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Reference ranges of uterine artery pulsatility index from first to third trimester based on serial Doppler measurements: longitudinal cohort study

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KEYWORDS: Doppler; longitudinal study; low-risk pregnancy; maternal–fetal wellbeing; placentation; pulsatility index; reference range; uterine artery

CONTRIBUTION

What are the novel findings of this work?
This study provides reference ranges of the mean uterine artery pulsatility index (UtA-PI) in a low-risk population from 10 + 0 to 39 + 0 gestational weeks, based on longitudinal prospective collection of serial Doppler measurements modeled in a multilevel framework with a rigorous methodology that has been validated in similar settings.

What are the clinical implication of this work?
Given the importance of UtA-PI as a marker for abnormal pregnancy outcomes related to placental dysfunction, it is crucial to provide reference ranges for clinical use that are based on high-quality data and rigorous statistical modeling in a low-risk population.

ABSTRACT

Objective *To provide gestational-age (GA)-specific reference ranges for mean uterine artery (UtA) pulsatility index (PI) based on longitudinal data assessment throughout pregnancy.*

Methods *This was a prospective longitudinal cohort study of singleton low-risk pregnancies with adequate health and nutritional status at the time of enrolment and without fetal anomaly, receiving prenatal care between January 2018 and July 2021 at the Maternal Fetal Medicine Unit of IRCCS San Raffaele Scientific Institute, Milan, Italy. Women were recruited at ≤ 12 + 6 weeks' gestation and underwent serial standardized ultrasound monitoring, including UtA-PI measurement, by experienced certified operators until delivery. Association of UtA-PI with GA was modeled with fractional polynomial regression. Equations for mean ± SD of the estimated curves were calculated, as well as GA-specific reference charts of centiles for UtA-PI from 10 + 0 to 39 + 0 gestational weeks.*

Results *We included 476 healthy, low-risk pregnant women and a total of 2045 ultrasound scans (median, 4 (range, 3–9) per patient) were available for analysis. Mean UtA-PI was 1.84 ± 0.55, 1.07 ± 0.38 and 0.78 ± 0.23 in the first, second and third trimesters of pregnancy, respectively. Goodness-of-fit assessment revealed that second-degree smoothing was the most accurate fractional polynomial for describing the course of UtA-PI throughout gestation; therefore, it was modeled in a multilevel framework for the construction of UtA-PI curves. We observed a rapid and substantial decrease in mean UtA-PI before 16 weeks, with subsequent smoother decrement of the slope and more stable values from 20 until 39 weeks. The 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 97th centiles according to GA for UtA-PI are provided, as well as equations to allow calculation of any value as a centile.*

Conclusions *UtA-PI shows a progressive non-linear decrease throughout pregnancy. The new reference ranges for GA-specific mean UtA-PI constructed using rigorous methodology may have a better performance compared with previous models for screening for placenta-associated*

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diseases in the early stages of pregnancy and for evaluating the potential risk for pregnancy-induced hypertension and/or small-for-gestational age later in pregnancy.

INTRODUCTION

The uterine artery (UtA) waveform on Doppler ultrasonography (US) reflects impedance to blood flow in the maternal compartment of the fetoplacental unit. The most common index used to describe quantitatively this impedance is the pulsatility index (PI). Measurement of UtA-PI has been validated worldwide as an accurate and reliable tool for early detection of increased impedance to blood flow that is associated with major obstetric diseases related to placental dysfunction, such as pre-eclampsia (PE), hypertensive disorders and fetal growth restriction (FGR)[1–4]. As such, UtA-PI measurement has been largely incorporated in antenatal care to assess maternal and fetal wellbeing. However, to date, the interpretation of UtA-PI values in low-risk pregnancies lacks internationally endorsed standards.

Because of the important clinical implications associated with classification as normal or abnormal, it is important to define reference ranges for common measurements in low-risk uncomplicated pregnancies. For this purpose, the INTERGROWTH-21st Project has developed international standards for several parameters such as fetal growth[5], newborn size at birth[6], postnatal growth of preterm infants[7] and, recently, for umbilical artery Doppler indices[8]. With respect to UtA Doppler, some authors have previously proposed reference values at 11–14 weeks of gestation[9]. However, these charts were derived from early screening for hypertensive disorders and associated complications in an unselected population and therefore may not be completely reliable in normal uneventful pregnancies. No previous large studies have provided reference values for UtA-PI in later trimesters of normal gestations; however, UtA assessment during the second and third trimesters plays a crucial role in monitoring pregnancy course, detecting placental dysfunction and in the eventual decision of anticipated delivery[10,11].

