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ORIGINAL RESEARCH ARTICLE

The predictive capacity of uterine artery Doppler for preterm birth—A cohort study

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Abstract

Introduction: Mid-trimester uterine artery resistance measured with Doppler sonography is predictive for iatrogenic preterm birth. In view of the emerging association between hypertensive disease in pregnancy and spontaneous preterm birth, we hypothesized that uterine artery resistance could also predict spontaneous preterm birth.

Material and methods: We performed a cohort study of women with singleton pregnancies. Uterine artery resistance was routinely measured at the 18-22 weeks anomaly scan. Pregnancies complicated by congenital anomalies or intrauterine fetal death were excluded. We analyzed if the waveform of the uterine artery (no notch, unilateral notch or bilateral notch) was predictive for spontaneous and iatrogenic preterm birth, defined as delivery before 37 weeks of gestation. Furthermore, we assessed whether the uterine artery pulsatility index was associated with the risk of preterm birth.

Results: Between January 2009 and December 2016 we collected uterine Doppler indices and relevant outcome data in 4521 women. Mean gestational age at measurement was 19^{+6} weeks. There were 137 (3.0%) women with a bilateral and 213 (4.7%) with a unilateral notch. Mean gestational age at birth was 38^{+6} weeks. Spontaneous and iatrogenic preterm birth rates were 5.7% and 4.9%, respectively. Mean uterine artery resistance was 1.12 in the spontaneous preterm birth group compared with 1.04 in the term group (P = 0.004) The risk of preterm birth was increased with high uterine artery resistance (OR 2.9 per unit; 95% CI 2.4-3.9). Prevalence of spontaneous preterm birth increased from 5.5% in women without a notch in the uterine arteries to 8.0% in women with a unilateral notch and 8.0% in women with a bilateral notch. For iatrogenic preterm birth, these rates were 3.9%, 13.6% and 23.4%, respectively. Likelihood ratios for the prediction of spontaneous preterm birth were 1.6 (95% CI 1.0-2.6) and 1.9 (95% CI 1.0-3.5) for unilateral and bilateral notches, respectively, and for iatrogenic preterm birth they were 3.6 (95% CI 2.5-5.2) and 6.8 (95% CI 4.7-9.9) for unilateral and bilateral notches, respectively. Of all women with bilateral notching, 31.4% delivered preterm.

Abbreviations: CI, confidence interval; GA, gestational age; OR, odds ratio; PI, pulsatility index; PTB, preterm birth; UtA, uterine artery.

Conclusions: Mid-trimester uterine artery resistance measured at 18-22 weeks of gestation is a weak predictor of spontaneous preterm birth.

KEYWORDS

Doppler ultrasound, prediction, spontaneous preterm birth, uterine artery

1 | INTRODUCTION

Preterm birth (PTB), defined as delivery before 37 weeks of gestation, remains a major burden in obstetric care, affecting over 15 million babies worldwide each year.[1,2] Despite various preventive measures, 1 million neonatal deaths are attributable to complications of PTB, which makes it the leading cause of death in children under the age of 5 years.[3] To reduce these numbers, it is crucial to understand the mechanisms underlying prematurity and develop targeted interventions for prevention.

During the normal development of the placental structure, trophoblast cells invade the myometrium and cause remodeling of maternal spiral arteries. These spiral arteries convert to a low-resistance, high-flow state.[4,5] The complete transformation of the decidual and myometrial segments of the spiral arteries is also known as deep placentation.[6] Defective deep placentation was first found in women with preeclampsia and intrauterine growth restriction,[7] but in recent years it was also found to be associated with spontaneous preterm labor.[8,9] The disease of the placenta vascular bed that underpins these complications is commonly known as the "great obstetrical syndrome".[6]

It has been suggested that women with manifestations of placental dysfunction have a higher impedance of uterine artery (UtA) blood flow and failure of physiological transformation of the spiral arteries.[10-13] This abnormal mid-trimester UtA resistance measured with Doppler sonography is known to be predictive for preeclampsia and, hence, for iatrogenic PTB.[12,14]

So far, studies have found conflicting results in the association between spontaneous PTB and UtA resistance.[15,16] In addition, it was found that women carrying a male fetus have higher second-trimester UtA resistance and a higher frequency of notching of the UtA.[17]

In view of the emerging association between hypertensive disease in pregnancy and spontaneous PTB,[18] we hypothesized that UtA resistance could also predict spontaneous PTB.

