Received: 23 March 2020 | Revised: 24 June 2020 | Accepted: 30 June 2020

DOI: 10.1111/aogs.13950

ORIGINAL RESEARCH ARTICLE

AOGS Acta Obstetricia et Gynecologica Scandinavica

# Volume blood flow-based indices of fetal brain sparing in the second half of pregnancy: A longitudinal study

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**Funding information**
This research was supported by the Northern Norway Regional Health Authority (Grant No. SFP873/ID1646).

## Abstract

**Introduction:** Cerebroplacental ratio (CPR) and umbilicocerebral ratio (UCR) are clinically used as a measure of fetal brain sparing. These are calculated as the ratios between the pulsatility indices (PIs) of middle cerebral (MCA) and umbilical (UA) arteries, and are an indirect representation of the balance between cerebral and placental perfusion. Volume blood flow (Q)-based ratios, ie Q-CPR or Q-UCR, would directly reflect the distribution of fetal cardiac output to the placenta and brain. Thus, we aimed to determine the development pattern of Q-CPR and Q-UCR during the second half of pregnancy, construct reference intervals, and evaluate their association with CPR and UCR.

**Material and methods:** In a longitudinal cohort study of low-risk pregnancies, the inner diameter of the fetal superior vena cava (SVC) and umbilical vein (UV) was measured and velocity waveforms were obtained from the MCA, UA, UV and SVC using ultrasound at approximately 4-weekly intervals from 20 to 41 weeks. The CPR was calculated as $PI_{MCA}/PI_{UA}$ and the inverse ratio was the UCR. Cerebral and placental blood flows were estimated as the product of mean velocity and cross-sectional area of the SVC and UV, respectively. Q-CPR was calculated as $Q_{SVC}/Q_{UV}$ and the inverse as the Q-UCR. Gestational age-specific reference intervals were calculated and associations between variables were tested using multilevel regression modeling.

**Results:** Longitudinal reference intervals of Q-CPR and Q-UCR were established based on 471 paired measurements of $Q_{SVC}$ and $Q_{UV}$ obtained serially from 134 singleton pregnancies. The mean Q-CPR increased from 0.4 to 0.8 during the second half of pregnancy and Q-UCR declined from 2.5 to 1.3, while the CPR and UCR had U-shaped curves but in opposite directions. No significant correlation was found between CPR and Q-CPR (R = 0.10; $P = .051$), or UCR and Q-UCR (R = 0.09; $P = .11$), and the agreement between PI-based and Q-based indices of fetal brain sparing was poor.

**Abbreviations:** CI, confidence interval; CPR, cerebroplacental ratio; MCA, middle cerebral artery; PI, pulsatility index; Q, volume blood flow; SVC, superior vena cava; TAMxV, time-averaged maximum velocity; UA, umbilical artery; UCR, umbilicocerebral ratio; UV, umbilical vein.

**Conclusions:** Indices of fetal brain sparing based on placental and cerebral volume blood flow differ from those calculated from UA and MCA PIs. They correlated poorly with conventional CPR and UCR, indicating that they may provide additional/different physiological information. Reference values of Q-CPR and Q-UCR established here can be useful to investigate their clinical value further.

**KEYWORDS**

brain sparing, cerebroplacental ratio, Doppler, fetal cerebral blood flow, fetus, placental blood flow, superior vena cava, umbilical vein, volume blood flow

## 1 | INTRODUCTION

Fetal brain is a prioritized organ with autoregulated blood supply that maintains a steady delivery of blood, oxygen and metabolic substrates. Under hypoxemic conditions, fetuses increase blood flow to the vital organs by redistributing their cardiac output in favor of brain, heart and adrenal glands at the expense of lungs, gut and carcass.[1-4] Impedance is an important mechanism of regulating blood flow distribution. Cerebroplacental ratio (CPR) or its inverse umbilico-cerebral ratio (UCR) reflecting the relative balance between cerebral and placental impedances is increasingly used to detect fetal brain sparing. In this study, we address the blood flow distribution assuming that it will provide additional and more direct information of clinical importance.

A naturally low oxygen level in the intrauterine environment promotes cerebral perfusion. Yet, normally, the cerebral vascular impedance is higher in the fetus compared with the placental vascular impedance. In fetal growth restriction, commonly associated with reduced $pO_2$ in the umbilical vein (UV), volume blood flow (Q) to the placenta is reduced[5-9] and placental vascular impedance is increased.[10] An increase in the middle cerebral artery (MCA) time-averaged maximum velocities[11] and a decrease in carotid artery resistance index (RI) or pulsatility index (PI) in association with hypoxia, hypercapnia and acidosis have been demonstrated in human fetuses by cordocentesis.[12,13] Direct invasive measurement of Q to the human fetal brain or upper body and placenta or lower body cannot be performed due to technical and ethical constraints. Noninvasive measurements are perceived to be difficult and prone to inaccuracy, although technically shown to be possible.[9,14] Therefore, the ratios between surrogate indices of cerebral and placental vascular impedances, such as CPR or UCR, rather than the Q have been used clinically to evaluate the degree of "brain sparing" in human fetuses. However, these indices do not necessarily reflect cerebral or placental perfusion, and the ratios may be abnormal even when both umbilical artery (UA) and MCA impedances expressed as their PIs are within the normal range.[15] Use of Q-based ratios, ie Q-CPR or Q-UCR, could potentially provide more direct information about relative distribution of fetal cardiac output to the placenta and brain. However, references values for such indices are lacking and their clinical utility has not been explored.

**Key message**

Cerebral and placental volume blood flow (Q)-based indices of fetal brain sparing (Q-CPR and Q-UCR) may provide complementary physiological information on fetal circulatory distribution in addition to that obtained from conventional pulsatility-based cerebroplacental ratio (CPR) or umbilico-cerebral ratio (UCR).

Thus, our objective was to determine the development pattern of Q-CPR and Q-UCR during the second half of pregnancy, construct reference intervals, and evaluate the associations and differences between flow-based and impedance-based indices of fetal brain sparing.

