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

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ABSTRACT

Objective: To develop reference ranges with gestational age 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 examine the maternal characteristics and medical history that affect these measurements.

Patients and methods: This was a cross-sectional study of 72,417 pregnancies undergoing routine ultrasound examination at 20^{+0} to 22^{+6} weeks' gestation (n=3,712), or at 31^{+0} to 33^{+6} weeks (n=29,035) or at 35^{+0} to 36^{+6} weeks (n=37,282) or at 41^{+0} to 41^{+6} weeks (n=2,388). 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, livebirth of morphologically normal neonate and ultrasonographic measurements by sonographers that 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 mothers had a pre-existing medical condition, such as diabetes mellitus, or a pregnancy complication, such as preeclampsia or suspected fetal growth restriction. Median and standard deviation (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 via 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 gestation 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 gestation from 20 to 42 weeks. Compared to the general population, significant deviations in

MoM values of UA-PI, MCA-PI and CPR were observed in subgroups of maternal age, BMI, racial origin, method of conception and parity.

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

INTRODUCTION

Fetal hypoxemia is associated with redistribution in 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 (AGA) fetuses, reported associations between low cerebroplacental ratio (CPR), due to decreased MCA-PI and/or increased UA-PI, and adverse perinatal outcome, including higher rates of perinatal death, cesarean section for fetal distress in labor, neonatal acidosis, low 5 minute 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 PAPP-A are not only dependent on gestational age, but they are also affected by weight and a series of other maternal characteristics; the level of PAPP-A in light women is lower than in heavier women and in Black women it is about 60% higher than 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 thin and Black women would be substantially lower than in heavier and 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 are first, to develop reference ranges with gestational age for UA-PI, MCA-PI and CPR and second, 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 singleton pregnancies 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 in the first visit and weight in each visit. Pregnancy dating was based on the measurement of the 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 the 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}, 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 of 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 for 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 mothers had a pre-existing medical condition, such as diabetes mellitus, or a pregnancy complication, such as preeclampsia 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 over representation of such cases. For example, if a woman with diabetes mellitus was having ultrasound scans every two 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, livebirth of morphologically normal neonate at ≥ 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 standard deviation (SD) models were fitted for UA-PI, MCA-PI and CPR with gestational age (GA) assuming a $\log_{10}$ Gaussian distribution. The median was obtained by regression analysis; plots of GA versus 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 (MAD). Assessment of goodness of fit of the models was by inspection of quantile to quantile (q-q) plots of z-scores calculated via 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 pregnancies at ≥ 24 weeks), and medical history of chronic hypertension and diabetes mellitus.

The statistical software package R was used for data analyses.[18]

RESULTS

The study population comprised of 72,417 pregnancies undergoing routine ultrasound examination at 20^{+0} to 22^{+6} weeks' gestation (n=3,712), or at 31^{+0} to 33^{+6} weeks (n=29,035) or at 35^{+0} to 36^{+6} weeks (n=37,282) or at 41^{+0} to 41^{+6} weeks (n=2,388). 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 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 is generally acceptable (Figures S1-S3). The 5th, 10th, 25th, 50th, 75th, 90th and 95th percentiles of UA-PI, MCA-PI and CPR with gestational age at mid gestational age 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 gestation 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 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 percentiles of MCA PI in our chart was similar to that of Ebbing *et al* [20] but our values were considerably lower. The median of Morales *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 of Parra-Cordero *et al* [21] were considerably higher than in our chart before 35 weeks and lower thereafter. The shape of the median and 10th percentiles of CPR in our chart was similar to that of Ebbing *et al* [20] but our values were considerably lower. The median of Morales-Rozello *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 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 IVF 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 this study

This study has established reference ranges with gestational age for UA-PI, MCA-PI and CPR. In our heterogeneous unselected population, the 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 gestation 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 from maternal age, BMI, racial origin, method of conception, smoking and parity.

