Ultrasound Obstet Gynecol 2024; **64**: 504–512
Published online 5 September 2024 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.27668.

Adverse perinatal outcomes are strongly associated with degree of abnormality in uterine artery Doppler pulsatility index

S. DOCKREE[1], C. AYE[1,2], C. IOANNOU[1,2], A. CAVALLARO[1], R. BLACK[1,2] and L. IMPEY[1,2], on behalf of the Oxford Growth Restriction Identification Programme Group (OxGRIP)

[1] *Oxford University Hospitals NHS Foundation Trust, Oxford, UK;* [2] *University of Oxford, Oxford, UK*

KEYWORDS: Doppler; fetal growth; pregnancy outcome; ultrasound; uterine artery

CONTRIBUTION

What are the novel findings of this work?
Using elevation $\geq 90^{th}$ percentile to define abnormality in the uterine artery (UtA) pulsatility index (PI) confers a significant improvement in predictive accuracy of adverse perinatal outcome over that associated with the usual cut-off (95^{th} percentile). The subgroup of women with very abnormal UtA Dopplers have a very high risk of early perinatal mortality, live birth with a severely small-for-gestational-age (SGA) neonate and iatrogenic preterm birth.

What are the clinical implications of this work?
If a binary UtA-PI threshold is to be employed in pregnancy management, it should be the 90^{th} percentile rather than the 95^{th}. Protocols should also be adjusted to take into account the degree of abnormality in the UtA-PI.

ABSTRACT

Objective *To investigate the association between varying degrees of abnormality in the Doppler uterine artery pulsatility index (UtA-PI) and adverse perinatal outcome.*

Methods *This was a prospective study of women with a singleton, non-anomalous pregnancy in whom UtA-PI was measured universally in midpregnancy and who gave birth in Oxford University Hospitals, Oxford, UK, between 2016 and 2023. Relative risk ratios (RRR) for the primary outcomes of extended perinatal mortality and live birth with a severe small-for-gestational-age (SGA) neonate were calculated using multinomial logistic regression, for early preterm birth (before 34 + 0 weeks' gestation) and late preterm/term birth (at or after 34 + 0 weeks). Risks were also investigated for iatrogenic preterm birth and a composite adverse outcome before 34 + 0 weeks.*

Results *Overall, 33 364 pregnancies were included in the analysis. Compared to those with a normal UtA-PI, the risk of extended perinatal mortality with delivery before 34 + 0 weeks was higher in women with UtA-PI $\geq 90^{th}$ percentile (RRR, 4.7 (95% CI, 2.7–8.0); P < 0.001), but this was not demonstrated in births at or after 34 + 0 weeks. The risk of live birth with severe SGA was associated strongly with abnormal UtA-PI for early births (RRR, 26.0 (95% CI, 11.6–58.2); P < 0.001) and later births (RRR, 2.3 (95% CI, 1.8–2.9); P < 0.001). Women with raised UtA-PI were more likely to have an early iatrogenic birth (RRR, 7.8 (95% CI, 5.5–11.2); P < 0.001). For each outcome before 34 + 0 weeks and the composite outcome, the risk increased significantly in association with the degree of abnormality in the UtA-PI (from $< 90^{th}$, $90–94^{th}$, $95–98^{th}$ to $\geq 99^{th}$ percentile) ($P_{trend} < 0.001$). When using the 90^{th} percentile as opposed to the 95^{th}, there was a significant improvement in the overall predictive accuracy (as determined by the area under the receiver-operating-characteristics curve) for the composite adverse outcome ($\chi^2 = 6.64$, P = 0.01) and iatrogenic preterm birth ($\chi^2 = 4.10$, P = 0.04).*

Conclusions *Elevated UtA-PI is a key predictor of iatrogenic preterm birth, severe SGA and perinatal loss up to 34 + 0 weeks' gestation. The 90^{th} percentile for UtA-PI should be used, and management should be tailored according to the degree of abnormality, as pregnancies with very raised UtA-PI measurement constitute a group at extreme risk of adverse outcome.* © *2024 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

Correspondence: Dr S. Dockree, Oxford University Hospitals NHS Foundation Trust, Oxford, UK (e-mail: samuel.dockree@ouh.nhs.uk)

Accepted: 10 April 2024

INTRODUCTION

Perinatal mortality rates remain high despite international efforts to optimize obstetric care[1,2]. The focus on small-for-gestational age (SGA) babies is shifting towards fetal growth restriction (FGR) as a manifestation of placental insufficiency. Pre-eclampsia[3–6], FGR/SGA[7] and stillbirth[8–10] are associated strongly with uterine artery (UtA) Doppler abnormality, and this is key to modern pregnancy screening.

Most studies investigating UtA Doppler indices have employed binary thresholds[6], typically defining abnormality as elevation of the pulsatility index (PI) above the 95th percentile according to one of several published reference standards[11,12]. However, the extent to which absolute UtA-PI values are associated with adverse perinatal outcome is less clear.

In Oxford University Hospitals, UtA-PI is measured routinely in midpregnancy, affording the opportunity to examine its predictive value in a large, unselected population, rather than in pregnancies with known risk factors, as is usually recommended[13,14]. The aim of this study was to investigate the relationship between adverse perinatal outcomes and the degree of elevation in the UtA-PI.

METHODS

Current practice

Oxford University Hospitals NHS Foundation Trust consists of a large tertiary obstetric unit and associated birthing units in Oxford, UK, with more than 7500 births per year. UtA-PI is measured between 18 + 0 and 20 + 6 weeks' gestation and a universal growth scan is performed at 35 + 0 to 36 + 6 weeks, as part of the Oxford Growth Restriction Identification Programme (OxGRIP)[15]. Women with an elevated UtA-PI (mean > 1.25, i.e. > 90th percentile) are offered additional growth scans at 28 and 32 weeks. Other scans are performed as clinically indicated: management and follow-up of suspected growth abnormalities before 34 weeks are carried out in accordance with the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines[13] and, from 34 weeks, management is based on a published protocol[16]. Further to its role in determining the frequency of surveillance, UtA-PI > 1.25 is considered an indication for expediting birth from 37 + 0 weeks in SGA fetuses (< 10th Hadlock percentile)[17], and iatrogenic delivery from 40 + 0 weeks is offered to women with UtA-PI > 1.5, regardless of other ultrasound findings.