Our objective was to investigate the utility of mid-trimester UtA Doppler in the prediction of spontaneous preterm delivery in a large cohort.

> **Key message**
>
> Risk of spontaneous preterm birth is higher in women with a higher uterine artery resistance, either manifested in notching or higher pulsatility index. However, the predictive capacity is rather limited.

2 | MATERIAL AND METHODS

2.1 | Study design

We performed a single-center cohort study among consecutive women with a singleton pregnancy who visited the fetal ultrasound department of the Academic Medical Center, Amsterdam for their routine fetal anomaly scan between 1 January 2009 and 31 December 2016. Data were collected using an ASTRAIA database. ASTRAIA is a local registry that is used for collection of all sonographic data and pregnancy outcomes.

2.2 | Inclusion and exclusion criteria

We studied all women with a singleton gestation who had an anomaly scan between 18 and 22 weeks of gestation. As the Academic Medical Center is a tertiary referral center, women attending antenatal care had pre-existing medical conditions or an increased risk for pregnancy complications. Moreover, the obstetric ultrasound department has a regional function for the surrounding midwifery practices, which leads to a large number of low-risk women being included in our cohort.

Women with a pregnancy complicated by congenital anomalies or antepartum fetal mortality were excluded. Furthermore, women were excluded if measures of interest were not available for both the left and right UtA Doppler, if outcome of pregnancy was unknown, or if the way in which labor started (spontaneous contractions, cesarean section, induction) was not specified.

2.3 | Data collection

All women received an intake by the sonographer in which obstetrical history, smoking during pregnancy, maternal height and weight, and method of conception (spontaneous, in vitro fertilization, ovulation induction or intracytoplasmic sperm injection) were recorded.

UtA Doppler measurement was performed by a certified sonographer. The UtAs were identified at the crossover with the external iliac artery by an abdominal approach (Figure 1). Both arteries were sampled and three consecutive waveforms were evaluated. All measurements were performed using a Voluson™ ultrasonograph (Voluson E8 or E10; GE Healthcare). Both quantitative assessments

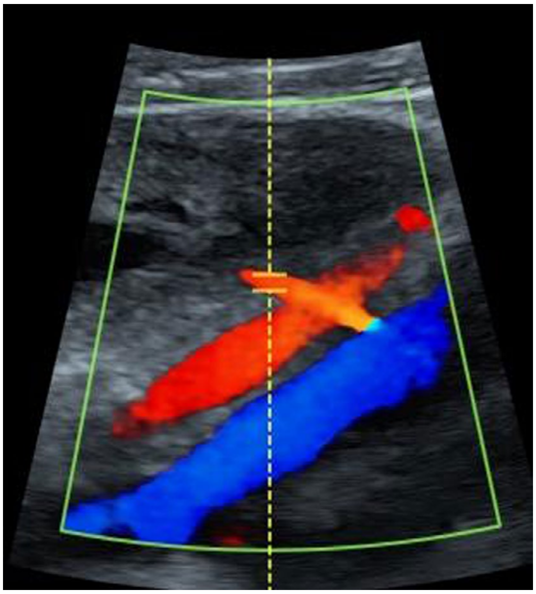


FIGURE 1 Doppler image of uterine artery at crossover iliac artery [Color figure can be viewed at wileyonlinelibrary.com]

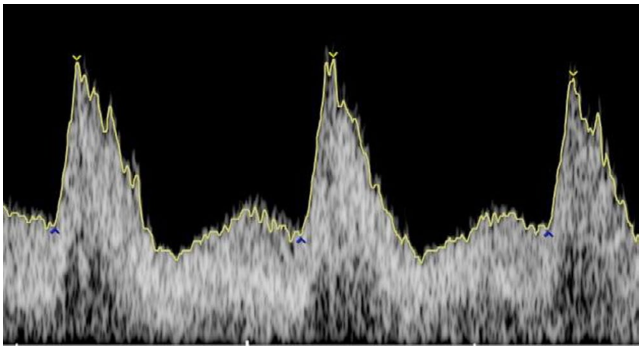


FIGURE 2 Notch waveform in uterine artery [Color figure can be viewed at wileyonlinelibrary.com]

of the wave by pulsatility index (PI) as well as qualitative analysis of the flow velocity waveform (notching) (Figure 2) were performed and reported in the local ultrasound database (ASTRAIA). Notching was defined as a persistent decrease in blood-flow velocity in the early diastole, below the diastolic peak velocity.[5] This can be objectified at none, one or both sides of the UtAs.