The aim of this study was to develop reliable reference charts with gestational-age (GA)-specific centiles for UtA-PI in low-risk pregnancy, based on high-quality longitudinal data and the rigorous methodology proposed by the INTERGROWTH-21st Project[5–8].

METHODS

Study design and setting

This was a longitudinal prospective cohort study carried out from January 2018 to July 2021 at the Fetal Medicine Department of IRCCS San Raffaele Scientific Institute, Milan, Italy. The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of IRCCS San Raffaele Scientific Institute as part of a broader prospective multipurpose research project on obstetric outcomes (protocol OSTE-PMA; No. 01END). All included women provided written informed consent to record their data for scientific purposes. The study was conducted and reported following the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines[12].

Population

Healthy low-risk women with a naturally conceived singleton pregnancy and with normal pregnancy course and neonatal outcome attending for routine antenatal care at our institute were assessed by serial US scans during the first, second and third trimesters of pregnancy. Only women who commenced antenatal care at $\leq 12+6$ weeks' gestation and who had at least one US scan in each trimester of pregnancy were included. Inclusion criteria were as follows: maternal age ≥ 18 years; singleton pregnancy; natural conception; known last menstrual period with regular cycle (defined as 28 ± 4 days); no relevant past medical history, with no need for long-term medication; no use of tobacco, recreational drugs or excessive alcohol (defined as > 5 units (50 mL pure alcohol) per week) since becoming pregnant; and adequate nutritional status. The latter was defined at enrolment according to first-trimester assessment of maternal body mass index (BMI; ≥ 18.5 and < 25 kg/m^2) and hemoglobin concentration (≥ 110 g/L), and whether the mother was taking any treatment for anemia or was following any specific dietary regimen (i.e. vegetarian, vegan or calorie restriction). Exclusion criteria included risk profile for adverse pregnancy/perinatal outcome due to maternal pregestational or gestational diseases (Type-I or Type-II diabetes, cardiovascular disease, malignancy, gynecological disease, endocrine disease, antiphospholipid syndrome, chronic hypertension and history of PE or preterm birth in any previous pregnancy) and chromosomal or major structural fetal abnormalities.

Standard ultrasound assessment

Women were enroled at $\leq 12+6$ weeks of gestation as determined by US measurement of crown–rump length[13] and were subsequently scanned every 6–12 weeks until delivery. At each US assessment, left and right UtA-PI were measured transabdominally in all participants by a single certified operator (P.I.C.) following the guidelines of the Fetal Medicine Foundation (FMF) and the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)[14–16]. According to these guidelines, UtA Doppler was recorded during the first trimester identifying each UtA along the side of the cervix and uterus at the level of the internal orifice; in the second and third trimesters, Doppler analysis was performed placing the sample volume 1 cm downstream from the crossover of the uterine arteries with the external iliac arteries.

Pulsed-wave Doppler of the UtAs was performed with a sampling gate set at 2 mm to cover the whole vessel and with an angle of insonation < 30°. UtA-PI was calculated when three similar consecutive waveforms were obtained, according to the following equation: (peak systolic velocity − minimum diastolic velocity) / time-averaged velocity. The left and right UtA-PI measurements were averaged to estimate a mean value. All Doppler US assessments were performed using high-end US machines (Samsung WS80 or Samsung HERA W10; Samsung, Seoul, South Korea) equipped with multifrequency convex transabdominal transducers. UtA-PI data recorded locally were automatically recorded in an electronic database.

Statistical analysis

Sample size considerations were performed before analyzing the prospectively collected data, based on several strategies. First, according to the statistical considerations for the development of prescriptive fetal and newborn growth standards indicated in the INTERGROWTH-21st Project[17], we considered that our sample size should be large enough to yield precise and accurate estimates of a single centile. Second, the sample size was designed in relation to the precision and accuracy of a single centile and regression-based reference limits[18]. Furthermore, we applied the standard formula for sampling variance of a centile of normal distribution to estimate the standard error of the P^{th} centile: $SE_p = SD \times \sqrt{((1 + 1/2 \times Z_p^2)/n)}$ (where SE_p = standard error, SD = standard deviation of the measurement, Z_p = standard normal distribution corresponding to the P^{th} centile and n = sample size)[19]. According to this formula, the precision achieved at 5th or 95th centile in SD will reach a SE = 0.07 SD for a sample size of 500 observations. Considering the sample size calculation for a generic regression line and using the SD of both dependent and independent variable plus the value of the slope, we found that 246 observations were needed to achieve a 90% power at a type-I error of 5%. Since our study population comprised 476 cases and 2045 observations, we felt that the sample size assumption was not violated. Finally, and importantly, it has been demonstrated that longitudinal studies of fetal growth require half the sample size of that of a cross-sectional study to estimate a given centile with the same power[20].