Strengths and limitations of the study

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 that 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 a 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.[16,20-23] Two of the studies examined longitudinally 130 and 161 patients, respectively,[16,20] and the other three were cross-sectional from the study of 171, 1,926 and 2,323 patients, respectively.[21,22,23] 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.[16,20-22] 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 abnormalities.

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 MoMs after adjustment for these variables and the values in pregnancies that delivered small for gestational age (SGA) neonates 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 with gestational age and then estimated z-scores for different maternal characteristics. These findings can then 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 preeclampsia and birth of SGA neonates, and adverse perinatal outcomes, including perinatal death and their surrogate markers of cesarean section for fetal distress in labor, low Apgar score, neonatal acidosis and admission in NICU, are associated with many and often different maternal characteristics.[25-33] 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 the outcome. Failure to do so would underestimate or overestimate the contribution of Dopler indices in the prediction of adverse outcome.

For example, Black race is associated with increased risk of preeclampsia, 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

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

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Figure legends

Figure 1. Median (solid line) and 10^{th} and 90^{th} percentiles (interrupted lines) of umbilical artery PI, middle cerebral artery PI and cerebroplacental ratio with gestational age.

Figure 2. Comparison of the 50^{th} (solid line) and 90^{th} (interrupted line) percentiles of umbilical artery PI and 50^{th} (solid line) and 10^{th} (interrupted line) percentiles of middle cerebral artery PI and cerebroplacental ratio with gestational age between the FMF and previous charts.

Figure 3. Forest plot on relation of maternal demographic characteristics and obstetric and medical history and z-score in UA-PI, MCA-PI and CPR.

Figure S1. Quantile to quantile (q-q) plots of z-scores for data on UA-PI.

Figure S2. Quantile to quantile (q-q) plots of z-scores for data on MCA-PI.

Figure S3. Quantile to quantile (q-q) plots of z-scores for data on CPR.

Table 1: Characteristics of the study population

Characteristic	**20^{+0} to 22^{+6} weeks (n=3,712)**	**31^{+0} to 33^{+6} weeks (n=29,035)**	**35^{+0} to 36^{+6} weeks (n=37,282)**	**41^{+0} to 41^{+6} weeks (n=2,388)**
Maternal age in years, median (IQR)	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 in meters, median (IQR)	165 (161, 169)	165 (160, 169)	165 (160, 169)	165 (161, 170)
Maternal weight in kg, median (IQR)	71.7 (63.8, 82.8)	75.7 (68.0, 86)	79.0 (70.4, 89.6)	81.9 (74.0, 91.7)
Maternal BMI in kg/m^2, median (IQR)	26.3 (23.5, 30.2)	27.9 (25.2, 31)	29.0 (26.1, 32.8)	29.9 (27.2, 33.4)
Maternal racial origin, n (%)				
- White	2,814 (75.8)	20,308 (69.9)	27,703 (74.3)	1,773 (74.3)
- Black	555 (15.0)	5,547 (19.1)	5,916 (15.9)	470 (19.7)
- South Asian	169 (4.6)	1,623 (5.6)	1,787 (4.8)	72 (3.0)
- East Asian	69 (1.9)	872 (3.0)	766 (2.1)	14 (0.6)
- Mixed	105 (2.8)	685 (2.4)	1,110 (3.0)	59 (2.5)
Conception, n (%)				
- Natural	3,548 (95.6)	27,964 (96.3)	36,003 (96.6)	2,338 (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)	1,077 (2.9)	34 (1.4)
Cigarette smoker, n (%)	260 (7.0)	2,686 (9.3)	3,077 (8.3)	176 (7.4)
Parity, n (%)				
- Nulliparous	1,668 (44.9)	14471 (49.8)	17,040 (45.7)	1,291 (54.1)
- Parous	2,044 (55.1)	14564 (50.2)	20,242 (54.3)	1,097 (45.9)
Medical disorders				
- 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 in weeks, median (IQR)	39.9 (39.0, 40.7)	40.0 (39.0, 40.9)	39.9 (39.0, 40.7)	41.7 (41.6, 42.0)
- Birthweight Z-score, median (IQR)	0.00 (-0.74, 0.64)	-0.08 (-0.79, 0.60)	-0.01 (-0.70, 0.66)	0.09 (-0.53, 0.71)
- Birth weight <10th percentile, n (%)	453 (12.2)	3,759 (12.9)	4,212 (11.3)	180 (7.5)

IQR = interquartile range; BMI = body mass index; GA = gestational age

Table 2. Median, 5th 10th, 25th, 75th, 90th and 95th percentiles of umbilical artery PI, middle cerebral artery PI and cerebroplacental ratio at mid gestational age.