If bilateral notching was observed during the fetal anomaly scan, increased surveillance was performed. Women with a bilateral notch were invited for a follow-up ultrasound at 24 weeks of gestation (fetal biometry and UtA Doppler). When there was a persistent bilateral notch in the UtAs, monitoring of fetal growth by ultrasound was suggested until fetal biometry was within the normal range at 30 weeks of gestation.

All included women were followed until delivery. Follow up of the pregnancies was retrieved by questionnaires that were distributed routinely after the 20-week fetal anomaly scan. In addition, we checked the hospital charts of the Academic Medical Center for any missing data.

2.4 | Outcome measures

Preterm birth was defined as a delivery before 37 completed weeks of gestation and categorized as spontaneous or iatrogenic. Gestational age (GA) was based on first trimester crown-rump length. If the first trimester scan was not performed, estimated due date was calculated using the last menstrual period or a second- or third-trimester ultrasound, in concordance with the national guideline.[19]

Our primary outcome was spontaneous PTB before 37 weeks of gestation. Secondary outcomes were overall PTB before 37 weeks, iatrogenic PTB before 37 weeks, spontaneous and iatrogenic PTB between 34 and 37 weeks, between 32 and 34 weeks and between 22 and 32 weeks of gestation, and GA at birth. We used mean UtA PI (left + right PI divided by 2) as a measure of UtA resistance. As UtA PI varies with GA, we constructed GA-adjusted centiles based on the women with a term delivery on our own data set. We defined increased PI as >90th centile (P90) and >95th centile (P95). The presence of notches could be either unilateral or bilateral.

2.5 | Statistical analyses

In case of missing data, multiple imputation was used to create several "complete" sets of data.[20] Both patient characteristics and outcomes were taken into account to impute missing data. We used an iterative Markov chain Monte Carlo method for the generation of missing values and created 10 imputed data sets to use the pooled estimates.

We assessed demographic and obstetric baseline characteristics. We performed univariate analysis for the comparison of baseline characteristics for the 3 groups (no notch, unilateral notch and bilateral notch) using the chi-squared test for categorical variables or 1-way analysis of variance with the post-hoc Bonferroni correction for comparison of means. Mean GA at birth was assessed for all groups. Incidence of spontaneous and iatrogenic PTB was estimated for the overall study population and for each group.

Overall prevalence of PTB was estimated for the total study population. UtA waveform was categorized into (a) no notch, (b) unilateral notch and (c) bilateral notch.

The association between the waveform in the UtA (no notch, unilateral notch or bilateral notch) and spontaneous or iatrogenic PTB was assessed using likelihood ratios. Time to delivery was expressed for all waveforms. A Kaplan-Meier survival curve was plotted to show any difference in GA at birth between different mid-trimester notching. In pregnancies in which labor was induced, time to delivery was censored.

To estimate the effect of the UtA PI on PTB, logistic modeling was used, expressed as an odds ratio (OR) with a 95% CI. A multivariable logistic regression was performed to adjust for possible confounders that were unequally distributed in the baseline demographics. We tested both the effect on PTB overall and also within the groups with spontaneous or iatrogenic start of labor separately.

After excluding women with an iatrogenic PTB, mean UtA PI, UtA PI > P90 and UtA PI > P95 were compared between women with and without spontaneous PTB < 37 weeks.

To investigate which measure of UtA resistance predicted best for spontaneous PTB < 37 weeks, we constructed receiver operating characteristic (ROC) curves with mean UtA, UtA PI > P90 and UtA PI > P95 and calculated an area under the curve (AUC) for each.