Several distributions and smoothing techniques were explored for the construction of the best-fitting curve on the basis of our data. Starting with the simplest model assuming a normal distribution, different degrees of fractional polynomials were compared using standard goodness-of-fit analyses. Once we identified the best

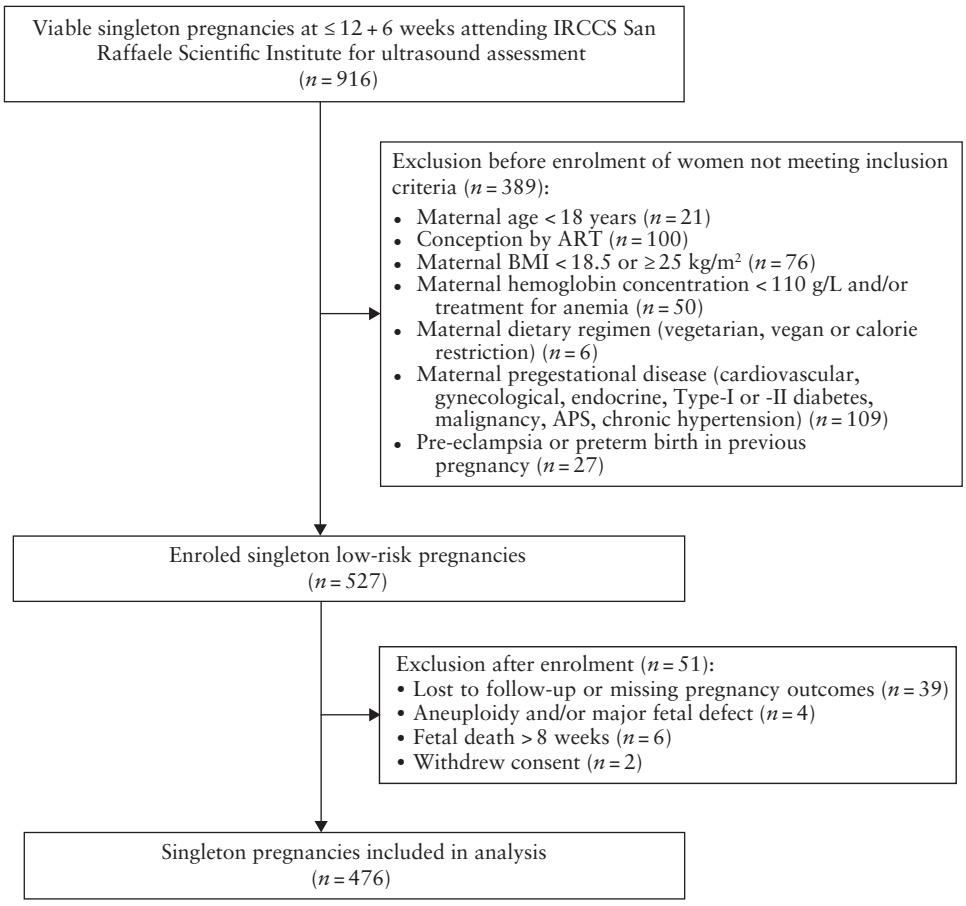

Figure 1 Strengthening the reporting of observational studies in epidemiology (STROBE) flowchart showing patient selection. APS, antiphospholipid syndrome; ART, assisted reproductive technology; BMI, body mass index.

fitting distribution based on Akaike information criterion (AIC) and Bayesian information criterion (BIC) values[21,22], a modulus exponential normal (MEN) model smoothed with second-degree fractional polynomial for the construction of the curves was implemented using the *xriml* module (2021) in STATA (StataCorp. LLC, College Station, TX, USA)[23]. Equations for mean (μ) and SD of the estimated curve were calculated. GA-specific reference charts of UtA-PI centiles from 10 + 0 to 39 + 0 gestational weeks were provided. STATA version 17 software (StataCorp. LLC) was used for statistical analysis.