Population selection and variables

This was a prospective cohort study using the OxGRIP dataset[15] of pregnant women receiving antenatal care and giving birth in Oxford University Hospitals. Women who gave birth between 1 October 2016 and 11 January 2023 were potentially eligible. Inclusion criteria were women of any age with a singleton pregnancy who underwent an ultrasound scan between 18 + 0 and 20 + 6 weeks and gave birth at an Oxford University Hospitals unit from 23 + 0 weeks. Exclusion criteria were multiple pregnancy, pregnancy loss or birth before 23 + 0 weeks, any fetal congenital abnormality or termination of pregnancy. Ethical approval was granted by the South-Central Hampshire Research Ethics Committee (reference 17/SC/0374).

Routine clinical data were recorded, including maternal age (years), parity (births from 24 + 0 weeks), ethnicity (white, Asian, black, mixed or other)[18], body mass index (kg/m^2), mode of birth (spontaneous vaginal, operative vaginal, elective Cesarean or emergency Cesarean), neonatal sex (male or female), gestational age at delivery (weeks), as defined by crown–rump length in the first trimester (or, if appropriate, embryo transfer), neonatal birth weight (g), age- and sex-adjusted UK90 birth-weight percentile[19], use of assisted reproductive therapy and perinatal outcome (alive or dead at birth and at 28 days).

UtA-PI was measured according to ISUOG guidelines[20] after a period of training and assessment. The mean PI was taken from the left and right UtAs. In the case that only one measurement was available, a single reading was used. We performed a sensitivity analysis to investigate whether there would be a material difference in the observed distribution of the primary outcome if these single readings were excluded. For reasons of simplicity and minimization of human error, a PI threshold of 1.25 was chosen, irrespective of the gestational age, to approximate the 90th percentile in this narrow gestational-age window. For the purposes of this study, PI values were reclassified as < 90th, 90–94th, 95th–98th and ≥ 99th percentiles, using the non-parametric ordinal method, based on our observed distribution. For comparison, we also calculated multiples of the median (MoM) based on the Fetal Medicine Foundation (FMF) reference standard[12].

Outcomes

The primary outcomes were extended perinatal mortality (intrauterine death or neonatal death before 28 days after birth) and live birth with severe SGA (birth weight < 3rd percentile) according to UK90 charts[19]. We stratified these outcomes according to gestational age: moderate-to-severe preterm birth (before 34 + 0 weeks) and late preterm or term birth (at or after 34 + 0 weeks). We chose this cut-off because previous work has shown that abnormal UtA Doppler indices are most strongly associated with adverse outcomes at earlier gestations[21].

Among the women delivering before 34 + 0 weeks, additional outcomes were: medically indicated birth by induction of labor or prelabor Cesarean section (in pregnancies not complicated by preterm prelabor rupture of membranes) and a composite of one or more of these outcomes. These latter analyses were restricted to births before 34 + 0 weeks because of the heterogeneous indications for intervention after this gestational age.

Statistical analysis

Statistical analysis was performed using native packages in Stata/SE version 17.0 for Windows (StataCorp., LLC, College Station, TX, USA). Relative risk ratios (RRR) were estimated using multinomial, univariate logistic regression models and are presented with 95% CIs. UtA-PI was investigated as a categorical variable, using the lowest stratum as the reference group and, where appropriate, a χ^2 test for linear trend was performed to estimate the risk across sequential groups. For each outcome, the sensitivity and specificity were calculated using 2 × 2 tables and, as a measurement of overall accuracy, the area under the receiver-operating-characteristics curve (AUC) was estimated as the mid-point between the sensitivity and specificity, using the Stata diagt package[22]. To quantifiably compare the overall predictive accuracy using different UtA-PI thresholds (90th and 95th percentiles), the AUCs were compared using a non-parametric method (χ^2, roccomp package). Other practical and theoretical examples of diagnostic accuracy studies using this method are published elsewhere[23,24].

Summary statistics for demographic data are presented as mean ± SD for normally distributed variables or median (interquartile range (IQR)) for other distributions. Participants with missing data for secondary demographic characteristics were included in the analysis. Statistical significance was assumed at the 5% level.

RESULTS

Participants and characteristics

In total, there were 42 286 singleton pregnancies during the study period. Of these, 34 436 were potentially eligible and 33 364 were included in the analysis. Reasons for exclusion are presented in Figure 1. The vast majority of scans were performed at or after 19 + 0 weeks (98.3%), and only 553 (1.7%) were carried out between 18 + 0 and 18 + 6 weeks. UtA-PI was measured from both arteries in 98.5% of cases, and in 489 (1.5%), this was obtained from one side only. The cohort consisted of 23 536 (70.5%) women who had one pregnancy and 9828 (29.5%) who had at least one other pregnancy during the study period. Maternal and neonatal characteristics are shown in Table 1.