Sensitivity, specificity, and positive and negative predictive values of the mean UtA PI were calculated for different cut-offs of GA (spontaneous PTB between 34 and 37, 32 and 34, 28 and 32 weeks, and at <28 weeks of gestation).

In The Netherlands, the official protocol for standardized ultrasound for dating pregnancies was introduced in September 2011. Previous research reported that the method used for GA estimates (last menstrual period or ultrasound) influences the PTB rates.[21] In the earlier years of our study cohort (2009-2011), standardized ultrasound for dating of the pregnancy was not common practice, so we performed a post-hoc sensitivity analysis over the last 4 years of our cohort to reduce dating errors as an explanation for our findings.

Data were analyzed using SPSS Statistics 24 (IBM SPSS). A $P < 0.05$ was supposed to indicate statistical significance.

2.6 | Ethical approval

In the Amsterdam University Medical Center all women participating in prenatal screening give written informed consent to use the data of the pregnancy and outcome for research. All measurements and pregnancy and delivery characteristics are stored in an ultrasound registry. The data extracted for our study were anonymous, so no further ethical approval was necessary. This study complies with the Declaration of Helsinki.

3 | RESULTS

We identified 6996 women with a singleton gestation during our study period. Women with a pregnancy complicated by congenital anomalies (n = 46), termination of the pregnancy for any reason (n = 11) and/or an intrauterine death (n = 48) were excluded. After excluding women whose pregnancy outcome was not available (n = 1716), or in whom the method of onset of labor was unknown (n = 654), data of 4521 women were available for analysis.

3.1 | Baseline characters

Maternal characteristics are shown in Table 1. There were 137 (3.0%) women with a bilateral notch and 212 (4.7%) with a unilateral notch. Mean GA at measurement was 19^{+6} weeks. History of PTB was more prevalent within the group with a bilateral notch compared with women without a notch (13.1% vs 7.0%). Women with a bilateral notch were significantly younger than women with a unilateral notch or with no notch (30.6 vs 30.8 and 31.8 years for unilateral and no notch, respectively, $P < 0.001$).

3.2 | Primary and secondary outcomes

An overview of birth outcomes is presented in Table 2. Mean GA at birth was 38^{+6} weeks. Figure 3 shows the time to delivery for women with different notch findings. The overall incidence of PTB before 37 weeks of gestation was 10.6% (n = 481), spontaneous PTB occurred in 6.3% (n = 259) whereas iatrogenic PTB occurred in 4.9% (n = 222) of the women.

The incidence of spontaneous PTB at <37 weeks increased from 5.5% in women without a notch in the UtAs to 8.0% in women with a unilateral notch as well as in women with a bilateral notch ($P = 0.02$) (Table 2). For iatrogenic PTB, these rates were 3.9%, 13.6% and 23.4%, respectively ($P < 0.001$).

Within the group with a bilateral notch, 5.8% of the women had a spontaneous PTB between 34 and 37 weeks compared with 3.3% of the women without a notch ($P < 0.001$). For the prediction of spontaneous PTB between 32 and 34 weeks and between 22 and 32 weeks, no significant differences were observed.

TABLE 1 Baseline characteristics of the whole cohort in relation to the presence or absence of notching (N = 4521)

Baseline characteristics	No notch N = 4171	Unilateral notch N = 213	Bilateral notch N = 137	*P*-value
GA at measurement	19^{+6}	19^{+6}	19^{+6}	0.98
Maternal age (y, mean)	31.6	30.8	30.6	0.01
Maternal BMI (kg/m^2, SD)	25.7 (5.3)	25.6 (5.6)	26.9 (6.9)	0.04
Smoking (n, %)	251 (6.7%)	18 (9.3%)	11 (9.1%)	0.24
Nulliparous (n, %)	1793 (44.6%)	98 (48.3%)	61 (45.2%)	0.58
ART (n, %)	61 (8.3%)	12 (7.3%)	8 (8.7%)	0.89
Previous preterm birth (n, %)	290 (7.0%)	22 (10.3%)	18 (13.1%)	0.005

Abbreviations: ART, assisted reproductive technology; BMI, body mass index; GA, gestational age.

