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Fetal Medicine Foundation reference ranges for umbilical artery and middle cerebral artery pulsatility index and cerebroplacental ratio

A. CIOBANU[1], A. WRIGHT[2], A. SYNGELAKI[1], D. WRIGHT[2], R. AKOLEKAR[3] and K. H. NICOLAIDES[1]

[1]*Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK;* [2]*Institute of Health Research, University of Exeter, Exeter, UK;* [3]*Fetal Medicine Unit, Medway Maritime Hospital, Gillingham, UK*

KEYWORDS: cerebroplacental ratio; Doppler ultrasound; fetal middle cerebral artery pulsatility index; reference range; umbilical artery pulsatility index

ABSTRACT

Objectives *To develop gestational age-based reference ranges for the pulsatility index in the umbilical artery (UA-PI) and fetal middle cerebral artery (MCA-PI) and the cerebroplacental ratio (MCA-PI/UA-PI), and to examine the maternal characteristics and medical history that affect these measurements.*

Methods *This was a cross-sectional study of 72 387 pregnancies undergoing routine ultrasound examination at 20 + 0 to 22 + 6 weeks' gestation (n = 3712), 31 + 0 to 33 + 6 weeks (n = 29 035), 35 + 0 to 36 + 6 weeks (n = 37 252) or 41 + 0 to 41 + 6 weeks (n = 2388). For the purpose of this study, we included data for only one of the second- or third-trimester visits. The inclusion criteria were singleton pregnancy, dating by fetal crown–rump length at 11 + 0 to 13 + 6 weeks' gestation, live birth of a morphologically normal neonate and ultrasonographic measurements by sonographers who had received the Fetal Medicine Foundation Certificate of Competence in Doppler ultrasound. Since the objectives of the study were to establish reference ranges, rather than normal ranges, and to examine factors from maternal characteristics and medical history that affect these measurements, we included all pregnancies having routine ultrasound examinations, irrespective of whether the mother had a pre-existing medical condition, such as diabetes mellitus, or a pregnancy complication, such as pre-eclampsia or suspected fetal growth restriction. Median and SD models were fitted between UA-PI, MCA-PI and CPR and gestational age. Assessment of goodness of fit of the models was by inspection of quantile-to-quantile (Q–Q) plots of Z-scores calculated using the mean and SD models. The distributions of MCA-PI, UA-PI and CPR Z-scores were examined in relation to maternal characteristics and medical history.*

Results *The relationship between the median and gestational age was linear for UA-PI and cubic for MCA-PI and CPR and the SD was log quadratic for all three. MCA-PI and CPR increased with gestational age from 20 weeks' gestation to reach a peak at around 32 and 34 weeks, respectively, and decreased thereafter, whereas UA-PI decreased linearly with gestational age from 20 to 42 weeks. Compared to the general population, significant deviations in multiples of the median values of UA-PI, MCA-PI and CPR were observed in subgroups of maternal age, body mass index, racial origin, method of conception and parity.*

Conclusion *This study established new reference ranges for UA-PI, MCA-PI and CPR, according to gestational age, and reports maternal characteristics and medical history that affect these measurements. Copyright © 2018 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Fetal hypoxemia is associated with redistribution of the fetal circulation, with increased blood flow to the brain at the expense of the viscera, reflected in reduced impedance to flow in the fetal middle cerebral artery (MCA) and increased impedance in the umbilical artery (UA)[1–5]. Studies in both small-for-gestational-age (SGA) and appropriate-for-gestational-age fetuses reported associations between low cerebroplacental ratio (CPR), due to decreased MCA pulsatility index (PI) and/or increased

Correspondence to: Prof. K. H. Nicolaides, Fetal Medicine Research Institute, King's College Hospital, 16–20 Windsor Walk, Denmark Hill, London SE5 8BB, UK (e-mail: kypros@fetalmedicine.com)

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UA-PI, and adverse perinatal outcome, including higher rates of perinatal death, Cesarean section for fetal distress in labor, neonatal acidosis, low 5-min Apgar scores and admission to the neonatal intensive care unit (NICU)[6–14].