Uterine artery Doppler

The distribution of UtA-PI values is displayed in Figure 2a. The non-parametric 90th, 95th and 99th percentiles were 1.25, 1.43 and 1.84, respectively. As this was not materially different when the analysis was restricted to women with only one pregnancy observed during the study period (1.26, 1.44 and 1.86, respectively; $n = 23\,536$), repeat measures were included in the analysis. All UtA-PI readings were included, whether they were derived from unilateral or bilateral measurements, as the distribution was essentially unchanged (Figure S1) when restricted

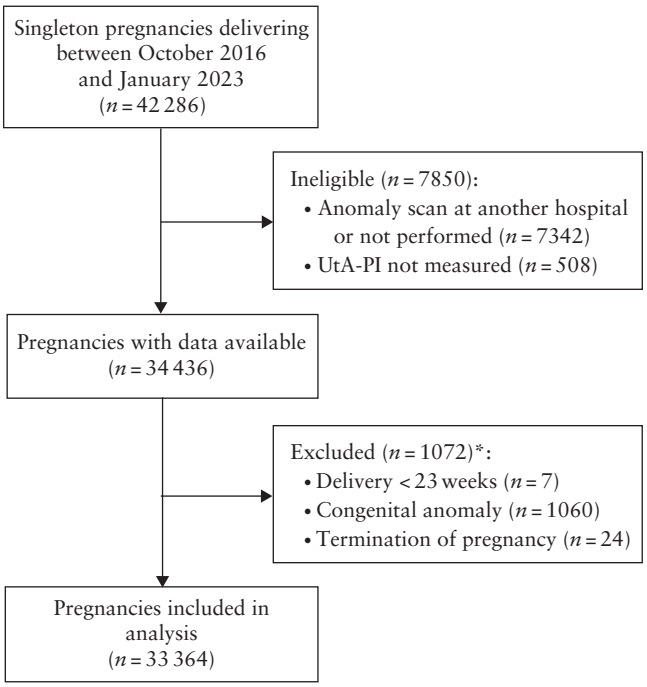

Figure 1 Flowchart summarizing population selection. *Some cases were excluded for more than one reason. UtA-PI, uterine artery pulsatility index.

Table 1 Demographic characteristics of study participants ($n = 33\,364$)

Characteristic	*Value*
Maternal age (years)	32 (28–35)
Parity	1 (0–1)
Nulliparous	15 096 (45.2)
Parous	18 268 (54.8)
Ethnicity	
White	28 421/33 292 (85.4)
Asian	3125/33 292 (9.4)
Black	796/33 292 (2.4)
Mixed	867/33 292 (2.6)
Other	83/33 292 (0.2)
Body mass index	
Underweight (< 18.5 kg/m^2)	1007/33 122 (3.0)
Normal weight (18.5–24.9 kg/m^2)	17 863/33 122 (53.9)
Overweight (25.0–29.9 kg/m^2)	8893/33 122 (26.8)
Class-1 obesity (30.0–34.9 kg/m^2)	3483/33 122 (10.5)
Class-2–3 obesity (≥ 35.0 kg/m^2)	1876/33 122 (5.7)
Assisted reproductive therapy	599 (1.8)
Mode of birth	
Spontaneous vaginal	19 569 (58.7)
Operative vaginal	5072 (15.2)
Elective Cesarean section	3534 (10.6)
Emergency Cesarean section	5189 (15.6)
Female neonatal sex	16 242 (48.7)
Onset of labor*	
Spontaneous	20 301/33 008 (61.5)
Induction	7879/33 008 (23.9)
Cesarean section before labor	4828/33 008 (14.6)
GA at delivery (weeks)	39 + 5 ± 0 + 6
Birth weight (g)	3457 ± 562

Data are given as median (interquartile range), *n* (%), *n*/*N* (%) or mean ± SD. *No data were missing for participants delivering before 34 + 0 weeks. GA, gestational age.

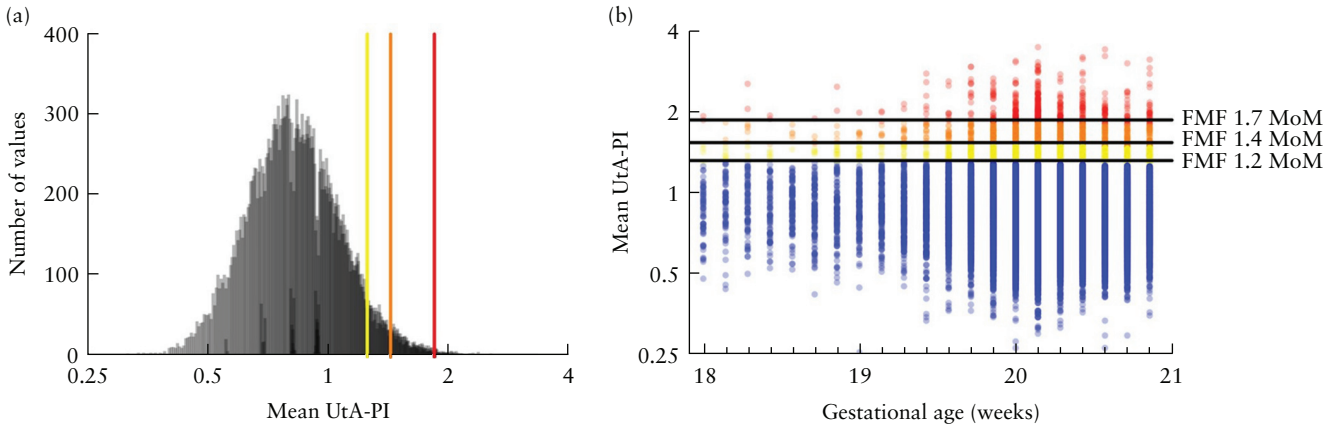

Figure 2 (a) Frequency distribution of uterine artery pusaltility index (UtA-PI) with 90th (—), 95th (—) and 99th (—) percentiles indicated. (b) Scatter diagram showing concordance between Oxford Growth Restriction Identification Programme (OxGRIP) distribution and distribution from which Fetal Medicine Foundation (FMF) reference was derived. MoM, multiples of the median. ●, OxGRIP < 90th percentile; ●, OxGRIP 90th–94th percentile; ●, OxGRIP 95th–98th percentile; ●, OxGRIP ≥ 99th percentile.

to the 98.5% of women with bilateral measurements (1.25, 1.43 and 1.83, respectively; $n = 32\,875$). Using the median gestational age at sampling (20 + 1 weeks), the FMF-MoM thresholds (1.2, 1.4 and 1.7 MoM) were consistent with the percentiles used in our study (90th, 95th and 99th percentiles) (Figure 2b) and with those of a previous smaller study[25].