## 2 | MATERIAL AND METHODS

This was part of a longitudinal cohort study of maternal and fetal hemodynamics in the second half of pregnancy. In this article, we report normative data on Q-based indices of fetal brain sparing. Data on PI-based CPR and UCR from the same study population that have been partly used in a previous report[16] are used here for comparison with Q-based ratios. In future, we plan to report Doppler velocity indices of superior vena cava (SVC), SVC volume blood flow, and proportionate distribution of fetal cardiac output to the brain/upper body and placenta from this study population. Women with low-risk singleton pregnancies attending for their routine second trimester ultrasound screening at 18-20 weeks at the University Hospital of North Norway, Tromsø, were invited to participate in the study and were enrolled during the period of February 2009 to December 2012 after obtaining written informed consent. Gestational age was confirmed by the measurement of biparietal diameter or head circumference. Inclusion criteria were: woman's age ≥18 years and gestational age ≥18 and <24 weeks at enrollment. Exclusion criteria were: history of any significant current or preexisting chronic maternal illness that is likely to have an adverse effect on the course and outcome of pregnancy, such as previous preeclampsia, chronic hypertension, diabetes

mellitus, antiphospholipid antibody syndrome, and detection of any major fetal structural or chromosomal abnormality.

The participants were evaluated at approximately 4-weekly intervals during 20-41 weeks of gestation. At each study visit, an ultrasound examination was performed by an experienced physician using a Vivid 7 Dimension ultrasound system (GE Vingmed Ultrasound AS, Horten, Norway) equipped with a 4MS sector transducer with frequencies of 1.5-4.3 MHz. A total of three obstetricians with at least 3 years of scanning experience performed fetal ultrasonography. After confirming fetal viability, blood flow velocity waveforms were obtained using pulsed-wave Doppler from the UA and umbilical vein (UV) at a free floating loop of the umbilical cord, from the MCA at its proximal end close to its origin from the circle of Willis, and from the SVC close to its entrance to the right atrium just behind the ascending aorta as previously described.[17-20] The Doppler insonation angle was kept close to zero and always below 30 degrees. Angle correction was used when the angle was not zero. The Doppler gate was adjusted liberally to ensure sampling of the maximum velocities from a relatively large area of the vessel depending on its size and gestational age of the fetus. Blood flow velocity waveforms were recorded approximately over six cardiac cycles. Temporal maximum blood velocity waveforms were traced automatically using the software available in the ultrasound machine. The UA and MCA velocities were measured, and their PIs were calculated as: PI = (peak systolic velocity − end-diastolic velocity)/time-averaged maximum velocity (TAMxV) over a cardiac cycle. The average value of three to six consecutive cardiac cycles was recorded.

The inner diameters of the UV and SVC were measured using two-dimensional ultrasonography in an insonation perpendicular to the vessel. The UV was measured at a free-floating loop of the umbilical cord and the SVC was measured at its inlet to the right atrium in a long axis view. The largest diameter during cardiac cycle was measured in a magnified image and an average of three measurements was recorded. Volume blood flow (Q) was calculated as the product of mean spatial velocity and cross-sectional area (CSA) of the respective blood vessels. CSA, $cm^2$ = 3.14*(vessel diameter, cm/2)$^2$. Umbilical vein volume blood flow ($Q_{UV}$) that represents placental blood flow was calculated as: $Q_{UV}$, ml/min = 0.5 * UV TAMxV, cm/s * UV CSA, cm * 60 assuming a parabolic spatial velocity profile of the UV blood flow.[18]

The SVC volume blood flow ($Q_{SVC}$) that represents the cerebral blood flow was calculated as: $Q_{SVC}$, ml/min = 0.7 * SVC TAMxV, cm/s * SVC CSA, cm * 60 assuming a blunted spatial velocity profile of the SVC blood flow.[20] The reproducibility of $Q_{uv}$ was previously reported.[18] The reproducibility of $Q_{SVC}$ was assessed using 413 paired measurements to calculate the intraobserver coefficient of variation (CV) and intraclass correlation coefficient (ICC).

Volume blood flow-based cerebroplacental ratio (Q-CPR) was calculated as Q-CPR = $Q_{SVC}/Q_{UV}$. The flow-based umbilicocerebral ratio (Q-UCR) was calculated as $Q_{UV}/Q_{SVC}$.

Impedance-based CPR was calculated as CPR = $PI_{MCA}/PI_{UA}$. The impedance-based UCR was calculated as $PI_{UA}/PI_{MCA}$.

The course of pregnancy was followed prospectively and complications arising during the antenatal period were recorded and managed according to local guidelines. The outcome of pregnancy including information on the mode of delivery, gestational age at birth and condition of the neonate was obtained from the electronic medical records.

## 2.1 | Statistical analyses

Sample size was calculated assuming that 15 measurements per gestational week (a total of 300 pregnancies/fetuses), would be adequate to construct gestational age-specific reference intervals covering a period between 20 and 40 weeks, using a cross-sectional design.[21] The corresponding number of pregnancies required to establish reference ranges using a longitudinal design was calculated to be 300/2.3 (130 fetuses), where 2.3 is the design factor as suggested by Royston and Altman.[22] Thus, we aimed to recruit approximately 140 pregnant women in our study to compensate for inability to obtain measurements, possible dropouts and loss of follow-up.

