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Doppler screening and predictors of adverse outcomes in high risk pregnancies affected by tobacco

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ABSTRACT

Objective: The purpose of this study was to investigate associations between Doppler measurements and adverse outcomes in an obstetric population with high tobacco use.
Methods: This retrospective study included patients with Doppler data (umbilical systolic/diastolic velocity ratios (S/D), uterine S/D, uterine left/right ratio index (RI)). Receiver operator characteristic curve analysis determined cut-off elevated Doppler indices. Stepwise logistic regression was used to predict adverse outcomes.
Results: 338 of 745 patients (45.4%) had adverse outcomes. Doppler artery indices identified significant associations with IUGR, preeclampsia, low birth weight, pre-term birth and composite adverse outcome variable. An elevated Umbilical S/D was 2.1 (95% Confidence Interval (CI): 1.5–2.9; $p < 0.001$) times was more likely to have an adverse outcome. For left uterine artery S/D and nulliparity, the odds ratios were 1.8 (95% CI: 1.3–2.5) and 1.4 (95% CI: 1.0–1.9), respectively.
Conclusion: Umbilical and uterine left S/D indices and nulliparity are significant independent predictors of adverse outcomes.

1. Introduction

Tobacco use is one of the few preventable causes of adverse pregnancy outcomes. It has been linked to placental abruption, preterm delivery, birth defects and intrauterine growth restriction [1,2]. In a study performed by the CDC in 2008, 23.0% of women admitted to smoking in the three months prior to pregnancy. In the state of West Virginia, 39.4% of women smoked during the three months prior to pregnancy which was the highest rate among the states studied [1]. Rogers showed in his epidemiologic review that if all women in the US stopped smoking there would be an 11% reduction in stillbirths and 5% reduction in neonatal deaths [3].

Many of the adverse effects of tobacco on pregnancy are related to the placenta. Tobacco has been shown to affect the blood flow through the placenta particularly by affecting the perfusion of the cytotrophoblasts [4]. Tobacco has also been demonstrated to directly affect uterine blood flow to the placenta by causing vasoconstriction. These events can cause hypoxic injury, that, when combined with hypoxemia from exposure to carbon monoxide from cigarettes, can result in intrauterine growth restriction and low birth weights [3]. Anderson et al., 2009 documented the effects of tobacco on the vasodilator nitric oxide (NO) on fetal endothelial vessels [4]. They measured levels of endothelial NO synthase (eNOS) as the proxy for production of vasodilatory NO in the fetal endothelial vessels, noting that smokers had lower measured endothelial NO synthase (eNOS) in the fetal umbilical arteries and vein compared to nonsmokers. This reduction in vasodilatory capacity appears to contribute to the decreased placental perfusion in smokers and contributes to growth delay. Further, they concluded that early tobacco cessation may ameliorate these effects. Secondhand smoke has been shown to cause similar effects [5].

While the effects of tobacco on the placenta have been investigated, the ideal strategy for an obstetrician and gynecologist to manage a pregnancy affected by tobacco remains uncertain. Albuquerque et al., 2004 showed evidence of increased vascular resistance in the umbilical, uterine and middle cerebral artery in smokers compared to nonsmokers [6]. Yildiz et al., 2011 found that even exposure to passive tobacco smoke was linked to increased

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Table 1
Maternal characteristics of the study cohort.

	Normal Outcome (n = 407) n(%) or ±SD	Adverse Outcome (n = 338) n(%) or ±SD	p value
Age (years)	26.7 ± 5.9	26.5 ± 5.9	0.591
Ethnicity/Race			0.305
White	374 (91.9)	314 (92.9)	
African American/Black	26 (6.4)	23 (6.8)	
Asian	6 (1.5)	1 (0.3)	
Pacific Islander	1 (0.2)	0 (0.0)	
Payer Group Classification			0.673
Public	127 (31.2)	102 (30.2)	
Private	277 (68.1)	235 (69.5)	
Self-Pay	3 (0.7)	1 (0.3)	
Tobacco Use (during pregnancy)	195 (47.9)	152 (45.0)	0.234
Gestational Age	33.7 ± 3.5	32.4± 3.6	**<0.001**
Nulliparity	198 (48.6)	190 (56.2)	**0.047**

resistance in the maternal vasculature and the fetal middle cerebral artery vasculature [7]. In contrast, Newnham et al., 1990 found no difference in umbilical systolic/diastolic velocity ratios (S/D) ratios between smokers and non-smokers [8]. Kalinka et al., 2005 in Poland, found that there was a significant correlation with serum cotinine and abnormal uterine artery systolic to diastolic ratios (S/D), resistance indices, and pulsatility indices (PI). They found that a midgestation (20–24 weeks) uterine artery S/D ratio >3 was a significant risk for growth delay [9].

