Sex-specific reference ranges of cerebroplacental and umbilicocerebral ratios: A longitudinal study

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Running head: Longitudinal reference ranges of CPR and UCR

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Contribution

What are the novel findings of this work?

Abnormal CPR or UCR reflect fetal cardiac output redistribution in favor of brain compared to placenta. They are shown to be useful in monitoring high-risk pregnancies, but longitudinal reference ranges of adequate sample size are lacking and gestational age related sex differences have not been examined.

What are the clinical implications of this work?

Longitudinal reference intervals of CPR and UCR were established which are more appropriate for serial monitoring of fetuses at risk of "brain sparing" due to placental insufficiency.
Considering sex-differences may refine the the evaluation further.

Abstract

Objectives: The ratio of middle cerebral artery (MCA) pulsatility index (PI) to umbilical artery (UA) PI, i.e. cerebro-placental ratio (CPR), has been suggested as a measure of fetal “brain sparing” phenomenon reflecting redistribution of fetal cardiac output as a response to placental insufficiency. Observational studies have shown that low CPR values predict increased risk of adverse perinatal outcomes although evidence from randomized clinical trials is lacking. The inverse ratio, i.e. umbilico-cerebral ratio (UCR), is preferred by some as it increases with increasing degree of fetal compromise. Monitoring fetal wellbeing requires serial assessment, and for this purpose, appropriate reference values should be based on data from longitudinal studies. However, longitudinal reference ranges for the UCR have not been established. Furthermore, the sex of the fetus influences its growth velocity, cord properties, *in utero* circadian rhythm, behavioral states and placental function, but whether gestational age-dependent changes in CPR or UCR differ between male and female fetuses has not been studied.

Thus, our objective was to investigate sex-specific, gestational age-associated serial changes in CPR and UCR during the second half of pregnancy and establish longitudinal reference ranges.

Methods: This was a dual-center prospective longitudinal study of singleton low risk pregnancies. Doppler blood flow velocity waveforms were obtained serially from the UA and MCA during 19-41 weeks of gestation, and PIs were determined. CPR and UCR were calculated as the ratios, MCA PI/ UA PI and UA PI/ MCA PI, respectively. The course and outcome of pregnancies was recorded. Sex of the fetus was determined after delivery. Reference intervals were constructed using multilevel modelling and gestational age-specific Z-scores of male and female fetuses were compared.

Results: Of a total of 299 pregnancies enrolled, 284 women and their fetuses (148 male and 136 female) were included in the final analysis, and 979 paired measurements of UA and MCA PIs were used to construct sex-specific longitudinal reference intervals. Both CPR and UCR had U-shaped curves of development during pregnancy, but with opposite directions. There was a small but significant (P=0.007) difference in z-scores of CPR and UCR between male and female fetuses throughout the second half of pregnancy.

Conclusions: We have established longitudinal reference ranges for CPR and UCR suitable for serial monitoring with possibilities to refine the assessment by fetal sex-specific ranges and the conditioning by a previous measurement. The clinical significance of such refinements needs further evaluation.

Introduction

A balance between blood flow to the fetal brain and placenta is vital to support physiological functions and normal intrauterine development. Cerebral blood flow (CBF) increases in proportion to the increase in brain energy metabolism[1] and autoregulation of CBF occurs over a range of blood pressures[2,3,4] from at least 23-24 weeks of gestation[5]. Fetal CBF and impedance are additionally regulated by pO_2 levels, and to a smaller extent by pCO_2 and blood glucose levels.[3,4,6] Fetal hypoxemia assessed by cordocentesis in fetal growth restriction (FGR) was associated with high blood flow velocity and low pulsatility index (PI) in the middle cerebral artery (MCA) determined by Doppler velocimetry.[7] On the other hand, placental blood flow is low in FGR[8] due to high placental vascular impedance.[9] As the blood flow and impedance in the fetal cerebral and placental circulation tend to change in opposite directions in hypoxemic situations, a ratio between cerebral and placental blood flow or impedance could be a useful parameter in the assessment of fetal wellbeing.

Bonnin et al. have shown a progressive and proportional decrease in fetal internal carotid artery resistance index (RI) and increase in umbilical artery (UA) RI with hypoxia, hypercapnia and acidosis in small for gestational age fetuses.[10] The ratio between common carotid artery pulsatility index (PI) to aortic mean velocity was observed to be most closely related to fetal blood gases and acid-base status assessed by umbilical vein blood sampling antenatally.[11] Experimentally, an imposed hypoxemia is associated with a relative circulatory redistribution prioritizing adrenals, heart and brain.[12,13] The ratio between MCA impedance (RI or PI) and UA impedance (RI or PI), so called cerebro-placental ratio (CPR), was suggested as a noninvasive measure of this circulatory response (brain sparing) that might predict perinatal outcomes better than the individual Doppler velocimetric parameters of MCA and UA separately.[14] It has been popularized and advocated recently as a measure of fetal adaptation to hypoxemia.[15] Several studies have reported its utility in predicting pregnancy outcomes[16-20] although its benefit in identifying fetuses at risk of adverse perinatal outcome and preventing perinatal death in pregnancies suspected of FGR has yet to be confirmed by properly designed clinical trials.[21-24]

The UA PI to MCA PI ratio, i.e. the umbilico-cerebral ratio (UCR), was demonstrated to be of value in monitoring FGR fetuses.[25] It was also found to be predictive of a nonreactive computerized cardiotocography and intraventricular hemorrhage.[26] Recently, the UCR was suggested to be a better predictor of perinatal outcome than the CPR.[22] While several reference ranges for CPR, including one longitudinal study of adequate sample size with terms for calculation of conditional ranges, have been published,[27] longitudinal reference intervals for the UCR are lacking. Furthermore, sex-differences are present in placental[28,29] and cerebral[30] circulations, but these have not been taken into account by any studies.