RESULTS

Among the 916 women who attended IRCSS San Raffaele Scientific Institute for US assessment at ≤ 12 + 6 weeks of gestation, 389 were excluded before enrolment because they did not meet the inclusion criteria. Of 527 singleton low-risk pregnancies enroled, 51 were excluded because of loss to follow-up or missing pregnancy outcomes ($n = 39$), diagnosis of aneuploidy or major fetal defect ($n = 4$), fetal death > 8 weeks ($n = 6$) or withdrawal of consent ($n = 2$). Therefore, data for analysis were obtained from 476 women. A total of 2045 scans with a median of four per patient (range, 3–9) were performed. The patient selection process is shown in Figure 1.

Maternal demographic characteristics, as well as pregnancy and neonatal outcomes of the 476 included women are reported in Table 1. The mean maternal age was 29.2 ± 4.3 years, 296 (62.2%) women were nulliparous and 96.2% were Caucasian. In accordance with the inclusion criteria, all examined cases had a normal prepregnancy BMI with a mean value of 22.3 ± 2.2 kg/m^2. The rates of perinatal complications were lower in relation to the expected rates in the general population, being 1.1%, 3.2% and 4.6% for PE, small-for-GA (SGA) and preterm birth (PTB), respectively. Moreover, there were no stillbirths, neonatal or maternal deaths or severe maternal morbidities requiring intensive care in our study group. These observations of very low perinatal mortality and morbidity confirmed that our population was healthy and low-risk.

The mean UtA-PI values were 1.84 ± 0.55, 1.07 ± 0.38 and 0.78 ± 0.23 in the first, second and third trimesters of pregnancy, respectively. Goodness-of-fit for several models smoothed with different degrees of fractional polynomials was evaluated by comparison of BIC and AIC estimated values. A MEN model smoothed with second-degree fractional polynomial provided the lowest information criteria (both AIC and BIC), thus resulting in the best-fitting regression function to estimate GA-specific mean and SD (i.e. model parameters) of UtA-PI. The scatterplot of residuals according to GA expressed in exact weeks (i.e. GA in days/7) and a normal quantile–quantile (Q–Q) plot of the distribution of *Z*-scores are shown in Figure S1. The equations of parameters for UtA-PI according to GA (in exact weeks) are shown in Table 2.

The GA-specific 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 97th fitted centile curves for mean UtA-PI are shown in Figure 2. The calculated GA-specific standard values for the 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 97th centiles of UtA-PI from 10 + 0 to 39 + 0 weeks' gestation are reported in Table 3.

Table 1 Maternal demographic characteristics and pregnancy and neonatal outcomes in study population of 476 singleton low-risk pregnancies

Characteristic	*Value*
Maternal age (years)	29.2 ± 4.3
Prepregnancy body mass index (kg/m^2)	22.3 ± 2.2
Caucasian ethnicity	458 (96.2)
Nulliparous	296 (62.2)
Gestational age at birth (weeks)	40 (38–41)
Birth weight (g)	3400 ± 500
Birth weight < 2500 g at ≥ 37 weeks	14 (2.9)
Pre-eclampsia	5 (1.1)
Small-for-gestational age*	15 (3.2)
Preterm birth (< 37 weeks)	22 (4.6)
Neonatal mortality	0 (0)

Data are given as mean ± SD, *n* (%) or median (interquartile range).
*Birth weight < 10th centile.

Table 2 Equations for uterine artery pulsatility index according to gestational age (GA) from 10 + 0 to 39 + 0 weeks' gestation, in healthy low-risk singleton pregnancies

Parameter	*Value/equation*
Skewness	1.06
Mean	$0.9262406 + 1.66 \times ((GA/10)^{-2} - 0.1791619462) - 0.0014061 \times ((GA/10)^{3} - 13.18655477)$
Coefficient of variation	$0.2887986 + 0.590136 \times ((GA/10)^{-2} - 0.1791619462) + 0.5782436 \times ((GA/10)^{-2} \times \ln(GA/10) - 0.1540313618)$

ln, natural logarithm.