A common approach in using biomarkers to identify high-risk groups for pregnancy complications is to use cut-offs on percentile charts for gestational age-specific ranges. This approach ignores the possible influence of maternal characteristics *per se* on such reference ranges. For example, in screening for Down syndrome by the first-trimester combined test, concentrations of pregnancy-associated plasma protein-A (PAPP-A) are not only dependent on gestational age, but are also affected by a series of other maternal characteristics; for example, the level of PAPP-A in black women is about 60% higher than that in white women[15]. The implication of this is that, if percentile charts are used for identifying the high-risk group, the detection rate of affected pregnancies in black women would be substantially lower than that in white women. Our approach to risk assessment and screening is to apply Bayes' theorem to combine the *a-priori* risk from maternal characteristics and medical history with the results of various combinations of biophysical and biochemical measurements. In the application of Bayes' theorem, it is essential to standardize the measured values of biomarkers for any variables included in the prior model; failure to do so may underestimate or overestimate the contribution of a given biomarker. The maternal factors and their relative importance in the prior model are not the same for all pregnancy complications and it may therefore be necessary to standardize the values of biomarkers for different maternal factors depending on the condition under investigation.

The objectives of this study were, first, to develop gestational age-based reference ranges for UA-PI, MCA-PI and CPR and, second, to examine factors from maternal characteristics and medical history that affect these measurements.

METHODS

Study population

The data for this study were derived from prospective examination of women booked for prenatal care at King's College Hospital, London and Medway Maritime Hospital, Kent, UK. In these hospitals, all women with a singleton pregnancy are offered routine ultrasound examinations at 11 + 0 to 13 + 6 and at 20 + 0 to 22 + 6 weeks' gestation. During a period (2011 to 2014), an additional scan was offered at 31 + 0 to 33 + 6 weeks, but subsequently (2014 to 2018) this was changed to 35 + 0 to 36 + 6 weeks. In Medway Maritime Hospital, an additional routine scan is carried out at 41 + 0 to 41 + 6 weeks. The first visit included recording of maternal demographic characteristics and medical and obstetric history. Maternal height was measured at the first visit and weight at each visit. Pregnancy dating was based on the measurement of fetal crown–rump length[16]. The ultrasound examinations were carried out by sonographers who had extensive training in ultrasound scanning and had obtained the Fetal Medicine Foundation Certificate of Competence in Doppler ultrasound. Transabdominal color Doppler ultrasound was used to visualize the UA and MCA and pulsed-wave Doppler was then used to assess impedance to flow and, when three similar consecutive waveforms were obtained, PI was measured[17,18].

For the purpose of this study, we included data for only one of the second- or third-trimester visits. First, we selected all data obtained at 41 + 0 to 41 + 6 weeks, then all data at 35 + 0 to 36 + 6 or 31 + 0 to 33 + 6 weeks and then used the data for the visit at 20 + 0 to 22 + 6 weeks only from pregnancies that did not have a routine third-trimester scan. The rationale for this approach of gestational-age selection was to maximize the number of patients examined in the third trimester, because this is the stage of pregnancy at which there is maximum utility of the CPR. Since the objectives of the study were to establish reference ranges, rather than normal ranges, and to examine factors from maternal characteristics and medical history that affect these measurements, we included all pregnancies having routine ultrasound examinations, irrespective of whether the mother had a pre-existing medical condition, such as diabetes mellitus, or a pregnancy complication, such as pre-eclampsia or suspected fetal growth restriction. However, care was taken to include routine scans and not follow-up scans for maternal medical conditions or pregnancy complications to avoid overrepresentation of such cases. For example, if a woman with diabetes mellitus was having an ultrasound scan every 2 weeks from 28 weeks onwards, during the study period of 2011 to 2014, we selected a scan during the interval of 31 + 0 to 33 + 6 weeks, whereas, during the study period of 2014 to 2018, we selected a scan during the interval of 35 + 0 to 36 + 6 weeks.

Written informed consent was obtained from the women agreeing to participate in a study on adverse pregnancy outcome, which was approved by the Ethics Committee of each participating hospital. The inclusion criteria for the study were singleton pregnancy, dating by fetal crown–rump length at 11 + 0 to 13 + 6 weeks' gestation and live birth of a morphologically normal neonate at $\geq$24 weeks' gestation. Pregnancy outcome was obtained from the computerized patient records of the participating hospitals or the medical practitioners of the women.

Statistical analysis

Median and SD models were fitted for UA-PI, MCA-PI and CPR with gestational age, assuming a $\log_{10}$ Gaussian distribution. The median was obtained by regression analysis; plots of GA *vs* daily medians of UA-PI, MCA-PI and CPR were used to identify suitable polynomial forms. For estimation of SDs, log transformations were first used to make the variation about the median more stable and symmetric. Quadratic regression models were then fitted to the SDs; the SDs for each gestational day were estimated using the median absolute deviation from the median. Assessment of goodness of fit of the models was by inspection of quantile-to-quantile (Q–Q) plots of Z-scores calculated using the mean and SD models.