Data were analyzed using IBM SPSS Statistics for Windows, Version 24.0. (IBM Corp., Armonk, NY, USA) and MATLAB R2019a (Matworks, Inc., Natick, MA, USA). Data distribution was checked and logarithmic or power transformations were performed to achieve best possible normal distribution using Box-Cox method. The Box-Cox transformation lambda values (λ) were calculated for each dependent variable and rounded to the nearest integer, which was close to zero. Based on this value, all the dependent variables were $\log_{10}$-transformed. The best fit for the fractional polynomials was chosen from a list of 44 regression models based on $R^2$ value to construct gestational age-specific mean curves of the CPR, Q-CPR, UCR and Q-UCR. Multilevel modeling was used to calculate the mean and percentiles for each gestational week accounting for the longitudinal design of the study, considering the variance between measurements within the same fetus as the first level and the variance between participating pregnant women as the second level. Association between CPR and Q-CPR and UCR and Q-UCR was tested using the mean vector for each variable from the mixed models. A $P$ value <.05 was considered significant. The agreement between CPR and Q-CPR and between UCR and Q-UCR was evaluated using Bland-Altman analysis, taking into consideration the repeated measures design of the study.[23]

## 2.2 | Ethics approval

The study was approved by the Regional Committee for Medical and Health Research Ethics – North Norway (REK Nord 105/2008, date of approval: December 16, 2008) and an informed written consent was obtained from each participant.

# 3 | RESULTS

Of 142 pregnant women enrolled, one woman was excluded because she was lost to follow-up and no data on delivery and birth

outcome were available. The SVC Doppler was not recorded in seven women. Thus, data from a total of 134 pregnancies were included in the final statistical analysis. The baseline demographic and clinical characteristics of these women and data on their birth outcomes are presented in Table 1.

Four (3%) women developed preeclampsia and one developed gestational diabetes. Labor was induced in 17 (12.7%), and 116 women (86.6%) had a spontaneous vaginal delivery. One (0.7%) woman had vacuum delivery and 17 (12.7%) were delivered by cesarean section. There were five (3.7%) preterm deliveries, of which one was a spontaneous vaginal delivery at $33^{+3}$ weeks and another was an emergency cesarean section due to placental abruption at $32^{+4}$ weeks of gestation.

All babies were liveborn and there were no perinatal deaths; however, five (3.7%) of them required admission to the neonatal intensive care unit. The one baby who was delivered due to fetal distress associated with placental abruption, had intraventricular bleeding leading to hydrocephalus requiring ventriculoperitoneal shunting. All other neonates were discharged from the hospital in good condition.

For $Q_{UV}$, the intraobserver CV was 13.0% (95% confidence interval [CI 8.0-16.5] and ICC was 0.74 (95% CI 0.42 −0.90) as reported previously.[18] For $Q_{SVC}$, intraobserver CV was 12.7% (95% CI 11.5-13.8) and ICC 0.98 (95% CI 0.97-0.98).

Gestational age-specific longitudinal reference values for Q-CPR and Q-UCR (based on 471 paired measurements of $Q_{SVC}$ and $Q_{UV}$) and CPR and UCR (based on 385 paired measurements of MCA PI and UA PI) with corresponding 2.5th, 5th, 10th, 50th, 90th, 95th and 97.5th percentiles are presented in Tables 2-5. The number of observations per gestational week, means and standard deviations (SD) for each of these variables are presented in Table 6. The reference charts for the CPR and Q-CPR and UCR and Q-UCR with fitted mean and 5th and 95th percentiles with corresponding 95% confidence limits are shown side- by-side in Figure 1A-D.

The mean for Q-based index of fetal brain sparing, Q-CPR, increased from 0.4 to 0.8, and conversely, the mean for Q-UCR decreased from 2.5 to 1.3 during the second half of pregnancy (Tables 3 and 5, Figure 1). Conventional impedance-based CPR and UCR were significantly associated with gestational age ($P < .001$), with CPR showing an inverted U-shaped development and UCR a U-shaped development during 20-40 weeks of gestation (Tables 2 and 4, Figure 1).

We found no linear correlations between CPR and Q-CPR (R = 0.10; $P = .051$) or UCR and Q-UCR (R = 0.09; $P = 0.110$), and Bland-Altman analysis showed poor agreement between PI-based and Q-based indices of fetal brain sparing (Figure 2A-F). Gestational age had a considerable impact on the relation between PI- and Q-based CPR and UCR (Figure 2B,E).

## 4 | DISCUSSION

Here we introduce blood flow-based indices, Q-CPR and Q-UCR, as an addition to the already existing PI-based CPR and UCR for the clinical assessment of fetal brain sparing, and provide gestational age-specific longitudinal reference ranges (Tables 3 and 5). We show that the flow ratios of SVC and UV are not directly correlated to the conventional PI-based CPR or UCR (Figure 2) and therefore may provide additional physiological information. One might argue that this lack of correlation could be due to the fact that the $Q_{SVC}$ represents venous return not only from the fetal brain, but also the upper body. However, serial measurements showed that Q-CPR and Q-UCR developed differently during pregnancy compared with PI-based CPR and UCR.

The conventional CPR and UCR are indices based on blood velocity waveforms that are composite reflections of downstream cerebral and placental vascular impedances. These ratios have been used as a surrogate for relative blood flow distribution, since flow is dependent on impedance, but their relation is not linear

**TABLE 1** Baseline characteristics of the study participants and their birth outcomes

| Variable | n | Median (range), mean (SD) or n (%) |
|---|---|---|
| Maternal age (years) | 134 | 30 (19-39) |
| Maternal weight at booking (kg) | 128 | 67 (11.58) |
| Maternal height (cm) | 131 | 167 (0.05) |
| Body mass index (kg/cm$^2$) | 128 | 23.90 (3.80) |
| Nullipara | 134 | 61 (45.5%) |
| Gestational age at birth (days) | 134 | 281 (234-297) |
| Birthweight of the neonate (g) | 134 | 3600 (2251-4636) |
| Length of the neonate (cm) | 130 | 50 (44-55) |
| Ponderal index of the neonate | 130 | 28.1 (2.5) |
| Sex of the neonate (boy/girl) | 134 | 74 (55%)/60 (45%) |
| Apgar score <7 at 1 min | 134 | 6 (2.2%) |
| Apgar score < 7 at 5 min | 134 | 2 (1.4%) |
| Placental weight (g) | 128 | 621 (124.3) |