Outcomes

In total, 147 perinatal deaths were recorded (4.4 per 1000 births), of which 109 (74.1%) were *in utero* and 38 (25.9%) were in the neonatal period. Of the *in-utero* deaths, 40 (36.7%) fetuses died before 34 + 0 weeks (median gestational age, 28 + 5 (IQR, 25 + 5 to 31 + 6) weeks), of which 36 (90.0%) weighed ≥ 400 g at birth. Eighty-nine cases died at or after 34 + 0 weeks (median gestational age, 39 + 0 (IQR, 37 + 1 to 40 + 4) weeks).

Live birth before 34 + 0 weeks occurred in 410 (1.2%) pregnancies. Overall, 417 (1.3%) babies were liveborn with a birth weight below the 3rd percentile, of which 31 were delivered before 34 + 0 weeks (7.6% of early live births), and 386 at or after 34 + 0 weeks (1.2% of later live births). Of the liveborn babies delivered before 34 + 0 weeks, 120 (29.3%) were born after induction of labor or Cesarean delivery (preterm prelabor rupture of membranes and spontaneous births were excluded). The composite adverse outcome of perinatal death, birth with severe SGA and/or iatrogenic preterm birth before 34 + 0 weeks occurred in 180 pregnancies (5.4 per 1000 births).

Perinatal mortality

Compared to women with normal UtA-PI, the risk of extended perinatal mortality with delivery before 34 + 0 weeks was significantly higher in women with UtA-PI ≥ 90th percentile (RRR, 4.7 (95% CI, 2.7–8.0); $P < 0.001$); this was similar for intrauterine deaths (RRR, 4.3 (95% CI, 2.2–8.3); $P < 0.001$) and neonatal deaths (RRR, 5.6 (95% CI, 2.2–14.5); $P < 0.001$). The overall risk of death was elevated further with greater degrees of abnormality, the highest risk being associated with UtA-PI ≥ 99th percentile (RRR, 26.9 (95% CI, 13.6–53.1); $P < 0.001$) (Table 2, Figure 3). The risk of perinatal mortality with late preterm or term delivery was not raised significantly in association with UtA-PI ≥ 90th percentile (RRR, 1.0 (95% CI, 0.5–2.0); $P = 0.997$), and there was no significant trend with further elevation in UtA-PI ($P_{trend} = 0.741$).

Severe small-for-gestational age

The relative risk of live birth with severe SGA before 34 + 0 weeks was raised significantly in association with UtA-PI ≥ 90th percentile (RRR, 26.0 (95% CI, 11.6–58.2); $P < 0.001$). Within this abnormal group, the risk rose according to the degree of abnormality in the UtA-PI, reaching an 85-fold higher risk in women with UtA-PI ≥ 99th percentile (RRR, 85.3 (95% CI, 30.8–236.8); $P < 0.001$). The risk of live birth with severe SGA at later gestations was also associated with UtA-PI ≥ 90th percentile (RRR, 2.3 (95% CI, 1.8–2.9); $P < 0.001$), but the magnitude of the risk was lower compared with that in earlier births, even for those cases with UtA-PI ≥ 99th percentile (RRR, 3.8 (95% CI, 2.1–6.8); $P < 0.001$) (Table 2, Figure 3).

Iatrogenic preterm birth

Women with raised UtA-PI were more likely to undergo early iatrogenic birth < 34 + 0 weeks (RRR, 7.8 (95% CI, 5.5–11.2); $P < 0.001$). This risk was associated with the degree of abnormality in the UtA-PI, with the highest risk in those with UtA-PI ≥ 99th percentile (RRR, 22.0 (95% CI, 12.4–39.1); $P < 0.001$) (Table 2, Figure 3).

Table 2 Risk of adverse perinatal outcome according to degree of abnormality in uterine artery pulsatility index (UtA-PI), for delivery < 34 + 0 weeks or ≥ 34 + 0 weeks

Outcome/UtA-PI percentile	n	*RRR (95% CI)*	*Absolute risk (per 1000 births)*	P_{trend}*
Birth < 34 + 0 weeks				
extPNM				< 0.001
< p90	38	1.0 (ref)	1.3	
p90–p94	6	2.8 (1.2–6.6)	3.5	
p95–p98	3	1.7 (0.5–5.6)	2.2	
≥ p99	11	26.9 (13.6–53.1)	33.1	
IUD				< 0.001
<p90	27	1.0 (ref)	0.9	
p90–p94	5	3.3 (1.3–8.5)	3.0	
p95–p98	2	1.6 (0.4–6.9)	1.5	
≥ p99	6	20.4 (8.4–49.7)	18.1	
NND				< 0.001
< p90	11	1.0 (ref)	0.4	
p90–p94	1	1.6 (0.2–12.4)	0.6	
p95–p98	1	2.0 (0.3–15.5)	0.7	
≥ p99	5	41.5 (14.3–120.1)	15.0	
Severe SGA				< 0.001
< p90	8	1.0 (ref)	0.3	
p90–p94	5	11.1 (3.6–34.1)	3.0	
p95–p98	11	31.2 (12.5–77.7)	8.4	
≥ p99	7	85.3 (30.8–236.8)	22.6	
IPB				< 0.001
< p90	64	1.0 (ref)	2.1	
p90–p94	13	3.6 (2.0–6.6)	7.7	
p95–p98	28	9.8 (6.3–15.3)	20.5	
≥ p99	15	22.0 (12.4–39.1)	45.0	
Composite				< 0.001
< p90	101	1.0 (ref)	3.4	
p90–p94	20	3.5 (2.2–5.7)	11.8	
p95–p98	33	7.3 (4.9–10.9)	24.2	
≥ p99	26	25.0 (16.0–39.1)	78.1	
Birth ≥ 34 + 0 weeks				
extPNM				0.741
< p90	80	1.0 (ref)	2.7	
p90–p94	3	0.6 (0.2–2.1)	1.8	
p95–p98	5	1.4 (0.6–3.4)	3.7	
≥ p99	1	1.2 (0.2–8.4)	3.1	
IUD				0.517
< p90	61	1.0 (ref)	2.0	
p90–p94	3	0.9 (0.3–2.8)	1.8	
p95–p98	4	1.4 (0.5–4.0)	2.9	
≥ p99	1	1.5 (0.2–10.9)	3.1	
NND				0.602
< p90	19	1.0 (ref)	0.6	
p90–p94	0	—	—	
p95–p98	1	1.2 (0.2–8.7)	0.7	
≥ p99	0	—	—	
Severe SGA				< 0.001
< p90	309	1.0 (ref)	10.3	
p90–p94	23	1.3 (0.9–2.0)	13.7	
p95–p98	42	3.1 (2.2–4.3)	31.2	
≥ p99	12	3.8 (2.1–6.8)	38.1	