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

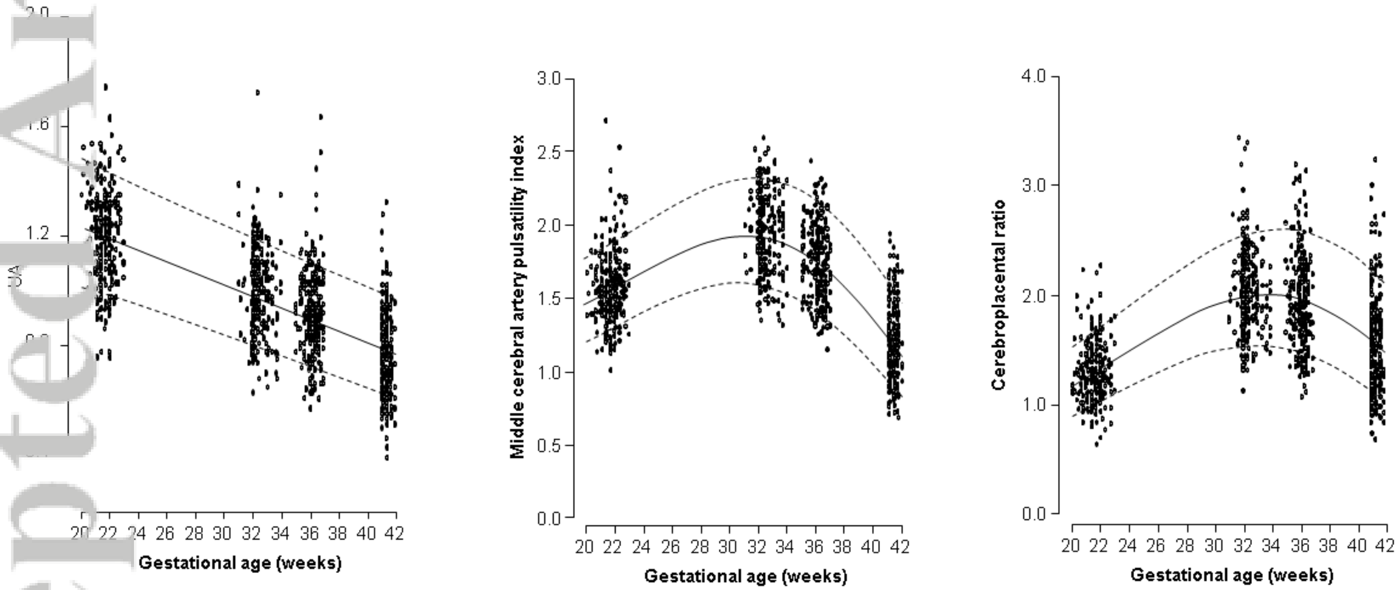
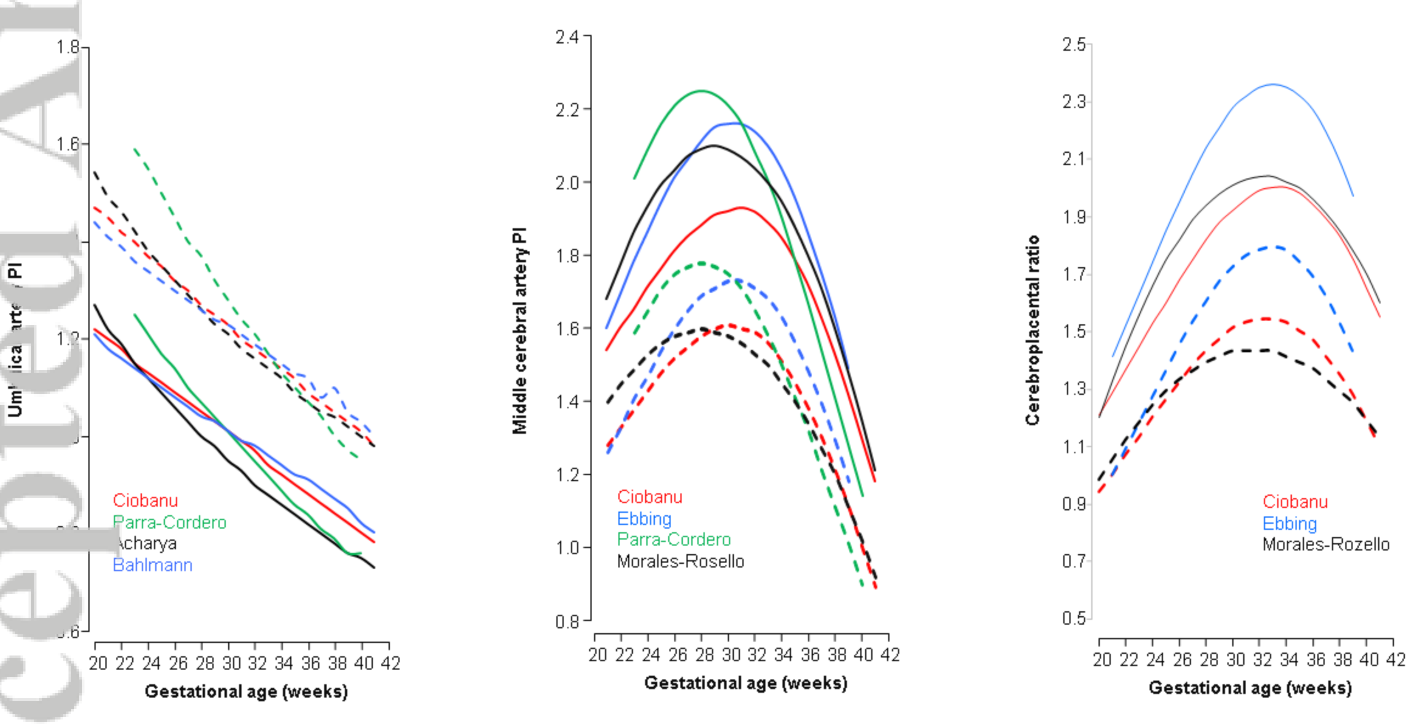