**TABLE 2** Percentiles of impedance-based cerebroplacental ratio (CPR) at 20-40 weeks of gestational age (GA)

| | Percentile | | | | | | |
|---|---|---|---|---|---|---|---|
| GA (weeks) | 2.5th | 5th | 10th | 50th | 90th | 95th | 97.5th |
| 20 | 0.79 | 0.85 | 0.92 | 1.23 | 1.64 | 1.77 | 1.90 |
| 21 | 0.86 | 0.92 | 1.00 | 1.34 | 1.79 | 1.94 | 2.09 |
| 22 | 0.92 | 0.99 | 1.08 | 1.45 | 1.95 | 2.12 | 2.28 |
| 23 | 0.99 | 1.06 | 1.15 | 1.56 | 2.10 | 2.29 | 2.46 |
| 24 | 1.04 | 1.13 | 1.23 | 1.66 | 2.25 | 2.46 | 2.65 |
| 25 | 1.10 | 1.19 | 1.29 | 1.76 | 2.40 | 2.62 | 2.83 |
| 26 | 1.15 | 1.24 | 1.36 | 1.85 | 2.54 | 2.77 | 2.99 |
| 27 | 1.19 | 1.29 | 1.41 | 1.94 | 2.66 | 2.92 | 3.15 |
| 28 | 1.23 | 1.33 | 1.46 | 2.01 | 2.78 | 3.04 | 3.30 |
| 29 | 1.26 | 1.36 | 1.50 | 2.07 | 2.88 | 3.16 | 3.42 |
| 30 | 1.28 | 1.39 | 1.52 | 2.12 | 2.96 | 3.25 | 3.53 |
| 31 | 1.29 | 1.40 | 1.54 | 2.16 | 3.02 | 3.32 | 3.61 |
| 32 | 1.29 | 1.41 | 1.55 | 2.18 | 3.06 | 3.37 | 3.67 |
| 33 | 1.29 | 1.40 | 1.55 | 2.18 | 3.09 | 3.40 | 3.70 |
| 34 | 1.27 | 1.39 | 1.53 | 2.17 | 3.09 | 3.41 | 3.71 |
| 35 | 1.25 | 1.36 | 1.51 | 2.15 | 3.06 | 3.39 | 3.70 |
| 36 | 1.22 | 1.33 | 1.47 | 2.11 | 3.02 | 3.35 | 3.65 |
| 37 | 1.18 | 1.29 | 1.43 | 2.06 | 2.96 | 3.28 | 3.59 |
| 38 | 1.13 | 1.24 | 1.38 | 1.99 | 2.88 | 3.19 | 3.50 |
| 39 | 1.08 | 1.19 | 1.32 | 1.92 | 2.78 | 3.09 | 3.39 |
| 40 | 1.03 | 1.13 | 1.25 | 1.83 | 2.67 | 2.97 | 3.25 |

**TABLE 3** Percentiles of volume blood flow-based cerebroplacental ratio (Q-CPR) at 20-40 weeks of gestational age (GA)

| | Percentile | | | | | | |
|---|---|---|---|---|---|---|---|
| GA (weeks) | 2.5th | 5th | 10th | 50th | 90th | 95th | 97.5th |
| 20 | 0.16 | 0.19 | 0.22 | 0.40 | 0.73 | 0.86 | 0.99 |
| 21 | 0.16 | 0.19 | 0.22 | 0.40 | 0.73 | 0.87 | 1.01 |
| 22 | 0.16 | 0.19 | 0.22 | 0.41 | 0.74 | 0.88 | 1.02 |
| 23 | 0.16 | 0.19 | 0.23 | 0.41 | 0.76 | 0.90 | 1.04 |
| 24 | 0.17 | 0.19 | 0.23 | 0.42 | 0.77 | 0.92 | 1.06 |
| 25 | 0.17 | 0.20 | 0.23 | 0.43 | 0.79 | 0.94 | 1.09 |
| 26 | 0.17 | 0.20 | 0.24 | 0.44 | 0.81 | 0.96 | 1.12 |
| 27 | 0.17 | 0.20 | 0.24 | 0.45 | 0.83 | 0.99 | 1.15 |
| 28 | 0.18 | 0.21 | 0.25 | 0.46 | 0.85 | 1.02 | 1.19 |
| 29 | 0.18 | 0.21 | 0.25 | 0.47 | 0.88 | 1.05 | 1.23 |
| 30 | 0.19 | 0.22 | 0.26 | 0.49 | 0.91 | 1.09 | 1.28 |
| 31 | 0.19 | 0.22 | 0.27 | 0.50 | 0.95 | 1.14 | 1.33 |
| 32 | 0.20 | 0.23 | 0.27 | 0.52 | 0.99 | 1.18 | 1.39 |
| 33 | 0.20 | 0.24 | 0.28 | 0.54 | 1.03 | 1.24 | 1.45 |
| 34 | 0.21 | 0.25 | 0.29 | 0.56 | 1.08 | 1.30 | 1.52 |
| 35 | 0.22 | 0.26 | 0.31 | 0.59 | 1.13 | 1.36 | 1.60 |
| 36 | 0.23 | 0.27 | 0.32 | 0.62 | 1.19 | 1.43 | 1.68 |
| 37 | 0.24 | 0.28 | 0.33 | 0.65 | 1.25 | 1.51 | 1.78 |
| 38 | 0.25 | 0.29 | 0.35 | 0.68 | 1.33 | 1.60 | 1.88 |
| 39 | 0.26 | 0.31 | 0.37 | 0.72 | 1.40 | 1.70 | 2.00 |
| 40 | 0.27 | 0.32 | 0.39 | 0.76 | 1.49 | 1.81 | 2.13 |