Composite adverse outcome was defined as at least one of: extended perinatal mortality (exPNM) (intrauterine death (IUD) or neonatal death (NND)), live birth with severe small-for-gestational age (SGA) or iatrogenic preterm birth (IPB). *χ^2 test for linear trend. p90/p94/p95/p98/p99, 90th/94th/95th/98th/99th percentile; ref, reference; RRR, relative risk ratio.

Composite adverse outcome

Overall, the risk of at least one adverse perinatal outcome before 34 + 0 weeks was associated strongly with the degree of abnormality in the UtA-PI ($P_{trend} < 0.001$) (Figure 3). These results were not materially changed by excluding the 1.5% of women with a unilateral UtA-PI measurement (Figure S1).

'Normal' uterine artery Doppler

In pregnancies with UtA-PI < 90th percentile (i.e. 'normal'), the risk of severe SGA with birth at or after 34 + 0 weeks did not differ significantly according to the decile of UtA-PI ($P_{trend} = 0.403$) (Figure 4). There were too few severe SGA births before 34 + 0 weeks to investigate the association with earlier births reliably, but the risk

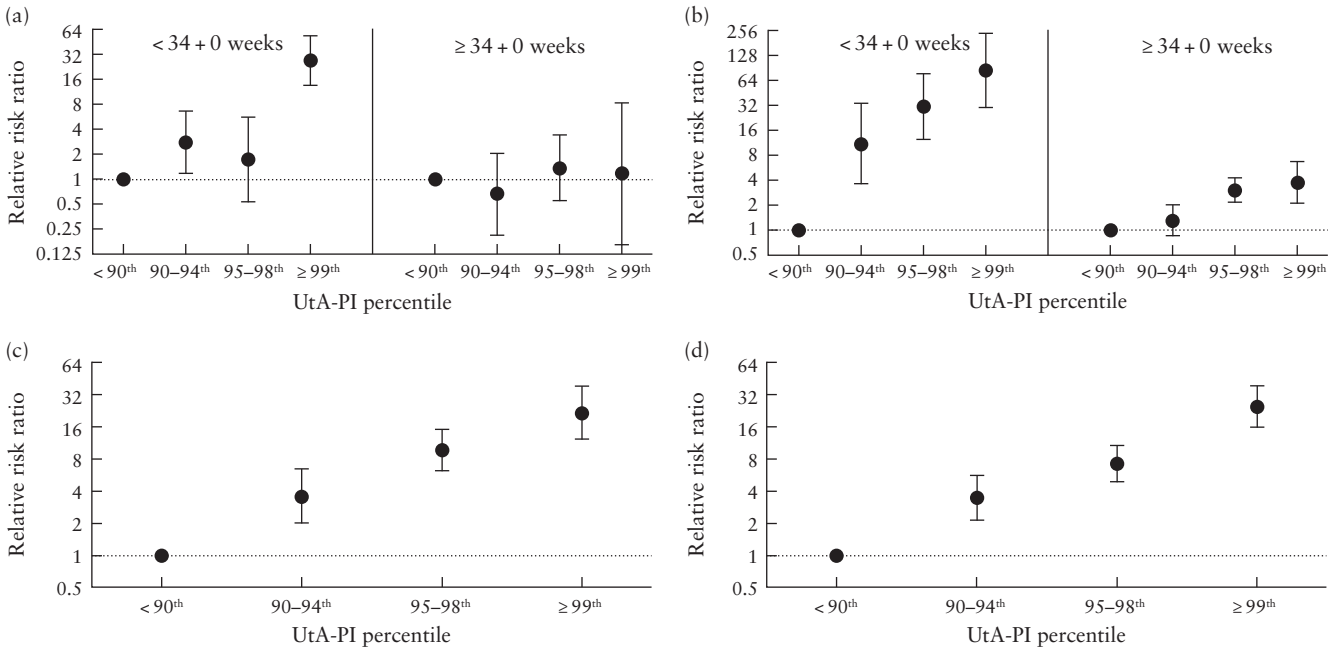

Figure 3 Risk of extended perinatal mortality (a), severe small-for-gestational age (birth weight < 3rd percentile) (b), iatrogenic birth before 34 + 0 weeks (c) and composite adverse outcome before 34 + 0 weeks (d), according to different cut-offs for raised uterine artery pulsatility index (UtA-PI) percentile. Composite adverse outcome was defined as at least one of: extended perinatal mortality, live birth with severe small-for-gestational age or iatrogenic preterm birth. Error bars are 95% CI.