The distributions of MCA-PI, UA-PI and CPR Z-scores were examined in relation to maternal age, body mass index (BMI), racial origin, method of conception, cigarette smoking during pregnancy, parity (parous or nulliparous if no previous pregnancy at $\geq$24 weeks), and medical history of chronic hypertension and diabetes mellitus.

The statistical software package R was used for data analyses[19].

RESULTS

The study population comprised 72 387 pregnancies undergoing routine ultrasound examination at 20 + 0 to 22 + 6 weeks' gestation (n = 3712), 31 + 0 to 33 + 6 weeks (n = 29 035), 35 + 0 to 36 + 6 weeks (n = 37 252) or 41 + 0 to 41 + 6 weeks (n = 2388). The ultrasound scans were carried out by a total of 525 sonographers. Pregnancy characteristics are summarized in Table 1.

The relationship between the median and gestational age was linear for UA-PI and cubic for MCA-PI and CPR and the SD was log quadratic for all three; the regression coefficients are given in Table S1. The Q–Q plots demonstrate that the goodness of fit of the models was generally acceptable (Figures S1–S3). The 5th, 10th, 25th, 50th, 75th, 90th and 95th percentiles of UA-PI, MCA-PI and CPR according to gestational age from mid-gestation for each week between 20 and 42 weeks are shown in Table 2. The 10th, 50th and 90th percentiles are shown in Figure 1. The median MCA-PI and CPR increased with gestational age from 20 weeks' gestation to reach a peak at around 32 and 34 weeks, respectively, and decreased thereafter, whereas UA-PI decreased with gestational age from 20 to 42 weeks.

The 50th, 10th and 90th percentiles are compared to those of commonly referred charts from previous publications in Figure 2 and Table S2[17,20–23]. The 90th percentile of the UA-PI in our chart was similar to that of Acharya *et al.*[17] and Bahlmann *et al.*[22]; the 90th percentile of Parra-Cordero *et al.*[21] was considerably higher than ours before 33 weeks and lower thereafter. Our median UA-PI was similar to that of Bahlmann *et al.*[22] but higher than that of Acharya *et al.*[17]. The shape of the median and 10th percentile of MCA-PI in our chart was similar to that of Ebbing *et al.*[20] but our values were considerably lower. The median MCA-PI

Table 1 Characteristics of study population of 72 387 pregnancies, according to gestational age

Characteristic	*20 + 0 to 22 + 6 weeks* (n = 3712)	*31 + 0 to 33 + 6 weeks* (n = 29 035)	*35 + 0 to 36 + 6 weeks* (n = 37 252)	*41 + 0 to 41 + 6 weeks* (n = 2388)
Maternal age (years)	32.0 (28.0–35.8)	31.2 (26.7–35.0)	31.6 (27.3–35.3)	31.5 (26.9–35.2)
Maternal height (cm)	165 (161–169)	165 (160–169)	165 (160–169)	165 (161–170)
Maternal weight (kg)	71.7 (63.8–82.8)	75.7 (68.0–86.0)	79.0 (70.4–89.6)	81.9 (74.0–91.7)
Maternal BMI (kg/m^2)	26.3 (23.5–30.3)	27.9 (25.2–31.6)	29.0 (26.1–32.8)	29.9 (27.2–33.4)
Maternal racial origin				
White	2814 (75.8)	20 308 (69.9)	27 682 (74.3)	1773 (74.3)
Black	555 (15.0)	5547 (19.1)	5911 (15.9)	470 (19.7)
South Asian	169 (4.6)	1623 (5.6)	1786 (4.8)	72 (3.0)
East Asian	69 (1.9)	872 (3.0)	764 (2.1)	14 (0.6)
Mixed	105 (2.8)	685 (2.4)	1109 (3.0)	59 (2.5)
Conception				
Spontaneous	3548 (95.6)	27 964 (96.3)	35 974 (96.6)	2338 (97.9)
Ovulation induction	16 (0.4)	310 (1.1)	202 (0.5)	16 (0.7)
In-vitro fertilization	148 (4.0)	761 (2.6)	1076 (2.9)	34 (1.4)
Cigarette smoker	260 (7.0)	2686 (9.3)	3077 (8.3)	176 (7.4)
Parity				
Nulliparous	1668 (44.9)	14 471 (49.8)	17 020 (45.7)	1291 (54.1)
Parous	2044 (55.1)	14 564 (50.2)	20 232 (54.3)	1097 (45.9)
Medical disorder				
Diabetes mellitus Type 1	15 (0.4)	115 (0.4)	154 (0.4)	1 (0.04)
Diabetes mellitus Type 2	25 (0.7)	199 (0.7)	311 (0.8)	2 (0.1)
SLE/APS	13 (0.4)	55 (0.2)	109 (0.3)	1 (0.04)
Chronic hypertension	37 (1.0)	406 (1.4)	446 (1.2)	2 (0.1)
Pregnancy outcome				
GA at delivery (weeks)	39.9 (39.0–40.7)	40.0 (39.0–40.9)	39.9 (39.0–40.7)	41.7 (41.6–42.0)
Birth-weight Z-score	0.00 (−0.74 to 0.64)	−0.08 (−0.79 to 0.60)	−0.01 (−0.70 to 0.66)	0.09 (−0.53 to 0.71)
Birth weight < 10th percentile	453 (12.2)	3759 (12.9)	4208 (11.3)	180 (7.5)