**TABLE 4** Percentiles of impedance-based umbilicocerebral ratio (UCR) at 20-40 weeks of gestational age (GA)

| | Percentile | | | | | | |
|---|---|---|---|---|---|---|---|
| GA (weeks) | 2.5th | 5th | 10th | 50th | 90th | 95th | 97.5th |
| 20 | 0.53 | 0.56 | 0.61 | 0.81 | 1.09 | 1.18 | 1.26 |
| 21 | 0.48 | 0.51 | 0.56 | 0.75 | 1.00 | 1.09 | 1.17 |
| 22 | 0.44 | 0.47 | 0.51 | 0.69 | 0.93 | 1.01 | 1.08 |
| 23 | 0.41 | 0.44 | 0.47 | 0.64 | 0.87 | 0.94 | 1.02 |
| 24 | 0.38 | 0.41 | 0.44 | 0.60 | 0.82 | 0.89 | 0.96 |
| 25 | 0.35 | 0.38 | 0.42 | 0.57 | 0.77 | 0.84 | 0.91 |
| 26 | 0.33 | 0.36 | 0.39 | 0.54 | 0.74 | 0.81 | 0.87 |
| 27 | 0.32 | 0.34 | 0.37 | 0.51 | 0.71 | 0.77 | 0.84 |
| 28 | 0.30 | 0.33 | 0.36 | 0.50 | 0.69 | 0.75 | 0.81 |
| 29 | 0.29 | 0.32 | 0.35 | 0.48 | 0.67 | 0.73 | 0.79 |
| 30 | 0.28 | 0.31 | 0.34 | 0.47 | 0.66 | 0.72 | 0.78 |
| 31 | 0.28 | 0.30 | 0.33 | 0.46 | 0.65 | 0.71 | 0.77 |
| 32 | 0.27 | 0.30 | 0.33 | 0.46 | 0.64 | 0.71 | 0.77 |
| 33 | 0.27 | 0.29 | 0.32 | 0.46 | 0.65 | 0.71 | 0.78 |
| 34 | 0.27 | 0.29 | 0.32 | 0.46 | 0.65 | 0.72 | 0.78 |
| 35 | 0.27 | 0.29 | 0.33 | 0.46 | 0.66 | 0.73 | 0.80 |
| 36 | 0.27 | 0.30 | 0.33 | 0.47 | 0.68 | 0.75 | 0.82 |
| 37 | 0.28 | 0.30 | 0.34 | 0.49 | 0.70 | 0.78 | 0.85 |
| 38 | 0.29 | 0.31 | 0.35 | 0.50 | 0.73 | 0.81 | 0.88 |
| 39 | 0.30 | 0.32 | 0.36 | 0.52 | 0.76 | 0.84 | 0.93 |
| 40 | 0.31 | 0.34 | 0.38 | 0.55 | 0.80 | 0.89 | 0.98 |

**TABLE 5** Percentiles of volume blood flow-based umbilicocerebral ratio (Q-UCR) at 20-40 weeks of gestational age (GA)

| | Percentile | | | | | | |
|---|---|---|---|---|---|---|---|
| GA (weeks) | 2.5th | 5th | 10th | 50th | 90th | 95th | 97.5th |
| 20 | 1.01 | 1.17 | 1.38 | 2.49 | 4.50 | 5.31 | 6.15 |
| 21 | 0.99 | 1.15 | 1.36 | 2.47 | 4.48 | 5.30 | 6.14 |
| 22 | 0.98 | 1.13 | 1.34 | 2.45 | 4.45 | 5.28 | 6.12 |
| 23 | 0.96 | 1.11 | 1.32 | 2.42 | 4.42 | 5.24 | 6.08 |
| 24 | 0.94 | 1.09 | 1.30 | 2.38 | 4.37 | 5.19 | 6.02 |
| 25 | 0.92 | 1.07 | 1.27 | 2.34 | 4.31 | 5.12 | 5.95 |
| 26 | 0.89 | 1.04 | 1.24 | 2.29 | 4.24 | 5.05 | 5.87 |
| 27 | 0.87 | 1.01 | 1.20 | 2.24 | 4.16 | 4.96 | 5.77 |
| 28 | 0.84 | 0.98 | 1.17 | 2.18 | 4.07 | 4.86 | 5.66 |
| 29 | 0.81 | 0.95 | 1.13 | 2.12 | 3.97 | 4.75 | 5.54 |
| 30 | 0.78 | 0.91 | 1.09 | 2.06 | 3.87 | 4.63 | 5.41 |
| 31 | 0.75 | 0.88 | 1.05 | 1.99 | 3.76 | 4.50 | 5.26 |
| 32 | 0.72 | 0.84 | 1.01 | 1.92 | 3.64 | 4.36 | 5.11 |
| 33 | 0.69 | 0.81 | 0.97 | 1.85 | 3.52 | 4.22 | 4.95 |
| 34 | 0.66 | 0.77 | 0.93 | 1.77 | 3.39 | 4.07 | 4.78 |
| 35 | 0.63 | 0.74 | 0.88 | 1.70 | 3.26 | 3.92 | 4.60 |
| 36 | 0.59 | 0.70 | 0.84 | 1.62 | 3.12 | 3.76 | 4.42 |
| 37 | 0.56 | 0.66 | 0.80 | 1.54 | 2.99 | 3.60 | 4.24 |
| 38 | 0.53 | 0.63 | 0.75 | 1.47 | 2.85 | 3.44 | 4.05 |
| 39 | 0.50 | 0.59 | 0.71 | 1.39 | 2.71 | 3.27 | 3.86 |
| 40 | 0.47 | 0.55 | 0.67 | 1.31 | 2.57 | 3.11 | 3.67 |