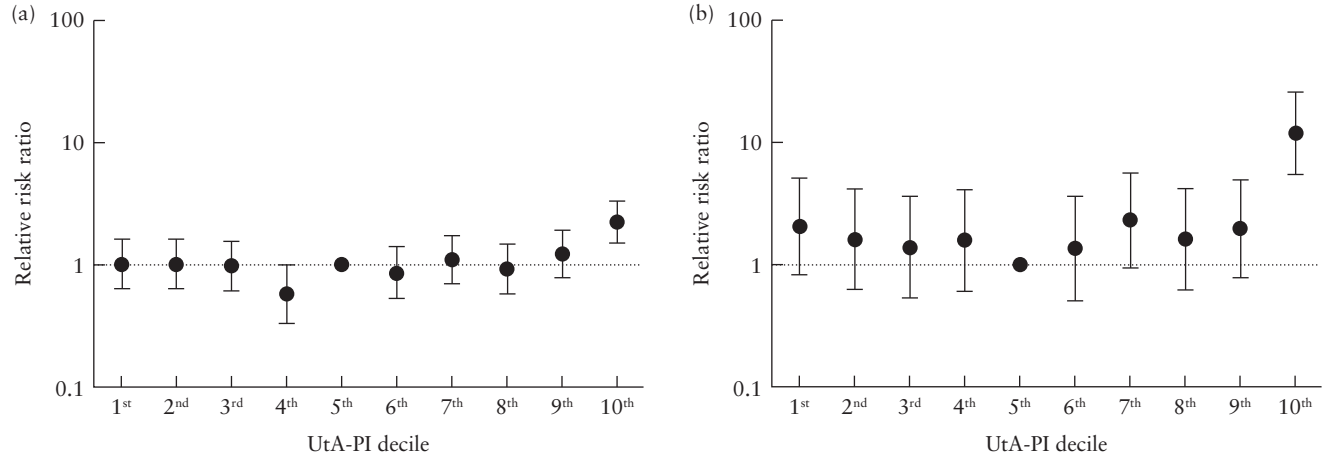

Figure 4 Risk of severe small-for-gestational age (birth weight < 3rd percentile) from 34 + 0 weeks (a) and composite adverse outcome before 34 + 0 weeks (b), according to uterine artery pulsatility index (UtA-PI) decile. Composite adverse outcome was defined as at least one of: extended perinatal mortality, live birth with severe small-for-gestational age or iatrogenic preterm birth. Error bars are 95% CI.

of any adverse outcome before 34 + 0 weeks (including severe SGA) did not differ by UtA-PI decile within this 'normal' range ($P_{trend} = 0.734$) (Figure 4).

Screening performance of uterine artery Doppler

Diagnostic summary statistics for adverse perinatal outcomes before 34 + 0 weeks were calculated in relation to UtA-PI, using different thresholds (≥ 90th and ≥ 95th percentiles), and are presented in Table 3. When using the 90th percentile as opposed to the 95th (i.e. at a cost to specificity), there was a significant improvement in the overall predictive accuracy (i.e. AUC) for the composite adverse outcome ($\chi^2 = 6.64$, $P = 0.01$) and iatrogenic preterm birth ($\chi^2 = 4.10$, $P = 0.04$), but not severe SGA ($\chi^2 = 2.71$, $P = 0.10$) or extended perinatal mortality ($\chi^2 = 1.71$, $P = 0.19$). The sensitivity of UtA-PI ≥ 90th percentile for severe SGA was 74%.

DISCUSSION

Main findings

This study investigated adverse perinatal outcomes according to UtA-PI in a large dataset in which UtA-PI was measured universally. Herein, we demonstrated that, first, for births before 34 + 0 weeks, abnormal UtA-PI is not only associated strongly with severe SGA, extended

Table 3 Predictive performance of 90th (p90) and 95th (p95) percentiles of uterine artery pulsatility index (UtA-PI) for adverse outcomes before 34 + 0 weeks of gestation

Outcome	*Sensitivity (%)*	*Specificity (%)*	*AUC*
UtA-PI ≥ p90			
IUD	32.5 (18.6–49.1)	89.9 (89.5–90.2)	0.61 (0.54–0.69)
NND	38.9 (17.3–64.3)	89.8 (89.5–90.2)	0.64 (0.53–0.76)
extPNM	34.5 (22.5–48.1)	89.9 (89.5–90.2)	0.62 (0.56–0.68)
Severe SGA	74.2 (55.4–88.1)	89.9 (89.6–90.3)	0.82 (0.74–0.90)
IPB	46.7 (37.5–56.0)	90.0 (89.6–90.3)	0.68 (0.64–0.73)
Composite	43.9 (36.5–51.5)	90.0 (89.7–90.3)	0.67 (0.63–0.71)
UtA-PI ≥ p95			
IUD	20.0 (9.1–35.6)	94.9 (94.7–95.2)	0.57 (0.51–0.64)
NND	33.3 (13.3–59.0)	94.9 (94.7–95.2)	0.64 (0.53–0.75)
extPNM	24.1 (13.9–37.2)	94.9 (94.7–95.2)	0.60 (0.54–0.65)
Severe SGA	58.1 (39.1–75.5)	95.0 (94.8–95.2)	0.77 (0.68–0.85)
IPB	35.8 (27.3–45.1)	95.0 (94.8–95.3)	0.65 (0.61–0.70)
Composite	32.8 (26.0–40.2)	95.1 (94.8–95.3)	0.64 (0.60–0.67)

Data in parentheses are 95% CI. Composite adverse outcome was defined as at least one of: extended perinatal mortality (exPNM) (intrauterine death (IUD) or neonatal death (NND)), live birth with severe small-for-gestational age (SGA) or iatrogenic preterm birth (IPB). Area under receiver-operating-characteristics curve (AUC) defined as (sensitivity + specificity)/2.

perinatal mortality and iatrogenic preterm birth, but that it follows a dose–response relationship when UtA-PI is raised above the 90th percentile. Second, UtA-PI as a single risk factor has a good sensitivity for preterm severe SGA at birth. Third, using the 90th percentile for UtA-PI, as opposed to the 95th percentile as is commonly recommended[20,26], affords a clinically significant improvement in predictive accuracy. Fourth, below the 90th percentile, UtA-PI has little or no relationship with adverse outcome. Finally, even for births at or after 34 + 0 weeks, the risk of severe SGA with abnormal UtA-PI is doubled, although no association with perinatal mortality was demonstrated and the association with the degree of abnormality is less clear.