Thus, our aim was to explore differences in UCR and CPR between male and female fetuses, establish sex- and gestational age-specific longitudinal reference ranges and their conditioning terms for serial measurements of CPR and UCR during the second half of pregnancy.

Methods:

This was a secondary analysis of prospectively collected data from a dual-center longitudinal observational cohort study conducted in Norway. Women attending antenatal clinics at Haukeland University Hospital, Bergen, and University Hospital of North Norway, Tromsø, for routine second trimester ultrasound examination were recruited consecutively during 2004 to 2006 in Bergen and 2009 to 2012, in Tromsø. The part of the study performed in Bergen has been described and CPR data have been published previously,[27] but UCR data and sex differences have not been analyzed and reported yet. Here we present results based on the analysis of the combined dataset. Another motivation for combining the two datasets was to improve the reliability of clinically relevant extreme ranges. The inclusion criteria were pregnant women ≥18 years of age with a low risk singleton pregnancy, gestation >17 weeks and <23 weeks at enrolment, and absence of any major placental or fetal structural or chromosomal abnormality. Exclusion criteria were multifetal pregnancy, previous history of preeclampsia, gestational diabetes, FGR, preterm birth before 34 weeks of gestation, pre-existing diseases requiring regular medical treatment or that are known to have significant effect on the outcome of pregnancy, such as chronic hypertension, diabetes, or autoimmune disease. Gestational age was confirmed by head biometry performed at 18-20 weeks of pregnancy.[31] Women were not included if the discrepancy between the last menstrual period-based and ultrasound biometry-based gestational age was >10 days. Women were examined approximately at 4-weekly intervals (range 3-5 weeks) from 19-41 weeks of gestation. A total of 4 physicians were involved in the ultrasound measurements, and they had at least 3 years of training and experience in ultrasonography. At each visit ultrasonography was performed with either a Vivid 7 Dimension (GE Vingmed Ultrasound AS, Horten, Norway) equipped with a 4MS sector transducer with frequencies of 1.5 to 4.3 MHz or a GE Voluson 730 Expert (GE Medical systems, Kretz Ultrasound, Zipf, Austria) equipped with 2-8 MHz curvilinear transabdominal transducers. After confirming fetal viability, determining placental location and checking amniotic fluid volume, fetal biometry was performed and fetal weight was estimated using Hadlock III formula.[32] Fetal sex was not ascertained during the ultrasound examination.

Blood flow velocity waveforms were obtained from the UA at a free-floating loop of the umbilical cord and from the proximal part of the MCA where it emerges from the circle of Willis. Color Doppler and pulsed-wave Doppler were used in line with the techniques described previously and shown to have acceptable reproducibility.[27,33] The Doppler gate (sample volume) was set liberal enough to ensure the recording of the maximum velocity in the blood vessel and the insonation was aligned with the vessel or as close to as possible, always below 15 degrees. The wall movement filter was set low (less than 100 Hz). The acquisition of the Doppler blood flow velocity waveforms was performed during fetal quiescence. In the center, where more than one operator, all ultrasound images were stored and randomly selected anonymized images were reviewed regularly to ensure the quality.

Using the software available in the ultrasound systems, Doppler blood flow velocity waveforms were traced automatically, the PI was calculated as (peak systolic velocity – end-diastolic velocity)/time-averaged maximum velocity and averaged for ≥5 pulses by the software of the ultrasound machine and displayed on the screen. Sensitivity of the trace was adjusted if required and angle correction was used to measure the velocities when it was not zero degree. An average of at least 3 consecutive cardiac cycles was recorded. The UCR was calculated as the ratio of the UA PI to MCA PI and the CPR was calculated as the ratio of the MCA PI to UAPI.

To ensure safety of ultrasonography, ALARA (as low as reasonably achievable) principle was used. Total scanning time never exceeded 60 minutes and mechanical (MI and thermal for bone (TIB) indices were always kept below 1.9 and 1.5. In the majority of the sessions they were below 1.0.

The course and outcome of pregnancy were recorded prospectively. Gestational age at birth, mode of delivery, sex of the neonate, birth weight, placental weight, Apgar score were obtained from the electronic medical records. All neonates were examined once by a pediatrician during the first three postnatal days and any abnormality was noted.

Sample size estimation:

To construct gestational age-specific reference ranges with adequate precision, 15 participants per gestational week has been suggested for cross-sectional studies of fetal biometry,[34] which would result in a total of 330 observations covering a period of 19 to 41 weeks. The corresponding number of fetuses of either sex required for the purpose of establishing sex-specific longitudinal reference ranges can be calculated as 330/2.3 (i.e.143 fetuses of each sex), where 2.3 is the design factor as suggested by Royston and Altman.[35,36] Thus, we estimated that a sample population of approximately 286 would be adequate to construct sex-specific reference ranges. The calculation of sample size required to construct sex-specific reference curves was performed post-hoc.