Data are given as median (interquartile range) or n (%). APS, antiphospholipid syndrome; BMI, body mass index; GA, gestational age; SLE, systemic lupus erythematosus.

Table 2 Median and 5^{th}, 10^{th}, 25^{th}, 75^{th}, 90^{th} and 95^{th} percentiles of umbilical artery pulsatility index (PI), middle cerebral artery PI and cerebroplacental ratio from mid-gestation

Gestational age		*Umbilical artery PI*							*Middle cerebral artery PI*							*Cerebroplacental ratio*						
Weeks	*Days*	*5th*	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*	*5th*	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*	*5th*	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*
20	143	0.955	1.007	1.102	1.218	1.346	1.472	1.553	1.162	1.227	1.344	1.486	1.644	1.800	1.901	0.872	0.938	1.059	1.212	1.388	1.567	1.686
21	150	0.939	0.990	1.083	1.197	1.322	1.446	1.526	1.213	1.278	1.396	1.540	1.699	1.855	1.956	0.934	1.002	1.129	1.289	1.471	1.657	1.780
22	157	0.922	0.973	1.064	1.176	1.299	1.420	1.499	1.263	1.330	1.450	1.595	1.755	1.913	2.015	0.996	1.068	1.201	1.367	1.557	1.750	1.877
23	164	0.906	0.956	1.045	1.155	1.276	1.395	1.472	1.313	1.381	1.503	1.651	1.813	1.973	2.075	1.059	1.134	1.273	1.447	1.645	1.845	1.977
24	171	0.889	0.938	1.026	1.134	1.253	1.370	1.446	1.360	1.430	1.554	1.705	1.870	2.033	2.137	1.121	1.200	1.345	1.526	1.732	1.942	2.079
25	178	0.871	0.920	1.006	1.113	1.230	1.346	1.420	1.405	1.476	1.603	1.757	1.926	2.091	2.197	1.181	1.263	1.415	1.605	1.820	2.038	2.180
26	185	0.854	0.901	0.987	1.092	1.207	1.322	1.395	1.445	1.517	1.648	1.805	1.978	2.147	2.255	1.237	1.324	1.482	1.680	1.904	2.132	2.281
27	192	0.836	0.883	0.967	1.070	1.185	1.298	1.371	1.478	1.553	1.686	1.848	2.024	2.198	2.309	1.290	1.380	1.545	1.751	1.985	2.223	2.378
28	199	0.818	0.864	0.948	1.049	1.162	1.274	1.346	1.504	1.580	1.717	1.883	2.064	2.243	2.357	1.336	1.430	1.602	1.817	2.061	2.309	2.471
29	206	0.800	0.846	0.928	1.028	1.140	1.251	1.322	1.521	1.599	1.739	1.909	2.095	2.278	2.395	1.375	1.473	1.651	1.875	2.129	2.388	2.557
30	213	0.782	0.827	0.908	1.007	1.118	1.228	1.299	1.527	1.607	1.750	1.924	2.115	2.303	2.424	1.406	1.507	1.692	1.924	2.189	2.457	2.634
31	220	0.763	0.807	0.888	0.986	1.096	1.205	1.275	1.521	1.603	1.749	1.926	2.122	2.316	2.440	1.426	1.530	1.722	1.962	2.237	2.516	2.700
32	227	0.744	0.788	0.868	0.965	1.074	1.182	1.252	1.503	1.586	1.734	1.915	2.115	2.314	2.441	1.436	1.543	1.740	1.988	2.272	2.562	2.753
33	234	0.725	0.769	0.847	0.944	1.052	1.160	1.229	1.472	1.555	1.705	1.889	2.093	2.296	2.426	1.434	1.543	1.745	2.000	2.293	2.593	2.790
34	241	0.706	0.749	0.827	0.923	1.030	1.137	1.207	1.427	1.511	1.662	1.848	2.055	2.260	2.393	1.419	1.531	1.736	1.997	2.298	2.607	2.811
35	248	0.687	0.730	0.807	0.902	1.009	1.115	1.184	1.369	1.453	1.604	1.791	1.999	2.207	2.342	1.392	1.505	1.713	1.979	2.286	2.603	2.813
36	255	0.668	0.710	0.787	0.881	0.987	1.093	1.162	1.300	1.382	1.532	1.718	1.927	2.136	2.272	1.353	1.466	1.676	1.944	2.256	2.579	2.795
37	262	0.649	0.691	0.766	0.860	0.966	1.071	1.140	1.219	1.300	1.448	1.632	1.839	2.048	2.184	1.301	1.414	1.624	1.894	2.209	2.537	2.756
38	269	0.630	0.671	0.746	0.839	0.944	1.050	1.118	1.129	1.208	1.352	1.532	1.736	1.943	2.078	1.239	1.350	1.558	1.827	2.143	2.474	2.696
39	276	0.610	0.651	0.725	0.818	0.923	1.028	1.097	1.032	1.108	1.246	1.421	1.620	1.823	1.956	1.167	1.275	1.480	1.747	2.061	2.392	2.615
40	283	0.591	0.631	0.705	0.797	0.901	1.006	1.075	0.931	1.002	1.134	1.302	1.494	1.691	1.821	1.086	1.192	1.391	1.653	1.963	2.291	2.514
41	290	0.572	0.612	0.685	0.776	0.880	0.985	1.053	0.827	0.894	1.018	1.177	1.360	1.548	1.674	1.000	1.101	1.294	1.547	1.851	2.174	2.394