**TABLE 6** Number of observations per gestational week (n), means and standard deviations (SD) of the pulsatility index (PI) based indices, cerebroplacental ratio (CPR) and umbilicocerebral ratio(UCR]), and volume blood flow (Q) based indices, (Q-CPR and Q-UCR) of fetal brain sparing during the second half of pregnancy

| Gestation (weeks) | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CPR | | | | | | | | | | | | | | | | | | | | | |
| n | 12 | 25 | 19 | 29 | 13 | 25 | 22 | 24 | 22 | 15 | 28 | 22 | 13 | 17 | 19 | 21 | 14 | 13 | 18 | 11 | 3 |
| mean | 1.440 | 1.434 | 1.531 | 1.519 | 1.719 | 1.832 | 1.990 | 2.086 | 2.104 | 2.508 | 2.095 | 2.245 | 2.368 | 2.278 | 2.141 | 2.206 | 2.162 | 2.226 | 1.994 | 2.169 | 1.448 |
| SD | 0.356 | 0.402 | 0.429 | 0.313 | 0.418 | 0.522 | 0.560 | 0.313 | 0.544 | 0.791 | 0.454 | 0.588 | 0.831 | 0.607 | 0.527 | 0.511 | 0.718 | 0.794 | 0.571 | 0.739 | 0.206 |
| Q-CPR | | | | | | | | | | | | | | | | | | | | | |
| n | 17 | 30 | 27 | 31 | 17 | 28 | 28 | 25 | 25 | 21 | 34 | 24 | 16 | 24 | 25 | 24 | 15 | 19 | 22 | 17 | 2 |
| mean | 0.566 | 0.501 | 0.380 | 0.460 | 0.454 | 0.480 | 0.440 | 0.475 | 0.478 | 0.420 | 0.668 | 0.604 | 0.605 | 0.555 | 0.824 | 0.742 | 0.670 | 0.589 | 0.898 | 0.766 | 0.356 |
| SD | 0.352 | 0.229 | 0.193 | 0.243 | 0.281 | 0.188 | 0.202 | 0.145 | 0.237 | 0.185 | 0.301 | 0.289 | 0.219 | 0.275 | 0.364 | 0.399 | 0.456 | 0.306 | 0.448 | 0.319 | 0.256 |
| UCR | | | | | | | | | | | | | | | | | | | | | |
| n | 12 | 25 | 19 | 29 | 13 | 25 | 22 | 24 | 22 | 15 | 28 | 22 | 13 | 17 | 19 | 21 | 14 | 13 | 18 | 11 | 3 |
| mean | 0.725 | 0.742 | 0.697 | 0.684 | 0.610 | 0.582 | 0.542 | 0.489 | 0.506 | 0.445 | 0.500 | 0.475 | 0.491 | 0.471 | 0.493 | 0.476 | 0.496 | 0.500 | 0.541 | 0.519 | 0.701 |
| SD | 0.141 | 0.174 | 0.174 | 0.136 | 0.135 | 0.141 | 0.151 | 0.072 | 0.131 | 0.167 | 0.110 | 0.124 | 0.242 | 0.133 | 0.113 | 0.104 | 0.113 | 0.161 | 0.157 | 0.198 | 0.109 |
| Q-UCR | | | | | | | | | | | | | | | | | | | | | |
| n | 17 | 30 | 27 | 31 | 17 | 28 | 28 | 25 | 25 | 21 | 34 | 24 | 16 | 24 | 25 | 24 | 15 | 19 | 22 | 17 | 2 |
| mean | 2.347 | 2.469 | 3.377 | 2.959 | 2.641 | 2.373 | 2.811 | 2.342 | 2.603 | 2.824 | 1.815 | 2.460 | 1.946 | 2.202 | 1.449 | 1.735 | 1.972 | 2.174 | 1.386 | 1.576 | 3.797 |
| SD | 1.268 | 1.217 | 2.093 | 2.000 | 0.980 | 0.870 | 1.364 | 0.868 | 1.197 | 1.169 | 0.869 | 2.161 | 0.967 | 0.957 | 0.621 | 0.882 | 0.967 | 1.199 | 0.671 | 0.755 | 2.735 |