Statistical analyses:

Statistical analysis of data was performed using IBM SPSS Statistics for Windows, Version 24.0. (IBM Corp, Armonk, NY) and MLWin Version 3.01 (MLWin, Centre for Multilevel Modelling, University of Bristol, Bristol, UK). Distribution of data was checked for normality and power transformations were performed if required in order to best meet the criteria of normal distribution. Fractional polynomials were used to achieve best-fitting curves in relation to gestational age for CPR and UCR. We used multilevel modelling to construct gestational age-specific reference percentiles from each fitted model,[36, 37] which takes into account the fact that the repeated measurements within individuals are not independent. The 2.5th, 5th, 10th, and 25th percentiles were calculated by subtracting 1.96 standard deviation (SD), 1.645 SD, 1.282 SD, and 0.674 SD from the mean, respectively and the 97,5th 90th, and 75th percentiles by adding similar SD values, respectively. 95% confidence intervals were calculated for the 5th, 50th, 95th percentiles. The conditional reference intervals were calculated from the conditional mean and variance, and the level-2 covariance; the level-1 covariance is assumed to be zero.[36] The comparison of gestational age-specific mean z-scores of CPR and UCR between male and female fetuses was done using independent samples t-test for continuous variables. The comparison of these Doppler ratios between male and female fetuses was performed for each gestational week. To test homogeneity of variances for UCR and CPR across centers and fetal sexes, we compared medians of level 1 (measurement) and level 2 (fetus) variances using independent samples Mann-Whitney U test. The level of statistical significance was set at a two-tailed p-value of <0.05.

Ethical approval: The study protocols were approved by the Regional Committees for Medical and Health Research Ethics -West and North Norway (REK Vest no. 203.03 and REK Nord 105/2008) and an informed written consent was obtained from each participant.

Results:

The baseline (at recruitment) demographic and clinical characteristics of the study population and data on outcome of pregnancies are presented in Table 1. Of a total of 299 pregnant women recruited to the study, 284 were included in the final analysis. Fifteen were excluded due to missing data (lack of paired UA and MCA PI). There were 148 male and 136 female fetuses. We were able to record Doppler velocity waveforms from both the MCA and UA in 979 out of 1218 (80.4 %) observations.

Gestational age-specific reference values for CPR and UCR for both sexes combined, and for the male and the female fetuses separately with corresponding 2.5th, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 97.5th percentiles are presented in Tables 2, 3, 4, 5, 6, 7. Reference charts with fitted mean and 5th and 95th percentiles with 95% confidence limits for the same variables (both sexes combined) are shown in Figures 1 and 2.

Regression equations and terms for calculating means and variances as well as unconditional and conditional (expected mean and SD based on a previous measurement) reference ranges for CPR and UCR are presented in Appendix S1 and S2, respectively (online). A calculator for computing gestational age specific unconditional and conditional centiles as well as means and z-scores is provided as a simple practical tool for routine clinical use (supplemental material).

The mean CPR increased from 1.20 at 19 weeks of gestation peaking at 2.31 at 33 weeks, and then decreased to 1.82 at 40 weeks. The mean UCR decreased from 0.83 at 19 weeks of gestation with the lowest value of 0.43 at 33 weeks, and then increased to 0.55 at 40 weeks.

The girls had a lower CPR, and slightly higher UCR than the boys. The mean difference of CPR z-scores between female and male fetuses was -0.17408 (95% CI: -0.29958 to -0.04858) that of UCR z-scores was 0,17414 (95% CI: 0.04857 to 0.2992), P=0.007 for both. The differences were more pronounced earlier in gestation (P=0.006) and not statistically significant after 33 weeks (P=0.42) (Figure 3). There was no association between MCA, PI, CPR or UCR with fetal head circumference or estimated fetal weight. Using Mann-Whitney U test we found similar medians of level 1 (measurement) and level 2 (fetal) variances between two centers and fetal sexes (p>0.05).

Discussion:

Principal findings

This study has established longitudinal reference ranges for CPR and UCR and has shown that these indices differ between male and female fetuses during the second half of pregnancy. We provide sex-specific reference charts and tables of these Doppler indices based on adequate sample size, and terms for calculating conditional reference ranges that will allow serial evaluation of the relation between cerebral and placental blood flow impedances, helping to detect fetal brain sparing phenomenon.

Strengths and limitations

There are several strengths of our study. The study had a prospective longitudinal design and a large enough sample size that allowed constructing reference intervals with adequate precision for both sexes. Cross-sectional reference ranges are not considered optimal for serial assessment of fetal wellbeing. Longitudinal studies have more power and are more efficient compared to cross-sectional studies.[38] However, only one longitudinal study of adequate sample size has reported CPR previously,[27] namely the Bergen part of the present study, but sex differences were not examined. In a recent systematic review[39] that study[27] was rated among the top three with highest methodological quality score, which is reassuring. In the present study, similar methodology was applied in both centers. We tested for homogeneity of variances of measurements across centers and sexes and found no evidence of systematic differences in distributions between centers or sexes. Three other studies with sufficient number of observations per gestational week have been published previously, but all of them had a retrospective cross-sectional design.[40,41,42] Combining data from two centers, we were able to achieve sufficient number of observations in the early part of mid-gestation and late term to construct reliable references also for these gestational weeks.

A limitation of our study is that the pregnancies were not dated by first trimester ultrasound but the gestational age was confirmed by second trimester fetal biometry. This is due to the fact that first trimester dating ultrasound is not a routine practice in Norway and it is offered only to women at high risk of pregnancy complications. However, almost all pregnant women attend second trimester ultrasound examination at 17-20 weeks and have their gestational age confirmed.

Interpretation of results

We found that the CPR increased with advancing gestational age from 19 weeks and peaked at around 33 weeks, then decreasing gradually until 41 weeks. The UCR had the opposite trend; it decreased from 19 to 33 weeks, and then increased slowly towards term. Similar trend of CPR has been reported previously by a longitudinal[27] and some cross-sectional studies.[41,42] However, our reference percentiles based on longitudinal data are different from those based on cross-sectional data.[40,41,43] In general, previously reported CPR values based on cross-sectional studies seem to be lower than the present based on longitudinal data. Furthermore, we found significant sex differences that have not been reported previously.