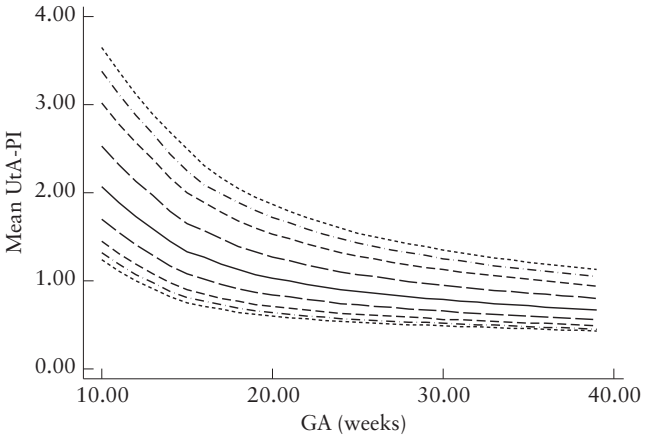

Figure 2 Smoothed centile curves for mean uterine artery pulsatility index (UtA-PI) according to gestational age (GA) from 10 + 0 to 39 + 0 weeks' gestation, in healthy low-risk singleton pregnancies. GA was calculated in exact weeks as: GA (days)/7. *y*-axis shows mean of left and right UtA-PI. The following fitted centiles according to GA are presented from bottom to top: 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 97th. Solid line represents 50th centile.

Table 3 Uterine artery pulsatility index centiles according to gestational age (GA) from 10 + 0 to 39 + 0 weeks' gestation, in healthy low-risk singleton pregnancies

	Centile								
GA (weeks)	*3rd*	*5th*	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*	*97th*
10	1.24	1.32	1.45	1.70	2.07	2.53	3.02	3.38	3.65
11	1.11	1.19	1.31	1.55	1.89	2.32	2.78	3.12	3.38
12	1.00	1.07	1.19	1.41	1.73	2.13	2.57	2.88	3.12
13	0.91	0.98	1.08	1.29	1.59	1.97	2.38	2.67	2.89
14	0.82	0.88	0.98	1.17	1.45	1.79	2.17	2.44	2.64
15	0.75	0.81	0.90	1.08	1.33	1.65	2.00	2.25	2.44
16	0.71	0.77	0.85	1.02	1.27	1.57	1.89	2.13	2.31
17	0.68	0.73	0.80	0.96	1.19	1.48	1.78	2.06	2.17
18	0.64	0.69	0.77	0.91	1.13	1.39	1.68	1.89	2.05
19	0.62	0.66	0.73	0.87	1.07	1.33	1.60	1.80	1.95
20	0.60	0.64	0.71	0.84	1.03	1.27	1.53	1.72	1.87
21	0.58	0.62	0.69	0.82	1.00	1.23	1.48	1.66	1.79
22	0.57	0.60	0.67	0.79	0.96	1.18	1.42	1.59	1.72
23	0.55	0.59	0.65	0.77	0.93	1.14	1.37	1.53	1.66
24	0.54	0.57	0.63	0.74	0.90	1.10	1.32	1.48	1.60
25	0.53	0.56	0.62	0.73	0.88	1.07	1.28	1.43	1.54
26	0.52	0.55	0.61	0.71	0.86	1.05	1.25	1.39	1.50
27	0.51	0.54	0.60	0.70	0.84	1.02	1.21	1.35	1.46
28	0.50	0.53	0.59	0.68	0.82	0.99	1.18	1.32	1.42
29	0.50	0.53	0.58	0.67	0.80	0.97	1.15	1.29	1.39
30	0.49	0.52	0.56	0.66	0.79	0.95	1.13	1.25	1.35
31	0.48	0.51	0.56	0.64	0.77	0.93	1.10	1.23	1.32
32	0.48	0.50	0.55	0.63	0.76	0.91	1.08	1.20	1.29
33	0.47	0.50	0.54	0.62	0.74	0.89	1.06	1.17	1.26
34	0.46	0.49	0.53	0.61	0.73	0.88	1.04	1.15	1.24
35	0.46	0.48	0.52	0.60	0.72	0.86	1.02	1.13	1.21
36	0.45	0.47	0.52	0.59	0.70	0.85	1.00	1.11	1.19
37	0.44	0.47	0.51	0.58	0.69	0.83	0.98	1.09	1.17
38	0.44	0.46	0.50	0.57	0.68	0.82	0.96	1.07	1.15
39	0.43	0.45	0.49	0.56	0.67	0.80	0.94	1.05	1.13

DISCUSSION

Main findings

This study provides robust reference ranges for GA-specific UtA-PI in a population of well-nourished healthy women with pregnancies at low-risk of obstetric complications. UtA-PI reduced progressively and rapidly below 16 weeks, with subsequent smoother decrement of the slope and stabilization of observed values.

