivery	15 (13.9)	12 (50.0)	41.2 (24.7, 59.3)	89.8 (82.0, 95.0)	58.3 (36.6, 77.9)	81.5 (72.9, 88.3)

PPV, positive predictive value; NPV, negative predictive value; UtA, uterine artery; PET, preeclampsia; PET < 37, preterm preeclampsia; SGA, small for gestational age; IUGR, intrauterine growth restriction;

^a Abnormal UtA means abnormal PI only.**Table 6**

Composite outcomes.

	Normal UtA (<i>n</i> = 108)	Abnormal UtA ^a (<i>n</i> = 24)	OR (95% CI)	<i>p</i> -value	Likelihood ratio+	Likelihood ratio–	Pretest probability	Posttest probability+	Posttest probability–
All PET or all SGA	19	17	11.4 (4.1, 31.2)	<i>p</i> < 0.001	6.48 (2.93, 14.30)	0.57 (0.42, 0.78)	27.3%	71.0%	17.6%
PET < 37 or SGA < 37	6	10	12.1 (3.8, 38.6)	<i>p</i> < 0.001	5.18 (2.78, 9.63)	0.43 (0.23, 0.81)	12.9%	43.4%	6.0%
All IUGR or all PET	12	13	9.5 (3.7, 25.8)	<i>p</i> < 0.001	5.06 (2.58, 9.93)	0.54 (0.35, 0.81)	18.9%	54.1%	11.1%
IUGR < 37 or PET < 37	4	9	15.6 (4.3, 57.0)	<i>p</i> < 0.001	5.49 (3.03, 9.97)	0.35 (0.16, 0.80)	10.6%	39.4%	3.9%

Significance *p* < 0.05 UtA, uterine artery; PET, preeclampsia; PET < 37, preterm preeclampsia; SGA, small for gestational age; SGA < 37, preterm small for gestational age less than 37 weeks gestation; IUGR, intrauterine growth restriction; IUGR < 37, preterm intrauterine growth restriction less than 37 weeks gestation.^a Abnormal UtA means abnormal PI only.

Abnormal UtA Doppler studies increased the likelihood of a more severe composite outcome of preterm PET or preterm IUGR from 11% to 39%; a negative UtA Doppler PI reduced the likelihood to 4%.

Discussion

Patients with abnormal serum analytes have an increased risk of adverse outcomes. For example, as Olsen

et al. previously demonstrated, AFP, inhibin, and hCG greater than 2.0 MoM conferred a 3–8-fold increase in preterm PET < 34 weeks compared with PET > 34 weeks [1]. Given the poor performance of analytes alone as a screening test, our group further stratified this population into those with normal vs. abnormal UtA Doppler indices. Our novel findings included the observations that subjects with abnormal UtA Doppler indices are at an almost 18-fold increased risk of developing preterm PET at less than 37 weeks' gestation, and have a 15-fold increased risk of a composite outcome of preterm PET or IUGR at less than 37 weeks. The latter translates into a posttest probability of 4% for a negative test, which is nearly identical to the baseline risk in our general obstetrical population.

Staff et al. [15] describe the heterogeneity of PET in a recent review, striving to redefine this pathology as placental or maternal. They suggest that PET diagnosed prior to 37 weeks leads to higher rates of growth restriction [16], as well as a higher recurrence rate [17] which is important in future preconception counseling. In order to facilitate optimal utilization of healthcare resources, it is useful to identify factors in early pregnancy that can predict adverse pregnancy outcomes.

Our research is the first to demonstrate such a significant association between abnormal UtA Doppler indices and PET and IUGR, particularly preterm PET. A study by Filippi et al. found a similarly-increased relative risk of adverse pregnancy outcomes, including low birth weight, stillbirth, gestational hypertension, placental abruption and preterm delivery, but only on the order of 2–3-fold [9]. They also did not see a significant association between abnormal UtA Doppler indices and PET; however, in contrast to our population, which was derived from multiple private clinics and an academic practice, they enrolled their subjects from a single academic institution. It is possible that in their specific patient group, there was an unusually low risk for adverse outcomes.