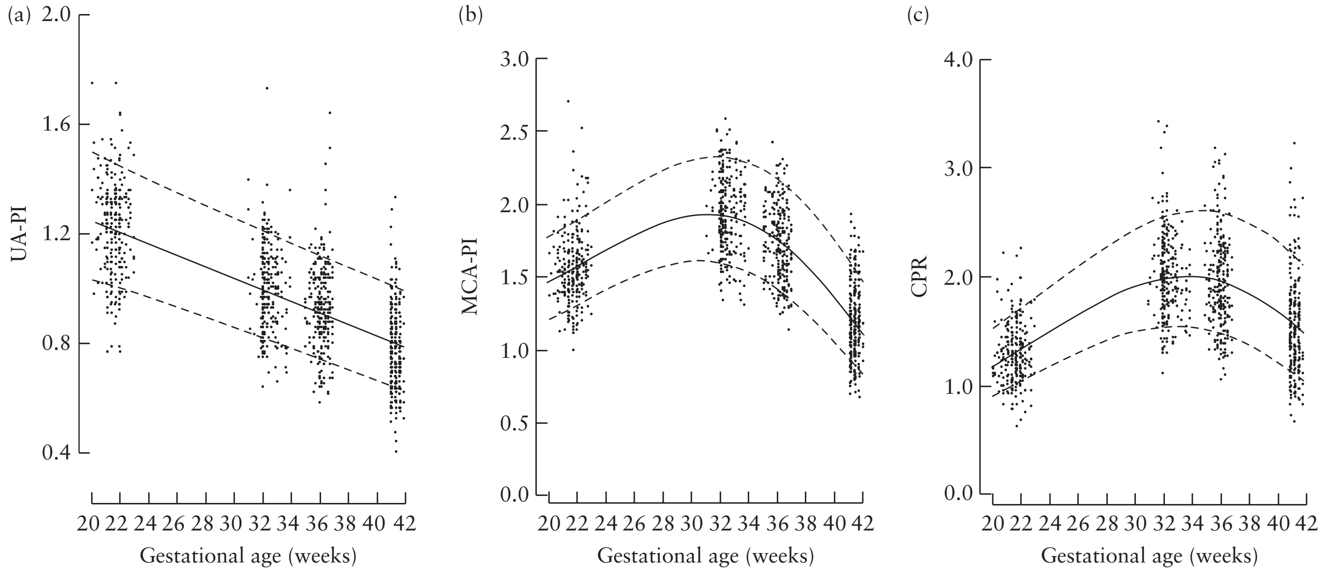

Figure 1 Median (——) and 10th and 90th percentiles (- - -) of umbilical artery (UA) pulsatility index (PI) (a), middle cerebral artery (MCA) PI (b) and cerebroplacental ratio (CPR) (c), according to gestational age.