TABLE 2 Outcomes

Outcomes	No notch N= 4171	Unilateral notch N = 213	Bilateral notch N = 137	*P*-value
GA at delivery	39^{+0}	38^{+1}	37^{+1}	<0.001
Total preterm births, n (%)				
<37 wk	392 (9.4%)	46 (21.6%)	43 (31.4%)	<0.001
34-37 wk	248 (6.0%)	27 (12.7%)	19 (13.9%)	<0.001
32-34 wk	53 (1.3%)	6 (2.8%)	7 (1.7%)	<0.001
22-32 wk	82 (2%)	13 (6.1%)	17 (12.4%)	<0.001
Spontaneous preterm births, n (%)				
<37 wk	231 (5.5%)	17 (8.0%)	11 (8.0%)	0.02
34-37 wk	138 (3.3%)	15 (7.0%)	8 (5.8%)	0.001
32-34 wk	37 (0.9%)	1 (16.7%)	1 (0.7%)	0.87
22-32 wk	47 (1.1%)	1 (0.5%)	2 (1.5%)	0.45
Iatrogenic preterm births, n (%)				
<37 wk	161 (3.9%)	29 (13.6%)	32 (23.4%)	<0.001
34-37 wk	110 (2.6%)	12 (5.6%)	11 (8.0%)	<0.001
32-34 wk	16 (0.4%)	5 (2.3%)	6 (4.4%)	<0.001
22-32 wk	35 (0.84%)	12 (5.6%)	15 (10.9%)	<0.001

Abbreviation: GA, gestational age.

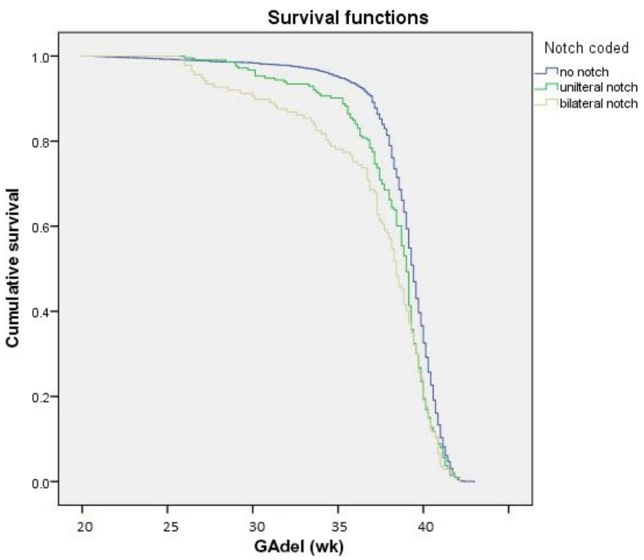


FIGURE 3 Time to delivery expressed for uterine artery waveform (no notch, unilateral notch, bilateral notch). GAdel, gestational age at delivery [Color figure can be viewed at wileyonlinelibrary.com]

Likelihood ratios for the prediction of spontaneous PTB were 1.6 (95% CI 1.1-2.6) and 1.9 (95% CI 1.0-3.5) for unilateral and bilateral notches, respectively. For iatrogenic PTB, presence of notching was significantly related to the risk of PTB (<37, 32-34, 32-22 weeks; $P < 0.001$). Corresponding positive likelihood ratios were 3.5 (95% CI 2.5-5.2) for unilateral notching and 6.8 (95% CI 4.7-9.9) for bilateral notching (Table 3). Of all women with bilateral notching, 31.4% delivered preterm.

Mean UtA resistance was 1.12 in the spontaneous PTB group compared with 1.04 in the term group ($P < 0.001$). The risk of overall PTB was increased with a higher UtA (OR 3.1; 95% CI 2.5-3.8). Adjustment for maternal age and previous PTB did not change this result (OR 2.9; 95% CI 2.4-3.7). Table 4 shows the relation between mean UtA resistance and spontaneous PTB for different GAs. Mean PI > P90 was the best predictor for spontaneous PTB between 32 and 37 weeks. Mean PI > P95 was associated with a higher risk for spontaneous PTB before 32 weeks.

Figure 4 shows the different ROC curves for the prediction of spontaneous PTB at <37 weeks. Mean UtA PI had the largest AUC (0.56; 95% CI 0.52-0.60).