Gestational age (weeks)
Middle cerebral artery pulsatility index
Gestational age (weeks)
Cerebroplacental ratio
Gestational age (weeks)

Figure 1.

Figure 2.


Gestational age (weeks)
Ciobanu
Parra-Cordero
Acharya
Bahlmann
Middle cerebral artery PI
Gestational age (weeks)
Ciobanu
Ebbing
Parra-Cordero
Morales-Rosello
Cerebroplacental ratio
Gestational age (weeks)
Ciobanu
Ebbing
Morales-Rozello

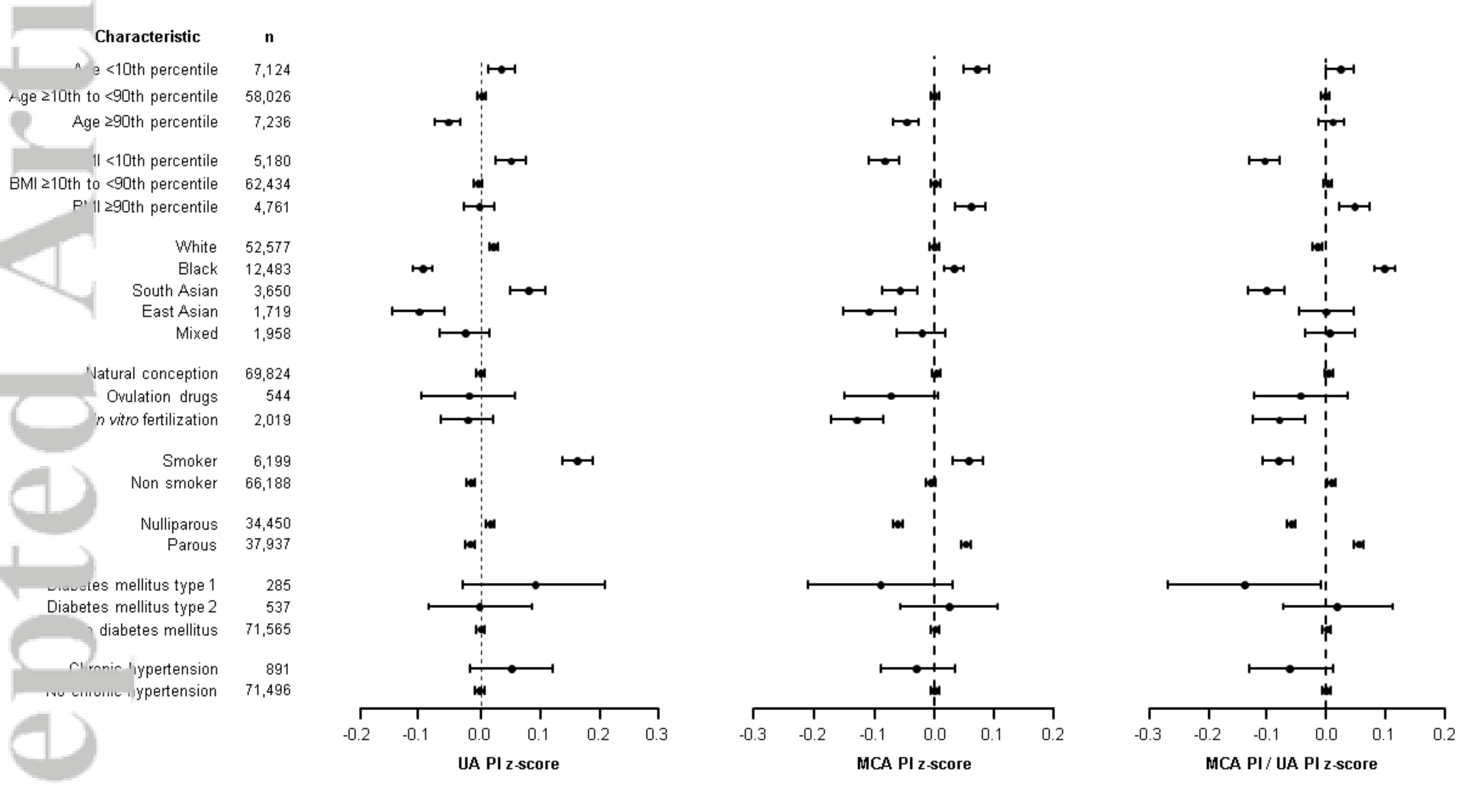

Characteristic
n
Age <10th percentile
7,124
Age ≥10th to <90th percentile
58,026
Age ≥90th percentile
7,236
BMI <10th percentile
5,180
BMI ≥10th to <90th percentile
62,434
BMI ≥90th percentile
4,761
White
52,577
Black
12,483
South Asian
3,650
East Asian
1,719
Mixed
1,958
Natural conception
69,824
Ovulation drugs
544
In vitro fertilization
2,019
Smoker
6,199
Non smoker
66,188
Nulliparous
34,450
Parous
37,937
Diabetes mellitus type 1
285
Diabetes mellitus type 2
537
No diabetes mellitus
71,565
Chronic hypertension
891
No chronic hypertension
71,496
-0.2 -0.1 0.0 0.1 0.2 0.3
UA PI z-score
-0.3 -0.2 -0.1 0.0 0.1 0.2
MCA PI z-score
-0.3 -0.2 -0.1 0.0 0.1 0.2
MCA PI / UA PI z-score

Figure 3.