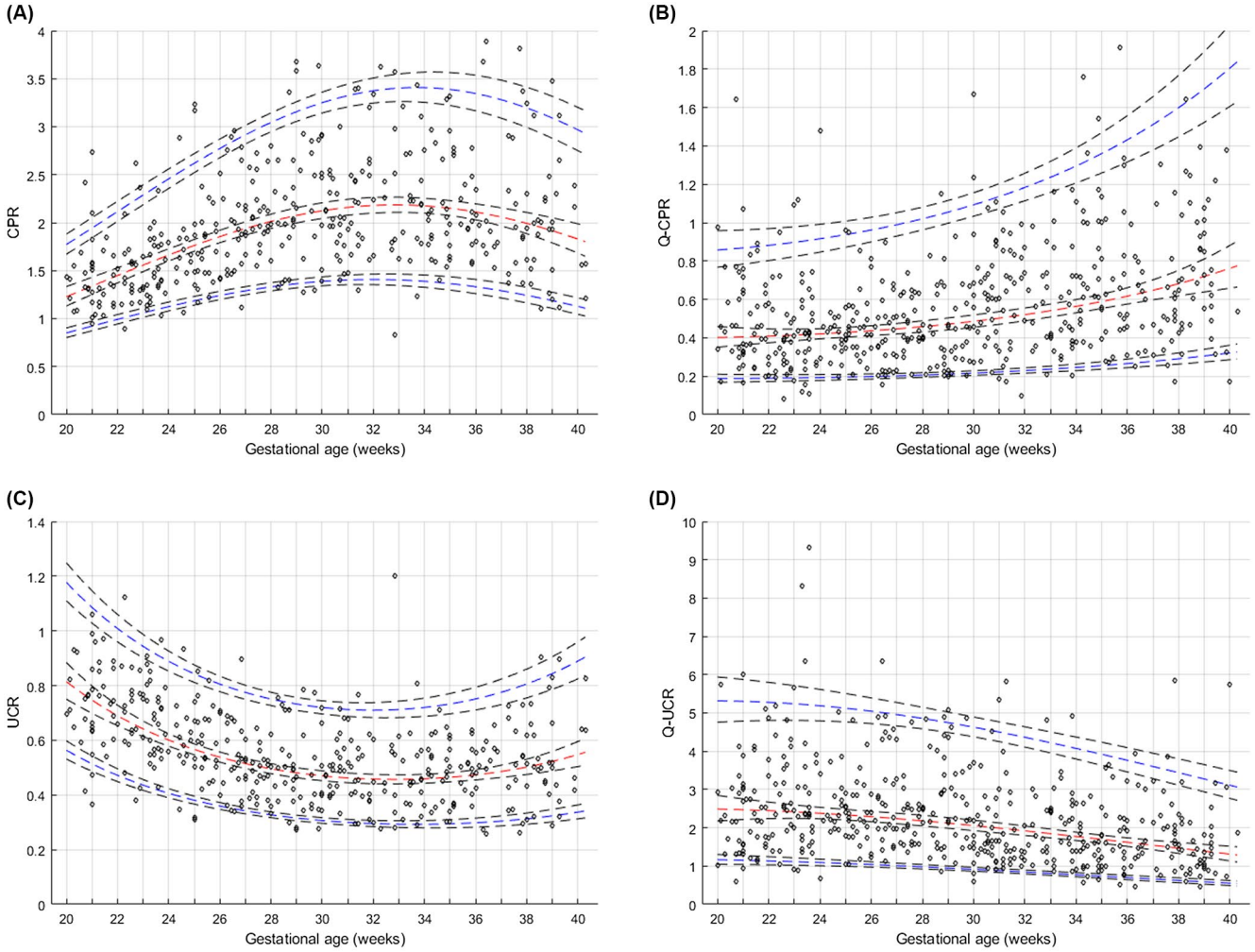


**FIGURE 1** Gestational age-specific reference intervals for (A) pulsatility index (PI)-based cerebroplacental ratio (CPR), (B) volume blood flow (Q)-based cerebroplacental ratio (Q-CPR), (C) PI-based umbilicocerebral ratio (UCR) and (D) Q-based umbilicocerebral ratio (Q-UCR) from 20-40 weeks. The dotted black lines represent the 95% confidence intervals for the 5th, 50th and 95th percentiles [Color figure can be viewed at wileyonlinelibrary.com]

(Figure 2) and has been shown to be logarithmic at best.[10] With gestation, differential organ growth, nutritional demands, vascular growth, endocrine regulation and placental capacity develop differently, which is reflected in increasing blood pressure and the relative changes of impedance and blood flow that support this development. This is particularly well demonstrated in the relation between CPR and Q-CRP (or UCR and Q-UCR) in Figure 2(B,E), where their relation is profoundly impacted by advancing gestational age. Therefore, the measurement of cerebral and placental blood flows, as done in this study, can be expected to provide additional and different information on the distributional perfusion compared with the conventional PI-based CPR alone. We believe that both the PI-based and Q-based indices of fetal brain sparing have their merits, as they are likely to provide complementary information, that is, if the technical challenges of measuring Q can be controlled.

Under physiological conditions, cerebral blood flow is relatively stable. Autoregulation occurs over a range of blood pressures[24] and is regulated mainly by $pO_2$ levels.[25,26] Relatively low oxygen tension and higher $pCO_2$ of the fetal blood facilitates cerebral blood flow by reducing cerebral vascular impedance.[27] However, the cerebral vascular impedance is normally higher than the placental vascular or peripheral vascular impedance, which is reflected in higher MCA or carotid artery PI than UA PI or descending aorta PI. Clinically, fetal brain sparing is diagnosed when this normal relation between cerebral and placental vascular impedances is reversed.

Previous studies have calculated CPR using either the ratio between carotid artery PI and descending aorta PI[13] carotid artery RI and UA RI,[12] MCA RI and UA RI[28] or MCA PI and UA PI.[19,29,30] An inverse ratio, UCR, has also been suggested.[31,32] However, the superiority of one ratio over another has not been proven. We provide longitudinal reference values for both Q-CPR and Q-UCR alongside the reference values for CPR and UCR that could be used for serial monitoring.

Blood flow-based indices, Q-CPR or Q-UCR, could theoretically better reflect cerebral perfusion by providing more physiological