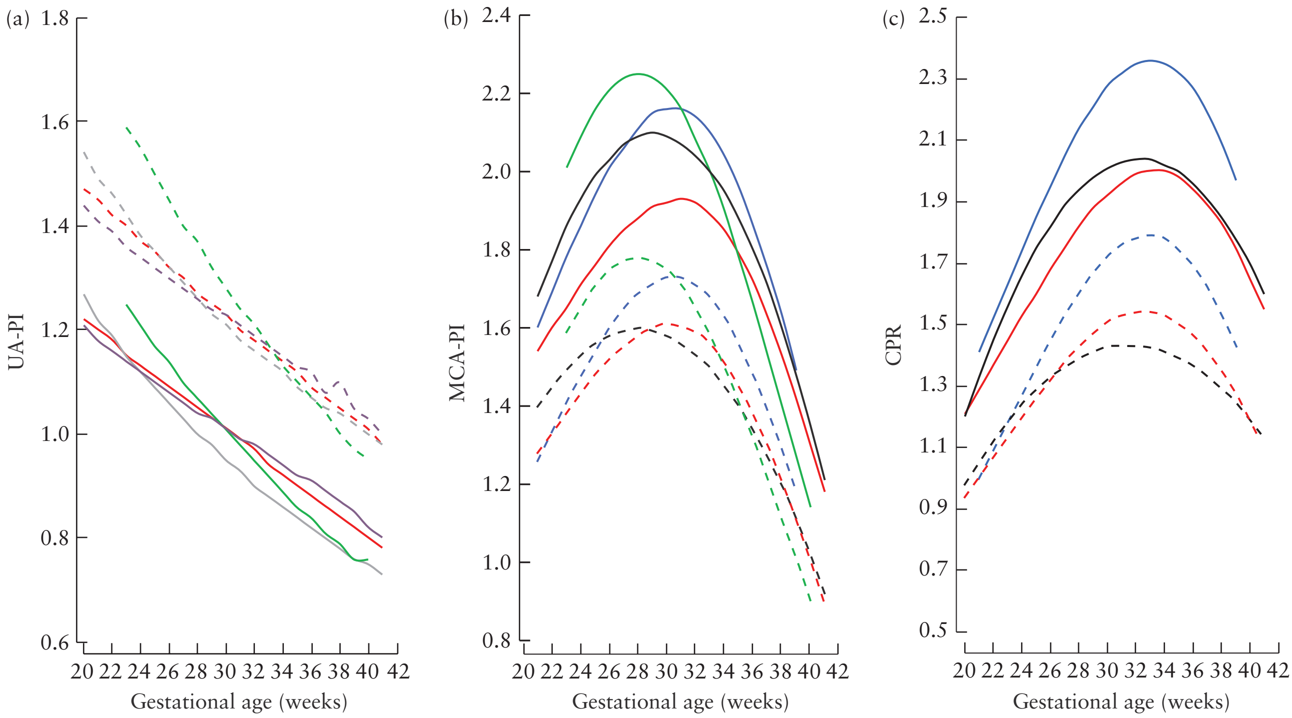

Figure 2 Comparison of 50th (solid lines) and 90th (dashed lines) percentiles of umbilical artery (UA) pulsatility index (PI) (a) and 50th (solid lines) and 10th (dashed lines) percentiles of middle cerebral artery (MCA) PI (b) and cerebroplacental ratio (CPR) (c), according to gestational age, between Fetal Medicine Foundation chart (——) and previous charts: Acharya *et al.*[17] (——); Ebbing *et al.*[20] (——); Parra-Cordero *et al.*[21] (——); Bahlmann *et al.*[22] (——); and Morales-Roselló *et al.*[23] (——).

of Morales-Roselló *et al.*[23] was considerably higher than in our chart; the 10th percentile was higher than ours before 29 weeks and similar thereafter. The median and 10th percentile MCA-PI of Parra-Cordero *et al.*[21] were considerably higher than in our chart before 35 weeks and lower thereafter. The shapes of the median and 10th percentile of CPR in our chart were similar to those of Ebbing *et al.*[20] but our values were considerably lower. The median CPR of Morales-Roselló *et al.*[23] was higher than in our chart before 34 weeks' gestation and similar thereafter; the 10th percentile was higher than ours before 26 weeks and lower thereafter.