Placental weight,[44] umbilical cord length[45] and UA PI[28,29] are known to be affected by the sex of the fetus, with girls having smaller placentas, shorter cords and higher UA PIs, although the magnitude these differences are small and may be modulated by parity and gestational age.[29,44] Male fetuses are known to have bigger head circumference than the females.[31] Examining 388 term fetuses before the onset of active labor (cervical dilation <3 cm), Prior *et al* have reported CPR to be slightly higher in female fetuses compared to males (1.81 vs. 1.74), although the difference was statistically not significant.[30] In our study, we found mean CPR to be slightly lower in female fetuses compared to males. We have reported similar findings from a cross-sectional study previously.[28] The discrepancy in findings between our study and the study by Prior *et al,*[30] could be related to the differences in study design (longitudinal vs. cross-sectional) and timing of examination (antenatal vs. in early latent phase of labor) and gestational age (19 - 41 weeks vs 37 - 42 weeks).

Clinical Implications

During intrauterine life, oxygen delivery to the fetus considerably exceeds its metabolic demand. This margin of safety is ensured by several physiological mechanisms, such as higher rates of organ blood flow, higher oxygen concentration in fetal hemoglobin and easier release of oxygen to fetal tissues at lower oxygen tensions.[46] Relatively low oxygen tension and higher pCO_2 of the fetal blood facilitate cerebral blood flow *in utero* by reducing cerebrovascular impedance.[47] However, this impedance is normally higher than that in the placenta. Existence of the brain sparing mechanism in fetuses during hypoxia is well known and experimentally validated.[48] Studying the distribution of fetal cardiac output to the placenta and brain by measuring volume blood flows may provide valuable information on fetal adaptive mechanisms related to suboptimal *in utero* conditions. However, direct invasive measurement of volume blood flow to the human fetal brain and placenta cannot be performed due to ethical reasons and non-invasive measurements using Doppler velocimetry are perceived as difficult and error prone, although technically possible.[8,49] Therefore, the ratio between the surrogate indices of cerebral (MCA PI) and umbilical (UA PI) vascular impedance has been used in clinical practice to reflect the degree of brain sparing in human fetuses.

UA Doppler alone is a poor discriminator of FGR in late gestation and abnormal CPR is suggested as the most reliable Doppler measure of late-onset FGR.[15] Abnormal CPR seems to be associated with increased risk of adverse perinatal outcome in pregnancies diagnosed with FGR.[50] However, several limitations of using CPR should be considered in clinical practice. Previous studies have calculated CPR using either the ratio between carotid artery and aortic PI,[11]MCA PI and UA PI,[27,42,43] carotid artery RI and UA RI,[10,14] or MCA RI and UA RI.[41] Therefore, standardization of terminology is important. In this study, we have used the MCA PI to UA PI ratio as the CPR and its inverse as the UCR.

CPR has been validated experimentally in sheep fetuses[48] to be a sensitive marker of acute reduction in pO_2. However, abnormal CPR can result due to an increased impedance in placental blood flow, a reduced impedance in cerebral blood flow, or both. However, the ratio may be abnormal even when both UA and MCA PI are within the normal range.[16] Thus, what is abnormal CPR has to be defined. A fixed CPR cut-off value ranging from 1.0 to 1.08 has been suggested by some,[16,51,52] while others recommend to use gestational age specific reference percentile to define abnormality.[43] In our study, serial evaluation of CPR and UCR showed its dependency with gestational age, therefore we recommend the use of longitudinal reference ranges rather than a fixed cut-off.

Validity of findings

Regarding validity of our study all ultrasound examinations were performed by qualified physicians with appropriate training and adequate experience and no participant was lost to follow up. We followed the tradition that once included, women are not excluded for any complication occurring during the course of pregnancy to avoid a supernormal population.

Only 5% of neonates had birthweight >90th percentile and 5.7% had <10th percentile based on Norwegian birthweight centiles,[53] and no neonate was diagnosed to have a congenital abnormality postnatally. As our study was performed in two centers in two different time periods some statisticians could consider inclusion of the 3rd level (site of study) in the multilevel model. We did perform statistical analysis of our data also including a 3rd level (center) in the regression model in addition to the measurement occasion (level 1) and fetus (level 2). However, it did not add significantly to the variance, therefore it was not included in the final model. The baseline characteristics and pregnancy outcome data confirm that the population studied was representative of the Scandinavian population. One could argue that the findings from a relatively homogenous Nordic population cannot be generalizable to other multi-ethnic populations, but Doppler blood flow studies in normal pregnancies are less likely to be affected by ethnic differences.[54]

Conclusions

We have established longitudinal reference ranges for CPR and UCR suitable for serial monitoring of fetal brain sparing phenomenon with possibilities to refine the assessment by fetal sex-specific ranges and the conditioning by a previous measurement. Significant sex differences were present in CPR and UCR during the second half of normal pregnancy. Therefore, use of sex-specific reference ranges might provide more precise physiological information. However, as the magnitude of difference was rather small, further studies are needed to ascertain the clinical value of using sex-specific reference ranges.

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Figure legends

Figure 1. Longitudinal references ranges of cerebro-placental ratio in the second half of pregnancy. The solid lines represent the 5th, 50th and 95th percentiles. The inturrupted lines represent their respective 95% confidence intervals.