Interpretation

The need to develop UtA-PI charts derived from the lack in the literature of recent longitudinal studies based on a standardized method, such as that proposed by the INTERGROWTH-21st Project, and already validated to estimate fetal growth and umbilical artery Doppler indices[5–8]. Indeed, previous studies assessing UtA Doppler were limited to narrower gestational-age ranges and lacked a longitudinal design. In the cross-sectional study of Gómez *et al.*[24], a model for mean UtA-PI between 11 and 41 weeks' gestation was developed based on a second-degree fractional polynomial in a study group of 620 women. The regression curve described in that study is different compared to ours (Table S1, Figure S2, Figure S3). First, the progression of reduction in UtA-PI values appears rather stable in the curves proposed by Gómez *et al.*[24], whereas based on our results, the slope of the curve is greater at GAs below 16 weeks. In clinical practice, this would lead to a lower rate of increased UtA-PI at that stage of pregnancy. Second, there is a paucity of normal values for the interpretation of UtA-PI in the early first trimester and our study contributes to the knowledge on this topic.

Classic polynomial regression is used widely for the description of continuous biometric data. However, up to their quadratic degree, they are somewhat limited in the range of curve profiles generated; different, high-order splines may produce artifacts such as edge effects and waves. Fractional polynomials are an alternative to regular polynomials providing flexible parameterization for continuous variables encompassing a wide range of shapes, including and overcoming all those generated by classical polynomials. Fractional polynomials differ from regular polynomials in allowing use of logarithms as well as non-integer and repeated powers[25]. Notably, in the model proposed by INTERGROWTH-21st and applied herein to fit longitudinally recorded Doppler values[5–8], the parameters of the distribution are modeled as functions of the GA using fractional polynomials. Therefore, this complex model allowed us to estimate

adequately cross-sectional reference intervals for UtA-PI (*y* variable) conditional on GA (*x* variable in the model)[26].

Strengths and limitations

To our knowledge this is the largest study in the literature evaluating longitudinal measures of UtA Doppler in a homogeneous population at low-risk for placental dysfunction and abnormal pregnancy outcome. According to the statistical considerations[19] described in the Methods, the 2045 Doppler assessments recorded longitudinally in this study would approach the power of a cross-sectional study with more than 4000 observations. Another strength of this work is attributable to the high quality of the data obtained within a single center and by a single operator with extensive expertise and experience in first- as well as second- and third-trimester fetal US and Doppler studies. Also, the longitudinal approach with serial (at least three) observations per patient, contributed to reducing heterogeneity and increasing robustness of the results. Finally, fractional polynomial analysis implemented in a complex statistical approach due to its inherent flexibility enabled a better depiction of the real pattern of UtA-PI throughout pregnancy.

Limitations of this study are related mainly to the impossibility to recruit all women who attended our institute during the study period for routine antenatal care, owing to exclusion of those who did not meet inclusion criteria and those who did not attend the department for follow-up. However, we believe that there was a low risk of selection bias and that data were missing at random. Finally, as this study was conducted at a single center and most of the included women were of Caucasian origin, the generalizability of the results to clinical practice in other settings may be limited. Nevertheless, our study design allowed us to avoid bias due to interobserver variability and also between-site and within-site differences.

Conclusions

In the current literature, there is a lack of UtA cut-offs based on serial US measures, obtained prospectively from low-risk singleton pregnancies in healthy women. This study overcomes the limitations of previous US studies by providing reliable and robust reference ranges for GA-specific UtA-PI estimated by the use of a novel statistical approach validated recently in similar settings. We believe that these reference ranges may be useful clinically and easily generalizable for low-risk populations similar to that described in this study. They may be used in the context of screening for PE, gestational hypertension, maternal thrombophilia and FGR or SGA. External validation of the herein proposed reference charts is required to further corroborate their predictive value for abnormal pregnancy outcomes in a clinical setting.

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SUPPORTING INFORMATION ON THE INTERNET

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

Table S1 Estimation of 5th and 95th uterine artery pulsatility index centiles according to our reference ranges compared with those of Gómez *et al.*[24]

Figure S1 Fractional polynomial fit of the model: (a) scatterplot of residuals according to gestational age (GA; in exact weeks); (b) normal quantile-quantile (Q–Q) plot of distribution of *Z*-scores.

Figure S2 Two-way scatterplot of 5th uterine artery pulsatility index (UtA-PI) centile across gestation, according to model of Gómez *et al.*[24] compared with ours. GA, gestational age.

Figure S3 Two-way scatterplot of 95th uterine artery pulsatility index (UtA-PI) centile across gestation, according to model of Gómez *et al.*[24] compared with ours. GA, gestational age.