Strengths and limitations

The principal strengths of this analysis are the near-universal measurement of UtA-PI in a large population and the availability of comprehensive ultrasound, pregnancy and neonatal outcome data. The quality of the UtA-PI measurements was ensured through training and audit, both of images and individuals' measurement distributions, and this is reflected in the distribution of UtA-PI measurements (Figure 2a).

We acknowledge limitations to our research. Firstly, in common with other analyses in which clinicians are unblinded to potential risk factors, the principal limitation is intervention paradox. This influences the associations of UtA-PI with both iatrogenic birth and, probably, mortality. For mortality, this paradox would be expected to reduce (underestimate) the observed risk through intervention. However, for iatrogenic preterm birth, the paradox could increase the strength of association. For severe SGA at birth, particularly in the earlier gestational period, the paradox should have little effect. Second, we did not use an *in-utero* definition of FGR (i.e. including ultrasound indicators, such as estimated fetal weight or umbilical artery Doppler indices[13]) because, as ultrasound was not performed universally at additional earlier gestations, this would introduce bias. Third, our analysis is of the screening performance of UtA-PI as a single risk factor in a manner that is easy to implement with minimal human error. Therefore, it was not adjusted for gestational age within the narrow window of 3 weeks. Nevertheless, the UtA-PI distribution in our study was similar to that of earlier work[25], and correlation with the FMF reference standard was demonstrated[12]. We also included the 1.5% of pregnancies in which only one measurement of UtA-PI had been recorded, reflecting imperfect but real-life practice. Sensitivity analysis showed that this did not materially affect the results. Notably, both these limitations would be expected to attenuate the associations of UtA-PI.

It is surprising that deciles of UtA-PI below the 90th percentile were not associated with the composite adverse outcome. Clinical management was unaltered by UtA-PI within this range, and the absence of any difference in the risks of severe SGA and the composite adverse outcome between deciles within a 'normal' range is clear. This should not preclude using UtA-PI as a continuous variable in future models but, within the 'normal' range, it may add little predictive value. Within the 'abnormal' range, continuous (or at least ordinal categorical) variables may be useful. Above this threshold, the loss of specificity incurred by using the 90th as opposed to the 95th percentile is offset by improved sensitivity. Before 34 + 0 weeks, even in the 90th–94th-percentile group (mild elevation), there is at least a doubling in the risk of perinatal mortality, and more than a 10-fold increase in the risk of severe SGA; even at/after 34 + 0 weeks, there is a modest increase in the risk of severe SGA. Our findings, at least for mortality, are supported by the sparse previous data available[9,25]. Despite this, the 95th percentile is used in many guidelines, such as in the UK, where this cut-off is used as part of the Saving Babies' Lives 3 initiative[26].

Adverse outcomes before 34 + 0 weeks

Before 34 + 0 weeks, the role of UtA-PI as an isolated screening test in our study was impressive, particularly for severe SGA, and is better than that reported previously[7]. Several of the studies included in the systematic review and meta-analysis of Zhi *et al.*[7] were of smaller and more heterogeneous populations and reported results for all gestational ages rather than stratifying according to early- *vs* late-onset SGA. Such a division is logical because it is thought that the pathology differs[27]. Nevertheless, Singh *et al.*[9] reported a higher sensitivity for intrauterine death at all gestational ages than that found in the present analysis, even in the preterm group, and reported an increased risk with a greater degree of abnormal UtA-PI. Smith *et al.*[10] also reported a higher sensitivity (58%) for intrauterine death up to 32 weeks, albeit using slightly different criteria. This difference is likely to be due to their higher-risk populations (i.e. targeted rather than universal screening), but may also reflect our more up-to-date management protocol.

Regardless, an increased risk of mortality before 34 + 0 weeks with abnormal UtA-PI remained in our population. This is despite following national and international guidelines on antenatal care and management of suspected growth abnormalities[13,14], including guidance on ultrasound frequency, blood pressure management and expedited delivery. Only one in ten of the preterm fetuses that died *in utero* weighed less than 400 g, with a median gestational age of 28 + 5 weeks. It is clear that the period before 28 weeks requires additional surveillance in those at highest risk and that, alongside best practice in fetal monitoring[28] and improved neonatal care, this may prevent some deaths, although the cost-effectiveness and impact on resource management of increased scan frequency should be evaluated.

Adverse outcomes at or after 34 + 0 weeks

The association between UtA-PI and later pregnancy loss is much less clear. Severe SGA at or after 34 + 0 weeks, for which we show UtA-PI to be a clear risk factor, is nevertheless absent in many deaths in later pregnancy[1]. Smith *et al.*[10] also described a much weaker association near term, but Singh *et al.*[9] reported a bimodal distribution of intrauterine deaths, with an increase near term. It is likely that our management of SGA (estimated weight $< 10^{th}$ percentile) near term[15,16], which regarded UtA-PI > 1.25 at 18 + 0 to 20 + 6 weeks as an indication for iatrogenic delivery from 37 + 0 weeks, together with our policy of offering iatrogenic delivery at term for all pregnancies in which UtA-PI was > 1.5, attenuated this association. Nevertheless, in contrast to earlier gestations, it remains clear that the role of midtrimester UtA-PI in the prediction and prevention of late stillbirth is limited.

Conclusions

Individual risk factors, rather than models, are often used to predict adverse pregnancy outcome and guide fetal and maternal monitoring. UtA-PI is a key predictor of the need for iatrogenic delivery and for severe SGA and perinatal loss up to 34 + 0 weeks. The 90^{th} percentile for UtA-PI should be used, and management should be tailored according to the degree of abnormality, as pregnancies with very raised UtA-PI measurement constitute a group at extreme risk of adverse outcome. Improving outcomes further, particularly at term, will require more complex models, but these should be developed using datasets in which UtA-PI is assessed universally.

ACKNOWLEDGMENT

We thank the sonographers and fetal medicine staff of Oxford University Hospitals.