Figure 2. Longitudinal references ranges of umbilico-placental ratio in the second half of pregnancy. The solid lines represent the 5th, 50th and 95th percentiles. The inturrupted lines represent their respective 95% confidence intervals.

Figure 3. Sex differences in cerebro-placental ratio (CPR) and umbilico-placental ratio (UCR) across the second half of pregnancy. The blue line represents the male fetuses and the red line represents the female fetuses.

Table 1. Baseline characteristics of the study population and birth outcomes

Variable	n	Median(range) or n(%)
Maternal age	299	30 (19-40)
Maternal weight (Kg)*	293	65 (43-122)
Maternal height (cm)	296	167 (150-183)
Maternal body-mass index (Kg/m^2)*	293	23.84 (3.94)
Primipara	299	143 (47.8%)
Smoking	299	7 (2.3%)
Gestational age at birth (days)	297	282 (234-298)
< 37 weeks		8 (2.7%)
< 34 weeks		1 (0.3%)
Pre-eclampsia	298	5 (1.7%)
Mode of delivery	298	
Normal delivery		247 (82.9%)
Operative vaginal delivery		14 (4.7%)
Cesarean section		35 (11.7%)
Vaginal breech delivery		2 (0.7%)
Birthweight (gram)	298	3630 (2251-4980)
Small for gestational age	298	15 (5.03%)
Large for gestational age	298	17 (5.70%)
Length (cm)	293	50 (44-55)
Ponderal index	293	28.1 (20.8-37.5)
Boy/Girl	298	156 (52.3%)/142 (47.7%)
Apgar score < 7 at 1 min	296	13 (4.4%)
Apgar score < 7 at 5 min	297	3 (1.0%)
NICU	298	14 (4.7%)
Placenta weight	287	650 (350-1200)
Umbilical cord length	253	60 (25-115)

The numbers (n) are not equal for all rows because of missing data for some variables. Data are presented as mean (SD), median (range) or n (%) as appropriate.

*Maternal weight and body-mass index at the first examination. One participant failed to attend after the first examination. Electronic medical records indicate that she died, but no other clinical details could be found.

Table 2. Longitudinal reference percentiles of cerebro-placental ratio (CPR) in male fetuses

Gestation (weeks)	2.5 percentile	5 percentile	10 percentile	25 percentile	50 percentile	75 percentile	90 percentile	95 percentile	97.5 percentile
19	0.74	0.81	0.90	1.06	1.27	1.50	1.74	1.89	2.03
20	0.80	0.88	0.97	1.15	1.36	1.61	1.86	2.02	2.17
21	0.87	0.95	1.05	1.23	1.46	1.72	1.98	2.15	2.31
22	0.94	1.02	1.13	1.32	1.56	1.83	2.11	2.29	2.45
23	1.00	1.09	1.20	1.41	1.66	1.95	2.24	2.43	2.60
24	1.07	1.16	1.28	1.49	1.76	2.06	2.37	2.56	2.74
25	1.13	1.23	1.36	1.58	1.86	2.17	2.49	2.69	2.88
26	1.20	1.30	1.43	1.66	1.95	2.28	2.61	2.82	3.02
27	1.25	1.36	1.49	1.74	2.04	2.38	2.72	2.94	3.14
28	1.30	1.41	1.55	1.80	2.12	2.47	2.82	3.05	3.26
29	1.35	1.46	1.60	1.86	2.19	2.55	2.91	3.15	3.36
30	1.38	1.50	1.64	1.91	2.24	2.62	2.99	3.23	3.45
31	1.41	1.53	1.67	1.95	2.29	2.67	3.05	3.30	3.53
32	1.42	1.54	1.69	1.97	2.32	2.70	3.09	3.35	3.58
33	1.42	1.54	1.70	1.98	2.33	2.72	3.12	3.37	3.61
34	1.41	1.53	1.69	1.97	2.32	2.72	3.12	3.38	3.61
35	1.38	1.51	1.66	1.94	2.29	2.69	3.10	3.36	3.60
36	1.34	1.47	1.62	1.90	2.25	2.65	3.05	3.31	3.55
37	1.29	1.41	1.56	1.84	2.18	2.58	2.98	3.24	3.48
38	1.22	1.34	1.49	1.76	2.10	2.49	2.88	3.14	3.38
39	1.14	1.26	1.40	1.66	2.00	2.38	2.77	3.02	3.25
40	1.05	1.16	1.30	1.55	1.88	2.25	2.62	2.87	3.10

Table 3. Longitudinal reference percentiles of cerebro-placental ratio (CPR) in female fetuses