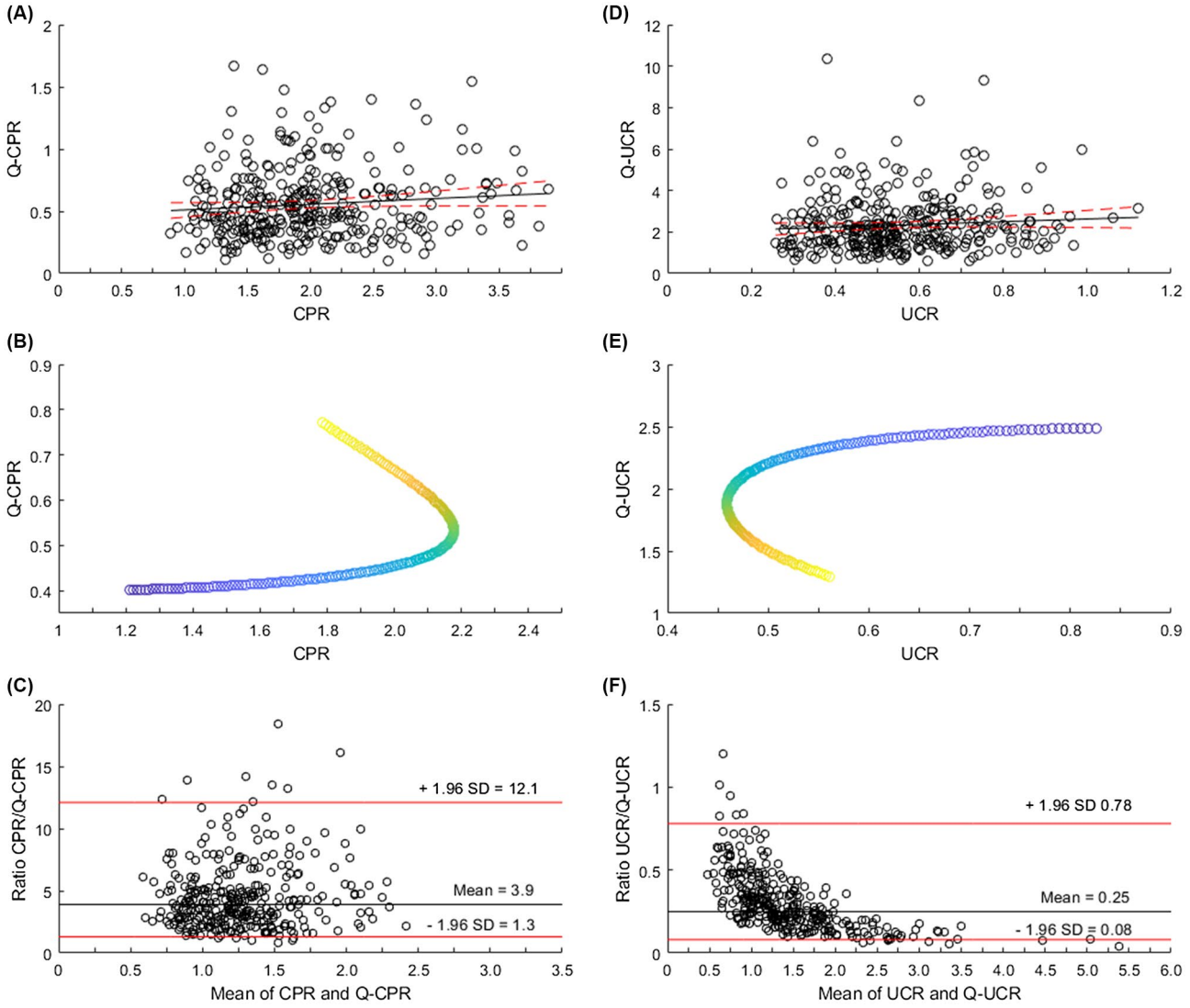


**FIGURE 2** Correlation between pulsatility index (PI)-based cerebroplacental ratio (CPR) and volume blood flow (Q)-based cerebroplacental ratio (Q-CPR) presented as a scatter plot of individual measurements with a linear regression line (solid line) and corresponding 95% confidence intervals (dotted lines) (A) and as a plot of their corresponding mean values, with the colors dark blue to yellow signifying gestational age increasing from 20 to 40 weeks (B), and Bland-Altman plot of CPR/Q-CPR vs mean of CPR and Q-CPR (C). Corresponding graphs are presented for the inverse parameters, PI-based umbilico-cerebral ratio (UCR) and flow-based Q-UCR (D-F) [Color figure can be viewed at wileyonlinelibrary.com]

information and might be more accurate in diagnosing fetal brain sparing. Furthermore, as the impedance-based and blood flow-based indices of brain sparing did not correlate with each other, measuring both could provide complementary information to improve and refine the diagnostic ability of Doppler ultrasonography.

Several studies have reported the utility of PI-based CPR and UCR in predicting pregnancy outcomes,[15,31-33] although their ability to identify fetuses at risk of adverse perinatal outcome and preventing perinatal death has not been confirmed.[34,35] The present longitudinal reference values for Q-based indices, Q-CPR and Q-UCR, which reflect directly the distribution of blood flow to the fetal brain and placenta, merit clinical evaluation and comparison with the current use of CRP and UCR in the serial monitoring of fetal circulatory adaptation in risk pregnancies.

Major strengths of our study are its physiological foundation, its prospective longitudinal design and sufficiently large sample size, which allowed the construction of reference intervals with adequate precision. However, technical difficulties, the level of expertise required and the possibility of errors associated with blood flow measurements could be considered limitations to the clinical use of Q-CPR or Q-UCR. Measurement of UV diameter and $Q_{UV}$ has been experimentally validated[36,37] but no such validation has been done for $Q_{SVC}$. Although several sources of error have been described,[38] errors in Q measurement mainly result from the inaccuracies in measurement of vessel diameter, from which the CSA is generally computed, as squaring the diameter in the formula used to calculate the CSA, squares the error as well. Accuracy of diameter measurement depends on the spatial resolution of the ultrasound system.

A typical ultrasound transducer with a frequency of 5 MHz has an axial resolution of 0.3 mm, and for vessels with a diameter of 10 mm, 5 mm or 3 mm, the associated error in the calculation of CSA and resulting Q can be expected to be approximately 6%, 12% and 20%, respectively.[39]

On the other hand, the physiological information provided by Q-based indices regarding the relative distribution of fetal cardiac output could be important to consider when making crucial management decisions. Technical challenges could be overcome by adequate training in ultrasonography to acquire appropriate skills in venous blood flow measurement technique. By meticulously adhering to a standardized methodology (eg insonation techniques and repeat measurements), volume flow measurements have been reproduced across operators, ultrasound equipments, and sites. If this is not done, differences may be substantial.

When using impedance-based references, a fixed CPR cut-off value has been suggested to diagnose brain sparing,[15] which may be less appropriate considering that these indices change significantly with gestational age.[19,28-30] Although Q-CPR and Q-UCR seem to vary less with gestation, we recommended the use of gestational age-specific reference ranges to utilize fully the diagnostic potential of these indices.

## 5 | CONCLUSION

Indices of fetal brain sparing based on placental and cerebral volume blood flow (Q-CPR and Q-UCR) are different from those based on UA and MCA PIs, and we have established their longitudinal references ranges for the second half of pregnancy. They represent a more direct assessment of blood flow distribution to the placenta and fetal brain, whereas the ratios between MCA and UA PI, which are based on blood velocity waveforms, basically reflect downstream impedance. These two types of ratios, reflecting volume flow and impedance, respectively, could be complementary and deserve clinical testing to clarify their merit in obstetric care.

### ACKNOWLEDGMENTS

We thank Bodil Hvingel and Norbert Szunyogh for their help with ultrasonography, and Åse Vårtun for her help with the recruitment of the study participants.

### CONFLICT OF INTEREST

None.

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**How to cite this article:** Stefopoulou M, Johnson J, Wilsgaard T, et al. Volume blood flow-based indices of fetal brain sparing in the second half of pregnancy: A longitudinal study. *Acta Obstet Gynecol Scand*. 2020;99:1717–1727. https://doi.org/10.1111/aogs.13950