3.3 | Sensitivity analysis

We performed a post-hoc sensitivity analysis for the period between years 2012 and 2016 because during the earlier years there was no routine first-trimester ultrasound scan for estimation of GA. Analysis of 3809 pregnancies in these last 4 years did not change our results (see Supplementary material, Table S1).

4 | DISCUSSION

In this study we assessed the utility of mid-trimester UtA Doppler measurement for the prediction of PTB. The main finding of this study is that women with a higher UtA resistance, either manifested in notching or higher PI, are at increased risk for spontaneous PTB before 37 weeks of gestation. The risk is particularly

TABLE 3 Rates and likelihood ratios (LR) for spontaneous preterm births, iatrogenic preterm births and term births

Notch	N	%	LR (95% CI)
Term births			
No notch	3779	90.6	1.15 (1.1-1.2)
Unilateral	167	78.4	0.40 (0.30-0.55)
Bilateral	94	68.6	0.25 (0.17-0.35)
Total	4040	89.4	

	Spontaneous			Iatrogenic			Total		
Notch	N	%	LR (95% CI)	N	%	LR (95% CI)	N	%	LR (95% CI)
Preterm birth <37 wk									
No notch	231	5.5	0.95 (0.91-1.0)	161	3.9	1.5 (1.4-1.7)	392	14.9	0.9 (0.83-0.91)
Unilateral	17	8	1.6 (1.0-2.6)	29	13.6	3.6 (2.5-5.2)	46	21.6	2.5 (1.8-3.4)
Bilateral	11	8	1.9 (1.0-3.5)	32	23.4	6.8 (4.7-9.9)	43	40	4.1 (2.9-5.8)
Total	259	5.7		222	4.9		481	10.6	
Preterm birth <34 wk									
No notch	93	2.2	1.0 (0.97-1.1)	51	1.2	0.62 (0.52-0.74)	144	3.4	0.83 (0.77-0.90)
Unilateral	2	0.9	0.46 (0.12-1.8)	17	8	5.5 (3.5-8.4)	19	8.9	2.5 (1.6-4.0)
Bilateral	3	2.2	1.1 (0.37-3.5)	21	15.3	10.7 (7.1-16.0)	24	17.5	5.2 (3.5-7.9)
Total	98	2.2		89	2		187	4.2	
Preterm birth <32 wk									
No notch	1	0.5	1.02 (0.96-1.09)	35	0.8	0.61 (0.49-0.76)	36	1.1	0.81 (0.73-0.90)
Unilateral	2	1.5	0.38 (0.05-2.6)	12	5.6	5.5 (3.3-9.1)	14	7.1	2.7 (1.6-4.5)
Bilateral	56	1.3	1.2 (0.31-4.8)	15	10.9	10.5 (6.6-16.6)	71	12.2	5.5 (3.4-8.8)
Total	59	1.3		62	1.4		121	2.7	

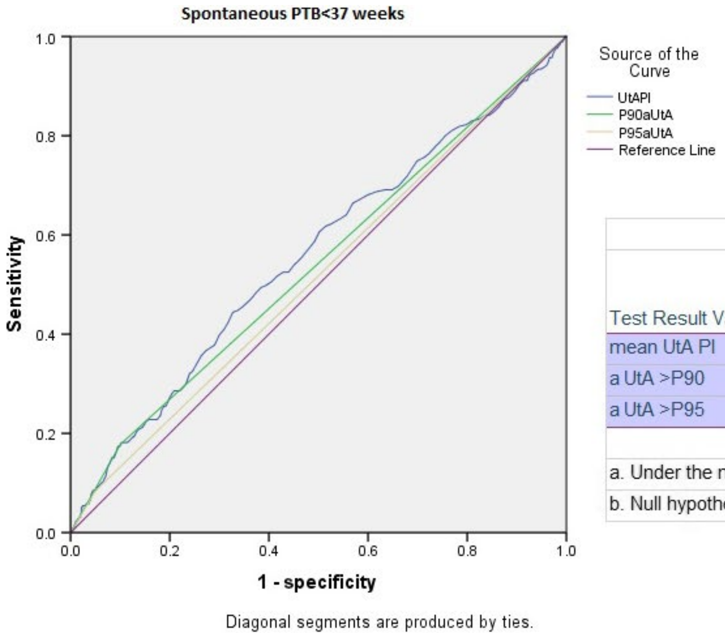
TABLE 4 Association between mean uterine artery pulsatility index and spontaneous preterm birth (PTB) at different gestational age cutoffs