Gestation (weeks)	2.5 percentile	5 percentile	10 percentile	25 percentile	50 percentile	75 percentile	90 percentile	95 percentile	97.5 percentile
19	0.75	0.80	0.87	0.99	1.14	1.30	1.46	1.56	1.65
20	0.81	0.87	0.94	1.07	1.24	1.42	1.60	1.71	1.82
21	0.86	0.93	1.01	1.16	1.34	1.54	1.75	1.87	1.99
22	0.92	1.00	1.09	1.25	1.45	1.67	1.90	2.04	2.17
23	0.98	1.06	1.16	1.34	1.56	1.80	2.05	2.20	2.35
24	1.04	1.13	1.23	1.43	1.67	1.93	2.20	2.37	2.53
25	1.10	1.19	1.31	1.51	1.77	2.06	2.35	2.53	2.70
26	1.16	1.26	1.38	1.60	1.87	2.18	2.49	2.69	2.87
27	1.21	1.31	1.44	1.67	1.97	2.30	2.63	2.84	3.04
28	1.25	1.36	1.50	1.75	2.05	2.40	2.75	2.98	3.18
29	1.29	1.41	1.55	1.81	2.13	2.49	2.86	3.10	3.31
30	1.33	1.44	1.59	1.86	2.19	2.57	2.95	3.20	3.42
31	1.35	1.47	1.62	1.90	2.24	2.63	3.02	3.27	3.51
32	1.36	1.49	1.64	1.92	2.27	2.67	3.07	3.33	3.56
33	1.37	1.49	1.64	1.93	2.28	2.68	3.09	3.35	3.59
34	1.36	1.48	1.63	1.92	2.27	2.67	3.08	3.34	3.58
35	1.34	1.46	1.61	1.89	2.24	2.64	3.04	3.30	3.54
36	1.30	1.42	1.57	1.84	2.19	2.57	2.97	3.22	3.46
37	1.26	1.37	1.52	1.78	2.11	2.49	2.87	3.11	3.34
38	1.20	1.31	1.45	1.70	2.01	2.37	2.73	2.97	3.18
39	1.13	1.24	1.37	1.60	1.90	2.23	2.57	2.79	2.99
40	1.06	1.15	1.27	1.49	1.76	2.07	2.38	2.59	2.77

Table 4. Longitudinal reference percentiles for cerebro-placental ratio (CPR) both sexes combined

Gestation (weeks)	2.5 percentile	5 percentile	10 percentile	25 percentile	50 percentile	75 percentile	90 percentile	95 percentile	97.5 percentile
19	0.73	0.80	0.88	1.02	1.20	1.40	1.61	1.74	1.86
20	0.79	0.86	0.95	1.10	1.30	1.52	1.74	1.88	2.01
21	0.86	0.93	1.02	1.19	1.40	1.64	1.87	2.03	2.17
22	0.92	1.00	1.10	1.28	1.50	1.76	2.01	2.17	2.32
23	0.99	1.07	1.18	1.37	1.61	1.88	2.15	2.32	2.48
24	1.05	1.14	1.25	1.46	1.71	2.00	2.29	2.47	2.64
25	1.12	1.21	1.33	1.55	1.81	2.12	2.42	2.62	2.80
26	1.17	1.28	1.40	1.63	1.91	2.23	2.55	2.76	2.95
27	1.23	1.34	1.47	1.71	2.00	2.34	2.67	2.89	3.09
28	1.28	1.39	1.53	1.78	2.09	2.44	2.79	3.01	3.22
29	1.32	1.44	1.58	1.84	2.16	2.52	2.89	3.12	3.34
30	1.36	1.47	1.62	1.89	2.22	2.59	2.97	3.21	3.44
31	1.38	1.50	1.65	1.92	2.26	2.65	3.04	3.29	3.52
32	1.39	1.52	1.67	1.95	2.29	2.69	3.08	3.34	3.57
33	1.39	1.52	1.67	1.95	2.31	2.70	3.10	3.36	3.60
34	1.38	1.51	1.66	1.94	2.30	2.70	3.10	3.36	3.60
35	1.36	1.48	1.63	1.92	2.27	2.67	3.07	3.33	3.57
36	1.32	1.44	1.59	1.87	2.22	2.62	3.02	3.28	3.51
37	1.27	1.39	1.54	1.81	2.15	2.54	2.93	3.19	3.42
38	1.21	1.32	1.46	1.73	2.06	2.44	2.82	3.07	3.30
39	1.13	1.24	1.38	1.63	1.95	2.31	2.68	2.92	3.15
40	1.04	1.15	1.28	1.52	1.82	2.17	2.52	2.75	2.96

Table 5. Longitudinal reference percentiles for umbilico-cerebral ratio (UCR) in male fetuses