In another study, first trimester analytes (PAPP-A and hCG) in conjunction with abnormal UtA Doppler indices detected a 5-fold increased risk of hypertensive disease [10]. This study discussed the possibility of incorporating second-trimester analytes to improve predictive value. Our study addressed this hypothesis, using abnormal analyte values from the first and second trimesters as entry criteria, then determining the value of UtA velocimetry for the identification of those at highest risk for PET or IUGR.

A significant strength of this analysis is the application of abnormal analyte cut-offs derived from the literature [12]. We also studied a diverse population from a wide referral base in a large metropolitan area providing generalizability. Additionally, we were able to leverage the California Department of Public Health's prenatal screening program for the identification of eligible patients. The diversity of our population closely reflects that of our geographic location.

The Doppler indices were obtained and interpreted by a small number of sonographers and physicians to minimize variability. As opposed to other studies, which relied on patient questionnaires, we were able to abstract our outcomes directly from the medical record, which avoids

patient and practitioner recall bias. An additional strength is the biologic plausibility of using measures of UtA Doppler indices and serum analytes (most of which are produced by villous cyto- and syncytiotrophoblast). These both reflect placental function, and further the association with abnormal placental outcomes, such as preterm PET and IUGR. There could be premature differentiation of cytotrophoblast cells resulting in placental insufficiency and changes in production and/or release of analytes into the serum, which can result in the clinical manifestations of PET and IUGR [18].

There are some limitations to our study, most notably its retrospective nature. In addition, the number of patients who were excluded from analysis due to lack of delivery outcomes is large (about 60%). Unfortunately, given our large referral base, patients deliver at a multitude of local hospitals and there are significant obstacles to obtaining objective data from the various medical record systems. It is possible that patients who deliver at a large tertiary institution could have a larger degree of pathology, thus biasing our outcomes away from the null hypothesis. We noted that notching decreased the specificity of UtA Doppler velocimetry for detection of adverse pregnancy outcomes without increasing the sensitivity. This could be because notching is more sensitive to the distance of the placenta from the midline [19]. To our surprise, our analysis showed that using elevated PI alone (without taking notching into consideration) outperformed notching alone, and notching AND elevated PI together for the identification of at-risk cases.

The authors acknowledge that we are screening for a condition for which there is no direct intervention at this point in time. However, there is clinical significance in identification of patients who fall into a high risk category and can establish care in a location where they can be safely managed in the event of complications.

Future studies with larger numbers of subjects and data collected at multiple institutions in a prospective randomized fashion will be required before definitive recommendations regarding the use of UtA Doppler screening can be made. If UtA Doppler velocimetry is found to be a valuable test in this context, a barrier to the implementation of this screening paradigm is that sonographers would need to be trained to measure UtA Doppler indices and compensation for these measurements by insurance companies would subsequently be needed.

Conclusions

In summary, in a patient population with abnormal first or second trimester serum analytes for aneuploidy, abnormal UtA PI is associated with increased risk for PET and SGA, particularly severe preterm disease. Moreover, the high specificity of UtA PI in our study population indicates that the post-test negative probability of an adverse event is low; healthcare providers can be reassured that a normal uterine artery study decreases the risk of preterm PET or severe growth restriction towards baseline rates. Our data support incorporating UtA Doppler screening in patients with abnormal analytes for the purpose of assigning patients to the appropriate level of

monitoring. As healthcare resources are scarce, there is value in accurate risk-stratification of patients: those at the high risk of adverse events can be assigned to a higher level of surveillance by a team with expertise in high-risk pregnancy, while low risk patients can be assigned to routine prenatal care.

Funding

The authors have no support or funding to report.

Competing interest

The authors have declared that no competing interests exist.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.preghy.2014.10.001>.