REFERENCES

1. Draper E, Gallimore I, Smith L, et al. MBRRACE-UK Perinatal mortality surveillance report. *UK Perinatal Deaths for Births From January to December 2020*. The Infant Mortality and Morbidity Studies, Department of Health Sciences: University of Leicester; 2022.
2. United Nations. Never Forgotten. The situation of stillbirth around the globe. Report of the United Nations Inter-agency Group for Child Mortality Estimation. 2022.
3. Yu CK, Khouri O, Onwudiwe N, Spiliopoulos Y, Nicolaides KH, Fetal Medicine Foundation Second-Trimester Screening Group. Prediction of pre-eclampsia by uterine artery Doppler imaging: relationship to gestational age at delivery and small-for-gestational age. *Ultrasound Obstet Gynecol*. 2008;31(3):310-313.
4. Khalil A, Garcia-Mandujano R, Maiz N, Elkhaouli M, Nicolaides KH. Longitudinal changes in uterine artery Doppler and blood pressure and risk of pre-eclampsia. *Ultrasound Obstet Gynecol*. 2014;43(5):541-547.
5. Jhee JH, Lee S, Park Y, et al. Prediction model development of late-onset preeclampsia using machine learning-based methods. *PLoS One*. 2019;14(8):e0221202.
6. Cnossen JS, Morris RK, ter Riet G, 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):701-711.
7. Zhi R, Tao X, Li Q, Yu M, Li H. Association between transabdominal uterine artery Doppler and small-for-gestational-age: a systematic review and meta-analysis. *BMC Pregnancy Childbirth*. 2023;23(1):659.
8. Nicolaides KH, Papastefanou I, Syngelaki A, Ashoor G, Akolekar R. Predictive performance for placental dysfunction related stillbirth of the competing risks model for small-for-gestational-age fetuses. *BJOG*. 2022;129(9):1530-1537.
9. Singh T, Leslie K, Bhide A, D'Antonio F, Thilaganathan B. Role of second-trimester uterine artery Doppler in assessing stillbirth risk. *Obstet Gynecol*. 2012;119(2 Pt 1):256-261.
10. Smith GC, Yu CK, Papageorghiou AT, Cacho AM, Nicolaides KH, Fetal Medicine Foundation Second Trimester Screening Group. Maternal uterine artery Doppler flow velocimetry and the risk of stillbirth. *Obstet Gynecol*. 2007;109(1):144-151.
11. Gómez O, Figueras F, Fernández S, et al. Reference ranges for uterine artery mean pulsatility index at 11-41 weeks of gestation. *Ultrasound Obstet Gynecol*. 2008;32(2):128-132.
12. Tayyar A, Guerra L, Wright A, Wright D, Nicolaides KH. Uterine artery pulsatility index in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol*. 2015;45(6):689-697.
13. Lees C, Stampalija T, Baschat A, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. *Ultrasound Obstet Gynecol*. 2020;56(2):298-312.
14. Royal College of Obstetricians and Gynaecologists. The investigation and management ofthe small−for−gestational−age fetus. Green−top Guideline No. 31. 2013.
15. Aderoba AK, Ioannou C, Kurinczuk JJ, et al. The impact of a universal late third-trimester scan for fetal growth restriction on perinatal outcomes in term singleton births: a prospective cohort study. *BJOG*. 2023;130(7):791-802.
16. Veglia M, Cavallaro A, Papageorghiou A, Black R, Impey L. Small-for-gestational-age babies after 37 weeks: impact study of risk-stratification protocol. *Ultrasound Obstet Gynecol*. 2018;52(1):66-71.
17. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements--a prospective study. *Am J Obstet Gynecol*. 1985;151(3):333-337.
18. Statistics OfN. Ethnic group, national identity and religion. 2021. https://www.ons.gov.uk/methodology/classificationsandstandards/measuringequality/ethnicgroupnationalidentityandreligion
19. Wright C, Booth I, Buckler J, et al. Growth reference charts for use in the United Kingdom. *Arch Dis Child*. 2002;86(1):11-14.
20. Bhide A, Acharya G, Baschat A, et al. ISUOG Practice Guidelines (updated): use of Doppler velocimetry in obstetrics. *Ultrasound Obstet Gynecol*. 2021;58(2):331-339.

21. Wadhwani P, Saha PK, Kalra JK, Gainder S, Sundaram V. A study to compare maternal and perinatal outcome in early vs. late onset preeclampsia. *Obstet Gynecol Sci*. 2020;63(3):270-277.
22. Seed P. DIAGT: Stata module to report summary statistics for diagnostic tests compared to true disease status. 2001. https://ideas.repec.org/c/boc/bocode/s423401.html
23. Wieand S, Gail MH, James BR, James KL. A family of nonparametric statistics for comparing diagnostic markers with paired or unpaired data. *Biometrika*. 1989;76(3):585-592.
24. Dockree S, Brook J, James T, Shine B, Impey L, Vatish M. Pregnancy-specific reference intervals for C-reactive protein improve diagnostic accuracy for infection: a longitudinal study. *Clin Chim Acta*. 2021;517:81-85.
25. Lees C, Parra M, Missfelder-Lobos H, Morgans A, Fletcher O, Nicolaides KH. Individualized risk assessment for adverse pregnancy outcome by uterine artery Doppler at 23 weeks. *Obstet Gynecol*. 2001;98(3):369-373.
26. NHS England. Saving babies' lives: version 3. A care bundle for reducing perinatal mortality. 2023.
27. Aviram A, Sherman C, Kingdom J, Zaltz A, Barrett J, Melamed N. Defining early vs late fetal growth restriction by placental pathology. *Acta Obstet Gynecol Scand*. 2019;98(3):365-373.
28. Visser GH, Bilardo C, Derks J, et al. Fetal monitoring indications for delivery and 2-year outcome in 310 infants with fetal growth restriction delivered before 32 weeks' gestation in the TRUFFLE study. *Ultrasound Obstet Gynecol*. 2017;50(3):347-352.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Sensitivity analysis comparing results of main analysis with those obtained when population is restricted to the 1.5% of women with unilateral uterine artery pulsatility index measurement (no material difference).