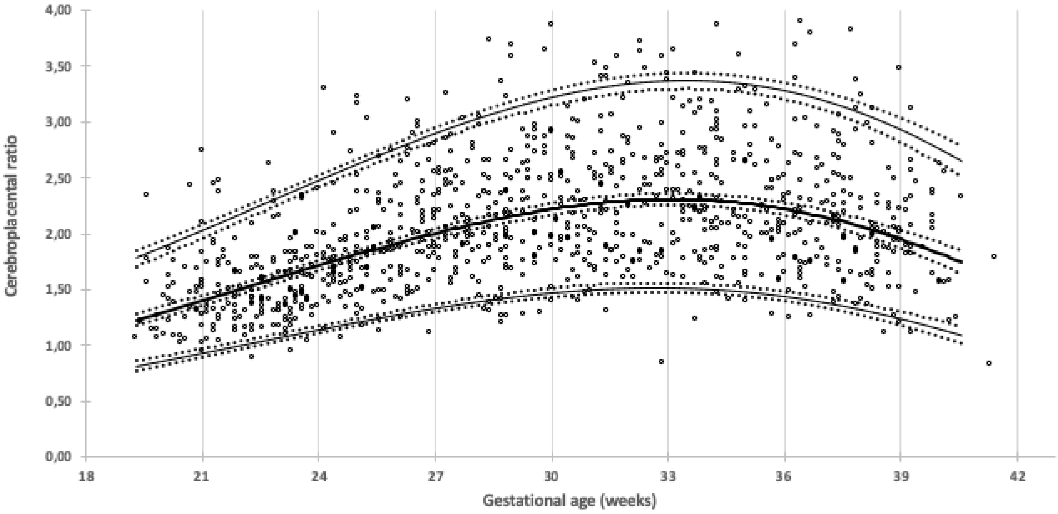
Gestation (weeks)	2.5 percentile	5 percentile	10 percentile	25 percentile	50 percentile	75 percentile	90 percentile	95 percentile	97.5 percentile
19	0.49	0.53	0.58	0.67	0.79	0.94	1.11	1.23	1.35
20	0.46	0.50	0.54	0.62	0.73	0.87	1.03	1.14	1.24
21	0.43	0.46	0.50	0.58	0.68	0.81	0.95	1.05	1.15
22	0.41	0.44	0.47	0.55	0.64	0.76	0.89	0.98	1.07
23	0.39	0.41	0.45	0.51	0.60	0.71	0.83	0.91	1.00
24	0.36	0.39	0.42	0.48	0.57	0.67	0.78	0.86	0.93
25	0.35	0.37	0.40	0.46	0.54	0.63	0.74	0.81	0.88
26	0.33	0.35	0.38	0.44	0.51	0.60	0.70	0.77	0.84
27	0.32	0.34	0.37	0.42	0.49	0.58	0.67	0.74	0.80
28	0.31	0.33	0.35	0.41	0.47	0.55	0.64	0.71	0.77
29	0.30	0.32	0.34	0.39	0.46	0.54	0.62	0.68	0.74
30	0.29	0.31	0.33	0.38	0.45	0.52	0.61	0.67	0.72
31	0.28	0.30	0.33	0.37	0.44	0.51	0.60	0.66	0.71
32	0.28	0.30	0.32	0.37	0.43	0.51	0.59	0.65	0.71
33	0.28	0.30	0.32	0.37	0.43	0.51	0.59	0.65	0.70
34	0.28	0.30	0.32	0.37	0.43	0.51	0.59	0.65	0.71
35	0.28	0.30	0.32	0.37	0.44	0.52	0.60	0.66	0.72
36	0.28	0.30	0.33	0.38	0.44	0.53	0.62	0.68	0.75
37	0.29	0.31	0.34	0.39	0.46	0.54	0.64	0.71	0.78
38	0.30	0.32	0.35	0.40	0.48	0.57	0.67	0.75	0.82
39	0.31	0.33	0.36	0.42	0.50	0.60	0.71	0.80	0.87
40	0.32	0.35	0.38	0.45	0.53	0.64	0.77	0.86	0.95

Table 6. Longitudinal reference percentiles for umbilico-cerebral ratio (UCR) in female fetuses

Gestation (weeks)	50 percentile	2.5 percentile	5 percentile	10 percentile	25 percentile	50 percentile	75 percentile	90 percentile	95 percentile	97.5 percentile
19	0.88	0.60	0.64	0.69	0.77	0.88	1.01	1.15	1.24	1.34
20	0.81	0.55	0.58	0.63	0.70	0.81	0.93	1.06	1.15	1.24
21	0.75	0.50	0.53	0.57	0.65	0.75	0.86	0.99	1.07	1.16
22	0.69	0.46	0.49	0.53	0.60	0.69	0.80	0.92	1.00	1.08
23	0.64	0.43	0.45	0.49	0.55	0.64	0.75	0.86	0.94	1.02
24	0.60	0.40	0.42	0.45	0.52	0.60	0.70	0.81	0.89	0.96
25	0.56	0.37	0.39	0.43	0.49	0.56	0.66	0.77	0.84	0.91
26	0.53	0.35	0.37	0.40	0.46	0.53	0.63	0.73	0.80	0.86
27	0.51	0.33	0.35	0.38	0.44	0.51	0.60	0.69	0.76	0.83
[illegible]	0.49	0.31	0.34	0.36	0.42	0.49	0.57	0.67	0.73	0.80
29	0.47	0.30	0.32	0.35	0.40	0.47	0.55	0.65	0.71	0.77
30	0.46	0.29	0.31	0.34	0.39	0.46	0.54	0.63	0.69	0.75
31	0.45	0.29	0.31	0.33	0.38	0.45	0.53	0.62	0.68	0.74
32	0.44	0.28	0.30	0.33	0.38	0.44	0.52	0.61	0.67	0.73
33	0.44	0.28	0.30	0.32	0.37	0.44	0.52	0.61	0.67	0.73
34	0.44	0.28	0.30	0.33	0.37	0.44	0.52	0.61	0.68	0.74
35	0.45	0.28	0.30	0.33	0.38	0.45	0.53	0.62	0.69	0.75
36	0.46	0.29	0.31	0.34	0.39	0.46	0.54	0.64	0.70	0.77
37	0.47	0.30	0.32	0.35	0.40	0.47	0.56	0.66	0.73	0.80
38	0.50	0.31	0.34	0.37	0.42	0.50	0.59	0.69	0.76	0.83
39	0.53	0.33	0.36	0.39	0.45	0.53	0.62	0.73	0.81	0.88
40	0.57	0.36	0.39	0.42	0.48	0.57	0.67	0.79	0.87	0.95

Table 7. Longitudinal reference percentiles for umbilicocerebral ratio (UCR) both sexes combined