Compared to the general population, maternal age < 10th percentile (< 23 years) was associated with increased UA-PI and MCA-PI, whereas age > 90th percentile (> 38.2 years) was associated with reduced

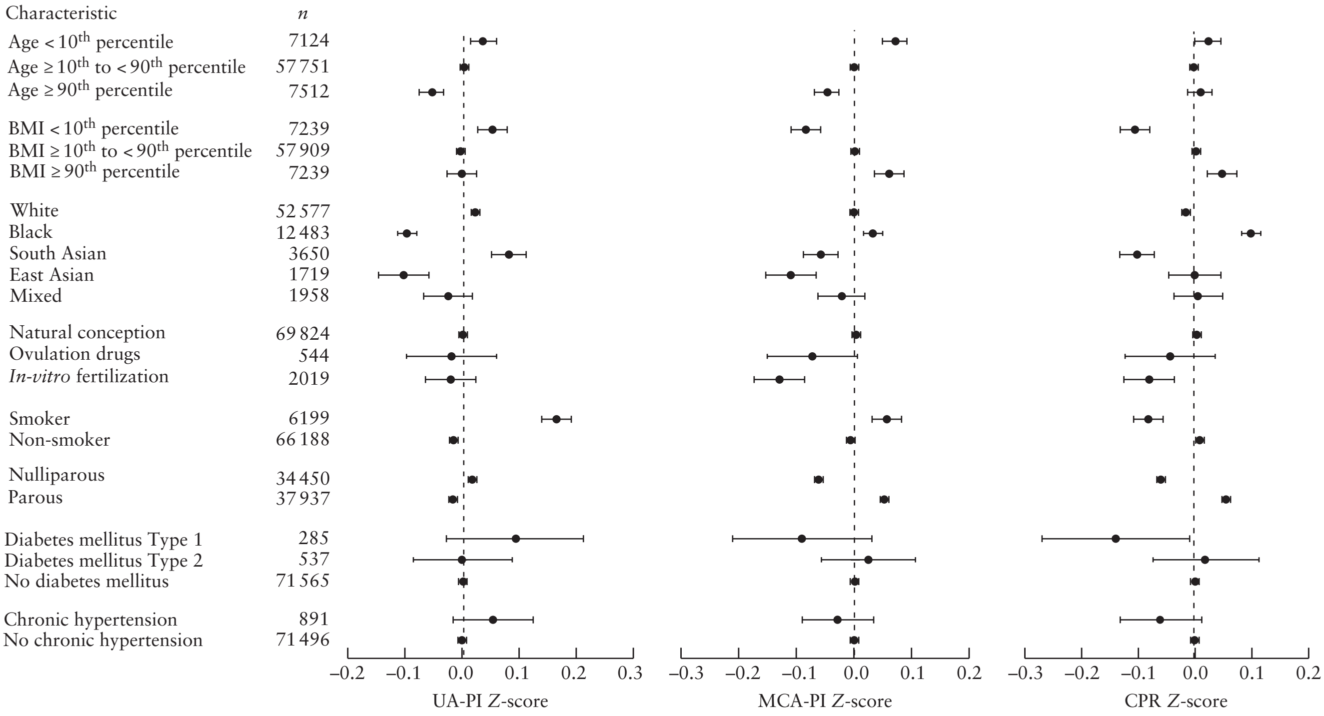

Figure 3 Forest plots showing relationship of maternal demographic characteristics and obstetric and medical history with umbilical artery (UA) pulsatility index (PI), middle cerebral artery (MCA) PI and cerebroplacental ratio (CPR) *Z*-scores. BMI, body mass index.

UA-PI and MCA-PI (Figure 3 and Table S3). Maternal BMI < 10th percentile (< 23.6 kg/m^2) was associated with increased UA-PI and reduced MCA-PI and CPR, whereas BMI > 90th percentile (> 36.5 kg/m^2) was associated with high MCA-PI and CPR. In white women, there was increased UA-PI and reduced CPR; in black women, there was low UA-PI and high MCA-PI and CPR; and in South Asian women, there was high UA-PI and low MCA-PI and CPR. In *in-vitro* fertilization conceptions, MCA-PI and CPR were reduced. In cigarette smokers, both UA-PI and MCA-PI were increased and CPR was reduced. In nulliparous women, UA-PI was increased and MCA-PI and CPR were reduced, whereas, in parous women, UA-PI was reduced and MCA-PI and CPR were increased. In women with diabetes mellitus Type 1 and in those with chronic hypertension, there was a tendency for increased UA-PI and reduced MCA-PI and CPR.

DISCUSSION

Principal findings of study

This study has established reference ranges according to gestational age for UA-PI, MCA-PI and CPR. In our heterogeneous unselected population, median MCA-PI and CPR increased with gestational age from 20 weeks to reach a peak at around 32 and 34 weeks, respectively, and decreased thereafter, whereas UA-PI decreased linearly with gestational age from 20 to 42 weeks.