There have been various studies on the value of using Doppler measurements to predict adverse birth outcome. Some have found the use of umbilical and uterine artery Dopplers to be effective in predicting poor pregnancy outcomes in pregnancies affected by intrauterine growth restriction [10]. Seyam et al., 2002 evaluated the use of umbilical artery Dopplers in pregnancies affected by intrauterine growth restriction and found that Doppler velocimetry is predictive of fetal outcome [11]. Yu et al., 2008 in their study of over 30,000 pregnancies found that an elevated uterine artery PI was associated with preeclampsia requiring preterm delivery [12].

As a result of these studies, and increased rate of smoking within West Virginia [13,14], we introduced both uterine and umbilical artery Dopplers in our ultrasound clinics as a means to screen for adverse events in pregnancy, ie preeclampsia and IUGR. As such, we had a large cohort of high risk patients with uterine artery Dopplers. Due to the high incidence of tobacco in our population (at least 39.5%), we desired to investigate the possible use of screening Dopplers to identify patients at risk for adverse outcomes. Therefore, the objective of this study was to investigate an association between elevated screening Doppler measurements and poor perinatal outcomes in a high risk obstetric population with a high rate of tobacco use.

2. Material and methods

A retrospective review of umbilical and uterine Doppler measurements, patient characteristics and pregnancy outcome data on a convenience sample of patients receiving prenatal sonograms at CAMC Women's and Children's Hospital between 1 January 2008-July 1 2014 was conducted. Doppler measurements were performed on patients serviced by the hospital's prenatal clinic and patients from private practices that do not offer sonography or referred patients to the maternal fetal medicine specialist. We received approval from the West Virginia University/CAMC Institutional Review Board prior to beginning the study. Exclusion criteria consisted of multiple gestations, no Doppler evaluation, no delivery at CAMC, >45 years of age (due to increased risk for aneuploidy), and fetal anomalies. All other pregnancies were included in our analysis. We defined adverse outcome in this study as a composite of one or more of the following: pre-term birth (<37 weeks), low birth weight (<2500 g), Intrauterine Growth Restriction (IUGR), preeclampsia, polyhydramnios, placental abruption, and fetal anomalies. The adverse and normal outcome groups were compared for maternal characteristics and comorbidities to further evaluate risk factors for adverse outcomes. We defined tobacco use from self-reporting on the medical history during prenatal care.

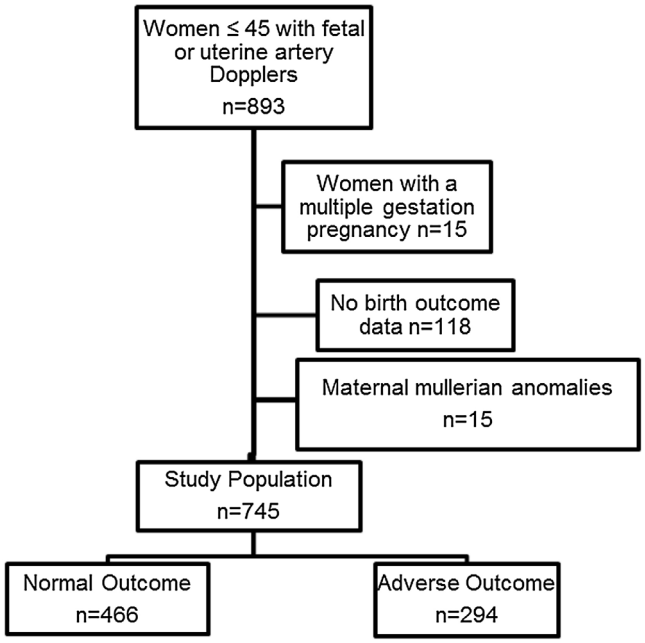

Fig. 1. Study Cohort.

A Receiver Operator Characteristic (ROC) curve analysis was used to determine cut-off points grouping Doppler indices into normal and elevated. If the area under the ROC curve was different from 0.5 (chance) at $p < 0.05$, then our findings were considered significant. To calculate our cut-off points, we used the Youden index (J). With this method, we assume that sensitivity and specificity have equal importance. Thus, we used the following formula (J = maximum sensitivity + specificity -1) in which J is defined as the maximum vertical distance between the ROC analysis and the diagonal line or the point on the curve farthest from chance [15,16]. Backwards stepwise logistic regression was used for multivariate analysis to predict adverse birth outcomes using Doppler measurements, comorbidities, and tobacco use as potential predictors.