Gestation (weeks)	2.5 percentile	5 percentile	10 percentile	25 percentile	50 percentile	75 percentile	90 percentile	95 percentile	97.5 percentile
19	0.54	0.58	0.62	0.71	0.83	0.98	1.14	1.26	1.37
20	0.50	0.53	0.58	0.66	0.77	0.91	1.05	1.16	1.26
21	0.46	0.49	0.53	0.61	0.71	0.84	0.98	1.07	1.17
22	0.43	0.46	0.50	0.57	0.66	0.78	0.91	1.00	1.08
23	0.40	0.43	0.47	0.53	0.62	0.73	0.85	0.93	1.01
24	0.38	0.40	0.44	0.50	0.58	0.69	0.80	0.87	0.95
25	0.36	0.38	0.41	0.47	0.55	0.65	0.75	0.83	0.90
26	0.34	0.36	0.39	0.45	0.52	0.61	0.71	0.78	0.85
27	0.32	0.35	0.37	0.43	0.50	0.59	0.68	0.75	0.81
28	0.31	0.33	0.36	0.41	0.48	0.56	0.66	0.72	0.78
29	0.30	0.32	0.35	0.40	0.46	0.54	0.63	0.70	0.76
30	0.29	0.31	0.34	0.39	0.45	0.53	0.62	0.68	0.74
31	0.28	0.30	0.33	0.38	0.44	0.52	0.61	0.67	0.72
32	0.28	0.30	0.32	0.37	0.44	0.51	0.60	0.66	0.72
33	0.28	0.30	0.32	0.37	0.43	0.51	0.60	0.66	0.72
34	0.28	0.30	0.32	0.37	0.44	0.51	0.60	0.66	0.72
35	0.28	0.30	0.33	0.37	0.44	0.52	0.61	0.67	0.74
36	0.28	0.31	0.33	0.38	0.45	0.53	0.63	0.69	0.76
37	0.29	0.31	0.34	0.39	0.47	0.55	0.65	0.72	0.79
38	0.30	0.33	0.35	0.41	0.49	0.58	0.68	0.76	0.83
39	0.32	0.34	0.37	0.43	0.51	0.61	0.73	0.81	0.89
40	0.34	0.36	0.40	0.46	0.55	0.66	0.78	0.87	0.96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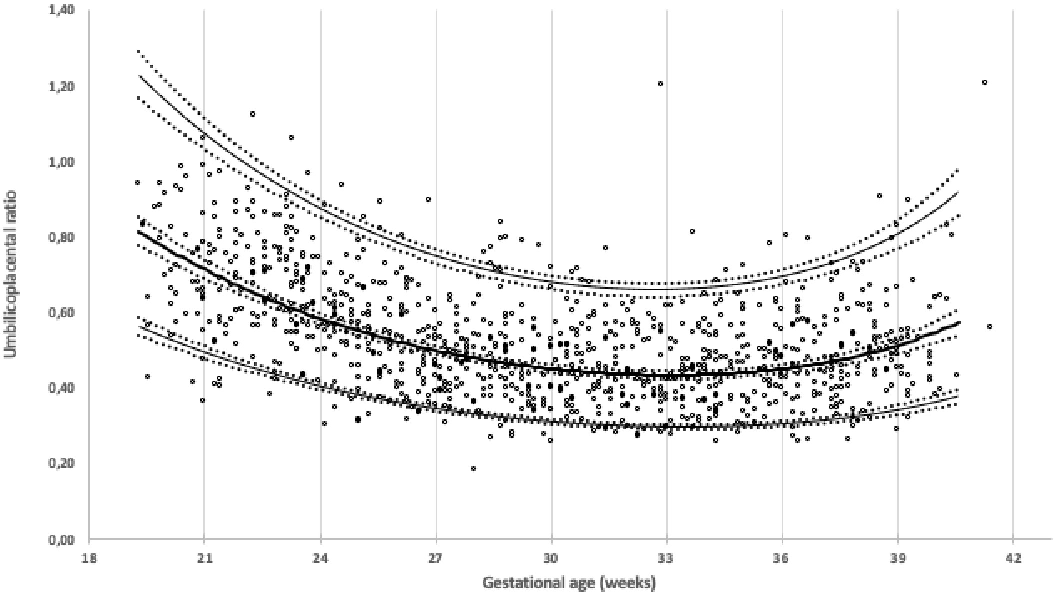
Gestational age (weeks)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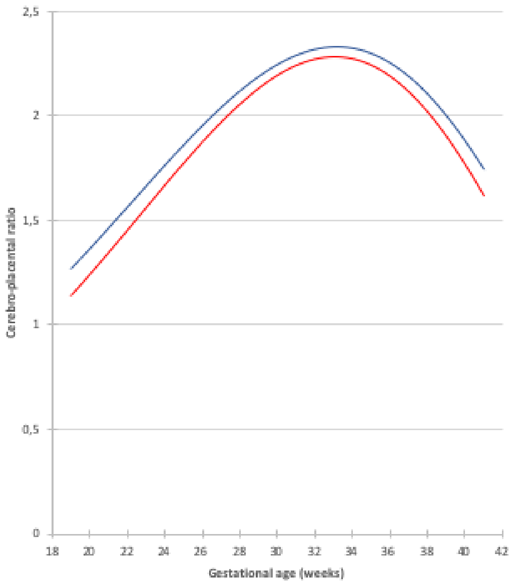
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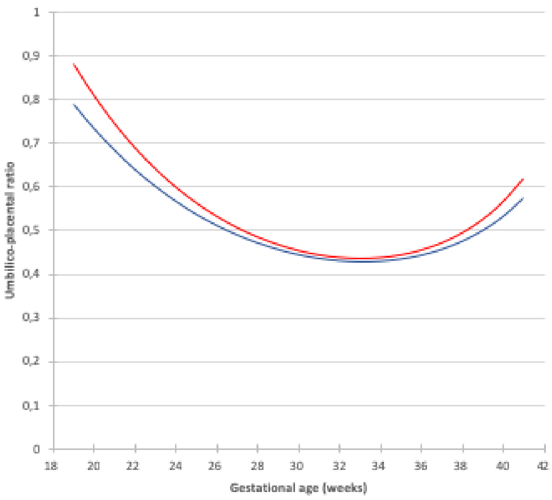
Gestational age (weeks)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Gestational age (weeks)