	Sensitivity	Specificity	NPV	PPV	Odds ratio
Mean uterine artery >P90					
Spontaneous PTB <37 wk	0.18 (0.14-0.23)	0.90 (0.90-0.90)	0.95 (0.94-0.95)	0.10 (0.08-0.13)	1.94 (1.39-2.71)
Spontaneous PTB 34-37 wk	0.20 (0-14-0.27)	0.90 (0.90-0.90)	0.97 (0.96-0.97)	0.07 (0.06-0.10)	2.20 (1.48-3.29)
Spontaneous PTB 32-34 wk	0.15 (0.06-0.31)	0.90 (0.90-0.90)	0.99 (0.99-0.99)	0.01 (0.01-0.03)	1.56 (0.65-3.74)
Spontaneous PTB 28-32 wk	0.27 (0.09-0.55)	0.90 (0.90-0.90)	0.10 (0.10-0.10)	0.01 (0.00-0.00)	3.12 (0.99-9.84)
Spontaneous PTB <28 wk	0.09 (0.03-0.22)	0.90 (0.89-0.90)	0.99 (0.99-0.99)	0.01 (0.00-0.00)	0.85 (0.30-2.39)
Mean uterine artery >P95					
Spontaneous PTB <37 wk	0.09 (0.06-0.14)	0.95 (0.95-0.95)	0.94 (0.94-0.94)	0.10 (0.06-0.14)	1.73 (1.09-2.73)
Spontaneous PTB 34-37 wk	0.09 (0.06-0.15)	0.95 (0.95-0.95)	0.96 (0.96-0.97)	0.07 (0.04-0.11)	1.89 (1.09-3.28)
Spontaneous PTB 32-34 wk	0.05 (0.01-0.18)	0.95 (0.95-0.95)	0.99 (0.99-0.99)	0.01 (0.00-0.03)	0.96 (0.23-4.0)
Spontaneous PTB 28-32 wk	0.20 (0.05-0.48)	0.95 (0.95-0.95)	1.00 (1.00-1.00)	0.01 (0.00-0.03)	4.5 (1.26-16.0)
Spontaneous PTB <28 wk	0.05 (0.01-0.17)	0.95 (0.95-0.95)	0.99 (0.99-0.99)	0.01 (0.00-0.03)	0.85 (0.20-3.53)

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; PTB, preterm birth.

present between 34 and 37 weeks of gestation. No statistically significant effect on spontaneous PTB before 34 weeks was observed.

Our study has both strengths and limitations. A major strength of this study is that we included a cohort with a large sample size. We recruited women with both a low-risk (midwifery practices) and high risk (tertiary center) for spontaneous PTB. Data were derived from a local ultrasound registry (ASTRAIA), in which both data on delivery and other pregnancy outcomes are registered. All ultrasound scans were conducted by certified sonographers.



Area under the curve

Test Result Variable(s)	Area	SE^a	Asymptotic Sig.[b]	Confidence interval Lower bound	Confidence interval Upper bound
mean UtA PI	0.56	0.019	0.00	0.52	0.59
a UtA >P90	0.54	0.019	0.04	0.50	0.58
a UtA >P95	0.52	0.019	0.36	0.48	0.55

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

FIGURE 4 Receiver operating characteristics curve for spontaneous preterm birth <37 wk for different measures of uterine artery resistance. UtA PI, uterine artery pulsatility index [Color figure can be viewed at wileyonlinelibrary.com]

A limitation of this study is that it was performed in a single tertiary center. The overall PTB rate for singletons in The Netherlands was 5.6% in 2015, of which 1.8% was medically indicated.[22] The overall PTB rate, and especially the iatrogenic PTB rate, in our study population was higher, which is possibly because the the selected population in a tertiary hospital in an urban area. Women visiting our hospital for their antenatal care more often have comorbidities or a complicated previous pregnancy. Furthermore, our clinic is visited by a relatively high number of women with a non-white ethnicity and low socio-economic status, both of which are known as risk factors for PTB.[23]

Preventive measures for spontaneous PTB were offered according to the local guidelines. The national guideline advises the use of progesterone (intramuscular injections) in women with a previous PTB before 34 weeks. Moreover, cervical length measurements are offered to these women between 16 and 24 weeks (every other week). If the cervical length is <25 mm women are counseled for a secondary cerclage.