In the construction of the reference ranges, we chose a log Gaussian model for simplicity and to facilitate the calculation of *Z*-scores. We found that, after allowing for gestational age, there were significant effects on UA-PI, MCA-PI and CPR of maternal age, BMI, racial origin, method of conception, smoking and parity.

Strengths and limitations

Strengths of our study include: first, a large population of women undergoing routine ultrasound examination in pregnancy and use of their data only once to avoid the potential correlation of measurements from different visits; second, pregnancy dating based on fetal crown–rump length; third, a large number of trained sonographers who carried out the Doppler measurements according to a standardized protocol; and fourth, examination of factors from maternal characteristics and medical history that affect the measurements. In the establishment of reference ranges, we included all pregnancies undergoing routine ultrasound examination and did not attempt to select only uncomplicated pregnancies in women with no medical conditions.

We wanted to include data arising from routine screening of the whole population and this inevitably restricted the data to four narrow gestational-age ranges. Despite the extensive extrapolation and interpolation of data, the model diagnostics demonstrated satisfactory fit of the models.

Comparison with previous studies

Commonly used charts from five previous studies were derived from a relatively small number of patients and, as illustrated in Figure 2, there are considerable variations in their reported values[17,20–23]. Two of the studies examined longitudinally 130 and 161 patients, respectively[17,20], and the other three were cross-sectional, examining 171, 1926 and 2323 patients, respectively[21–23]. In all studies, the measurements were taken by a very small number of operators and, in four, there was a wide range of exclusion criteria, such as maternal medical conditions, smoking and previous and current pregnancy complications[17,20–22]. Our objective was to construct reference ranges based on routine clinical practice; the measurements were carried out by a large number of appropriately trained operators and the only exclusion criterion was fetal abnormality.

In a previous study of 34 433 pregnancies at 30–38 weeks' gestation, we used multiple linear regression analysis to define the contribution of variables from maternal demographic characteristics and medical history that influence the measured UA-PI and MCA-PI; models were fitted to express UA-PI, MCA-PI and CPR as multiples of the median after adjustment for these variables and the values in pregnancies that delivered a SGA neonate were compared to those without this pregnancy complication[24]. In this study, we examined pregnancies from 20–42 weeks' gestation, established reference ranges of UA-PI, MCA-PI and CPR according to gestational age, and then estimated *Z*-scores for different maternal characteristics. These findings can be used to standardize the values of Doppler indices for different maternal factors depending on the condition under investigation.

Implications for clinical practice

Pregnancy complications, such as pre-eclampsia and birth of a SGA neonate, and adverse perinatal outcomes, including perinatal death, and their surrogate markers, Cesarean section for fetal distress in labor, low Apgar score, neonatal acidosis and admission to NICU, are associated with many, and often different, maternal characteristics[13,14,25–30]. In screening for each of these adverse outcomes by UA-PI, MCA-PI and CPR, it is essential that the appropriate adjustments are made for those maternal factors that affect outcome. Failure to do so would underestimate or overestimate the contribution of Doppler indices in the prediction of adverse outcome.

For example, black race is associated with increased risk of pre-eclampsia, SGA, Cesarean section for fetal distress and low Apgar score. These adverse outcomes are often associated with high UA-PI and low MCA-PI, but we found that, in black women, there is low UA-PI and high MCA-PI. Consequently, failure to make the appropriate adjustments for black race would underestimate the contribution of UA-PI and MCA-PI in the prediction of adverse outcome in this racial group.

Conclusions

This study established new gestational age-based reference ranges of UA-PI, MCA-PI and CPR, and reports maternal characteristics and medical history that affect these measurements.

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SUPPORTING INFORMATION ON THE INTERNET

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

Figure S1 Quantile-to-quantile (Q–Q) plots of *Z*-scores for data on umbilical artery pulsatility index.

Figure S2 Quantile-to-quantile (Q–Q) plots of *Z*-scores for data on fetal middle cerebral artery pulsatility index.

Figure S3 Quantile-to-quantile (Q–Q) plots of *Z*-scores for data on cerebroplacental ratio.

Table S1 Regression coefficients for median and SD of umbilical artery (UA) pulsatility index (PI), middle cerebral artery (MCA) PI and cerebroplacental ratio (CPR), according to gestational age (GA)

Table S2 Median and 10th and 90th percentiles of umbilical artery pulsatility index (PI), middle cerebral artery PI and cerebroplacental ratio, according to gestational age (GA), in current study and previous reports

Table S3 Mean and 95% CI of *Z*-score in umbilical artery pulsatility index (PI), middle cerebral artery PI and cerebroplacental ratio, according to maternal demographic characteristics and obstetric and medical history