References

- [1] Olsen RN, Woelkers D, Dunsmoor-Su R, Lacoursiere DY. Abnormal second-trimester serum analytes are more predictive of preterm preeclampsia. *Am J Obstet Gynecol* 2012;207(3):228e1–7.
- [2] Dugoff L. First- and second-trimester maternal serum markers for aneuploidy and adverse obstetric outcomes. *Obstet Gynecol* 2010;115(5):1052–61.
- [3] Dugoff L, Hobbins JC, Malone FD, Vidaver J, Sullivan L, Canick JA, et al. Quad screen as a predictor of adverse pregnancy outcome. *Obstet Gynecol* 2005;106(2):260–7.
- [4] Morris RK, Cnossen JS, Langejans M, Robson SC, Kleijnen J, Ter Riet G, et al. Serum screening with Down's syndrome markers to predict pre-eclampsia and small for gestational age: systematic review and meta-analysis. *BMC Pregnancy Childbirth* 2008;8:33.
- [5] Matijevic R, Johnston T. In vivo assessment of failed trophoblastic invasion of the spiral arteries in pre-eclampsia. *Br J Obstet Gynaecol* 1999;106(1):78–82.
- [6] Lin S, Shimizu I, Suehara N, Nakayama M, Aono T. Uterine artery Doppler velocimetry in relation to trophoblast migration into the myometrium of the placental bed. *Obstet Gynecol* 1995;85(5 Pt 1):760–5.
- [7] Cnossen JS, Morris RK, ter Riet G, Mol BW, van der Post JA, Coomarasamy A, et al. Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis. *CMAJ* 2008;178(6):701–11.
- [8] Stout MJ, Goetzinger KR, Tuuli MG, Cahill AG, Macones GA, Odibo AO. First trimester serum analytes, maternal characteristics and ultrasound markers to predict pregnancies at risk for preterm birth. *Placenta* 2013;34(1):14–9.
- [9] Filippi E, Staughton J, Peregrine E, Jones P, Huttly W, Peebles DM, et al. Uterine artery Doppler and adverse pregnancy outcome in women with extreme levels of fetoplacental proteins used for Down syndrome screening. *Ultrasound Obstet Gynecol* 2011;37(5):520–7.
- [10] Dane B, Dane C, Kiray M, Cetin A, Koldas M, Erginbas M. Correlation between first-trimester maternal serum markers, second-trimester uterine artery doppler indices and pregnancy outcome. *Gynecol Obstet Invest* 2010;70(2):126–31.
- [11] Karsidag AY, Buyukbayrak EE, Kars B, Suyugul U, Unal O, Turan MC. The relationship between unexplained elevated serum markers in triple test, uterine artery Doppler measurements and adverse pregnancy outcome. *JPMA J Pak Med Assoc* 2010;60(3):181–6.
- [12] Gagnon A, Wilson RD, Audibert F, Allen VM, Blight C, Brock JA, et al. Obstetrical complications associated with abnormal maternal serum markers analytes. *J Obstet Gynaecol Can JOGC* 2008;30(10):918–49.
- [13] Papageorgiou AT, Yu CK, Nicolaides KH. The role of uterine artery Doppler in predicting adverse pregnancy outcome. *Best Pract Res Clin Obstet Gynaecol* 2004;18(3):383–96.
- [14] ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. *Obstet Gynecol* 2002;99(1):159–67.
- [15] Staff AC, Benton SJ, von Dadelszen P, Roberts JM, Taylor RN, Powers RW, et al. Redefining preeclampsia using placenta-derived biomarkers. *Hypertension* 2013;61(5):932–42.
- [16] Xiong X, Demianczuk NN, Saunders LD, Wang FL, Fraser WD. Impact of preeclampsia and gestational hypertension on birth weight by gestational age. *Am J Epidemiol* 2002;155(3):203–9.
- [17] Hnat MD, Sibai BM, Caritis S, Hauth J, Lindheimer MD, MacPherson C, et al. Perinatal outcome in women with recurrent preeclampsia compared with women who develop preeclampsia as nulliparas. *Am J Obstet Gynecol* 2002;186(3):422–6.
- [18] Fitzgerald B, Levytska K, Kingdom J, Walker M, Baczyk D, Keating S. Villous trophoblast abnormalities in extremely preterm deliveries with elevated second trimester maternal serum hCG or inhibin-A. *Placenta* 2011;32(4):339–45.
- [19] Hernandez-Andrade E, Brodzki J, Lingman G, Gudmundsson S, Molin J, Marsal K. Uterine artery score and perinatal outcome. *Ultrasound Obstet Gynecol* 2002;19(5):438–42.