Since June 2014, nulliparous women or multiparous women without previous PTB before 34 weeks, were offered a cervical length measurement during the fetal anomaly scan. If cervical length was <35 mm (18-22 weeks of gestation) they could be randomized between vaginal progesterone and cervical pessary (Quadruple P trial).

These targeted interventions might have influenced our results. As cervical length is not related to UtA Doppler we expect this influence to be rather limited. Furthermore we have included a mixed population with both high-risk and low-risk women.

A previous study assessing the relation between second-trimester UtA Doppler and spontaneous PTB reported no significant correlation.[24] This was a historical cohort study performed between 1999 and 2002 in the UK. A total of 234 pregnancies complicated by spontaneous preterm labor were compared with 5472 women who delivered at term. The distribution of the different notches in the spontaneous PTB group was comparable with our cohort (84% no notch, 9.8% unilateral notch and 4.7% bilateral notch in the study by Cobian-Sanchez et al vs 89% no notch, 6.6% unilateral notch and 4.2% bilateral notch in our cohort). No statistical difference in UtA Doppler measurements between the group with a spontaneous PTB and the group with a term birth was found (resistance index >95th centile spontaneous PTB 6% vs 4% in the term group; $P = .14$). A difference between both studies is the earlier GA at scanning in our group (mean GA 19^{+6} weeks, compared with 21^{+1} weeks in the historical cohort). The study by Cobian-Sanchez et al[24] does not present data for iatrogenic PTB, so we are not able to make a direct comparison between overall PTB rates in the studies. In 2006, Fonseca et al[16] also reported on the relation between second-trimester UtA PI and spontaneous PTB. They showed that UtA PI was higher in women with a spontaneous PTB before 33 weeks. However, compared with maternal characteristics and obstetrical history, measurement of the UtA PI did not result in a better prediction. These results are in line with our data.

Guidelines for estimation of GA were not available at the beginning of our study period, which could have influenced our results. Limiting our analysis to the period 2012-2016 (n = 3809 pregnancies) did not change the results, which indicates that the association is less likely to be to the result of erroneous determination of expected date of delivery.

Identification of UtA Doppler as an influencing factor in the risk for a (spontaneous) PTB may lead to new opportunities for the development of predictive models. Measurement of the UtA Doppler is a relatively quick and low-cost intervention, which can be easily performed during the routine fetal anomaly scan that is embedded in the national screening program. However, although we found an association between UtA Doppler and spontaneous PTB, the predictive capacity was rather limited. A likelihood ratio of 1.9 is usually not enough to justify the use of a test in clinical practice. Indeed, a change in the probability of PTB from 5.5% to 8.0% does not justify general screening. Also, UtA Doppler was not predictive for spontaneous preterm delivery before 34 weeks.

Our results, with a higher risk of late spontaneous PTB in women with an abnormal UtA Doppler, strengthen the hypothesis that impaired placental function has a relation with spontaneous PTB. Current research focuses on antiplatelet therapy as a new strategy in the prevention of PTB.[25-28] Recent studies report a reduction in spontaneous PTB before 34 weeks if antiplatelet therapy is started between 13 and 25 weeks of gestation.[29] We suggest increased surveillance in women with an abnormal UtA Doppler in the second trimester. Further prospective studies should evaluate if abnormal UtA Doppler contributes to the multivariable etiology that is underlying spontaneous PTB.

5 | CONCLUSION

In conclusion, abnormal UtA Doppler indicates not only a higher risk of iatrogenic PTB, but also, though with a weaker association, spontaneous PTB. Further prospective studies are needed to evaluate if UtA Doppler contributes to a multifactorial model that predicts spontaneous PTB.

CONFLICT OF INTEREST

BWM reports consultancy for ObsEva, Merck and Guerbet. MvZ, BK, RS, BK and EP report no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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