Counter Opinion

Ratio of umbilical and cerebral artery pulsatility indices in assessment of fetal risk: numerator and denominator matter

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Kalafat and Khalil make a case for preferring the cerebroplacental ratio (CPR) over the umbilicocerebral ratio (UCR)[1]. CPR was first described by Arbeille *et al.*[2] and UCR by Arduini *et al.*[3], both in 1987. It is true that, in recent years, nearly all studies have used the CPR, though it is unclear why CPR gained dominance over UCR as, to our knowledge, no study has compared the two parameters head-to-head. In our opinion, one ratio cannot be considered simply the inverse of the other.

The only prospective study that has assessed whether UCR or CPR might be more appropriate for clinical use is a secondary analysis of the TRUFFLE (Trial of Randomized Umbilical and Fetal FLow in Europe) study[4]. The TRUFFLE study randomized pregnancies with early preterm fetal growth restriction (FGR) at $26 + 0$ to $31 + 6$ weeks' gestation to three arms, according to whether the decision to deliver was based on: (i) abnormal computerized cardiotocography (cCTG) findings; (ii) early ductus venosus (DV) Doppler changes (DV pulsatility index (PI) $> 95^{th}$ percentile) or highly abnormal cCTG; or (iii) late DV changes (no or reversed A-wave flow) or highly abnormal cCTG[5]. The study concluded that delivery based on late DV changes or highly abnormal cCTG increased the likelihood of 2-year infant survival without neurological impairment.

A secondary analysis of these data included all women (374/503; 74%) with available information on the primary endpoint (2-year infant survival without neurological impairment) and who underwent fetal Doppler examination within 1 week before delivery[4]. At inclusion, 80% of fetuses had UCR $> 95^{th}$ percentile, 20% between the 50th and 95th percentiles and only one

$< 50^{th}$ percentile. Both UCR and CPR were assessed, with CPR calculated as 1/UCR. The study found that, using a monitoring protocol based on DV Doppler and cCTG in early FGR ($26 + 0$ to $31 + 6$ weeks), the impact of middle cerebral artery (MCA) Doppler and its ratios (CPR and UCR) on 2-year neurodevelopmental outcome is modest and less marked than that of birth weight and gestational age at delivery (Figure 1).

A ratio consisting of parameters that change in opposite directions, as is the case with UCR and CPR, is always skewed. If the numerator is larger than the denominator, the ratio can become very large, as in the case of abnormal UCR. However, if the numerator is smaller than the denominator, as in the case of abnormal CPR, the ratio is lower than 1 but never smaller than 0. Figure 2 shows a plot of UCR and CPR values obtained at inclusion in the 374 women included in the secondary analysis of the TRUFFLE study. In the abnormal range, UCR increases almost linearly, while CPR runs nearly horizontally with little change. The much larger range of UCR allows for more marked differentiation of the extent of the fetal arterial Doppler abnormalities. For example, in a FGR fetus with umbilical artery (UA)-PI of 2 and MCA-PI of 1 at $32 + 0$ weeks and with UA-PI of 4 (reversed end-diastolic flow) and MCA-PI of 1 at $32 + 2$ weeks,
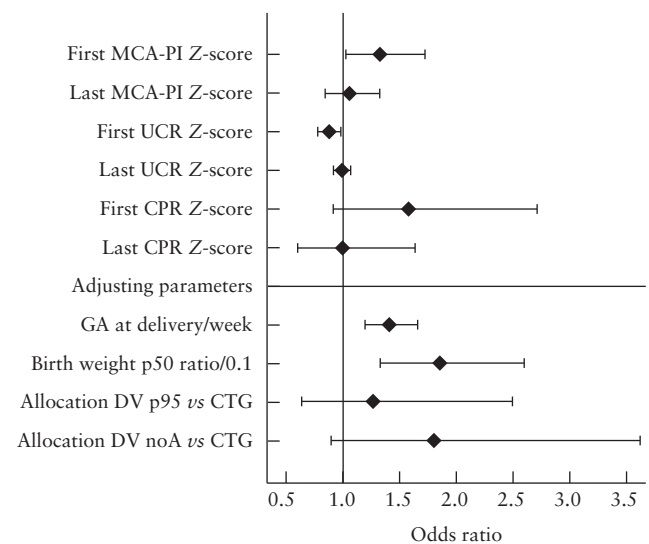

Figure 1 Odds ratios for infant survival without neurodevelopmental impairment at 2 years of age of Z-scores of fetal middle cerebral artery (MCA) pulsatility index (PI), umbilicocerebral ratio (UCR) and cerebroplacental ratio (CPR) at inclusion (first) and within 1 week before delivery (last), adjusted for birth weight to 50th percentile ratio, gestational age (GA) at delivery and study randomization allocation (DV p95 (early changes in ductus venosus; DV-PI $> 95^{th}$ percentile), DV noA (late changes in ductus venosus; no or reversed A-wave flow) or cardiotocography (CTG) group). Reproduced from Stampalija *et al.*[4].
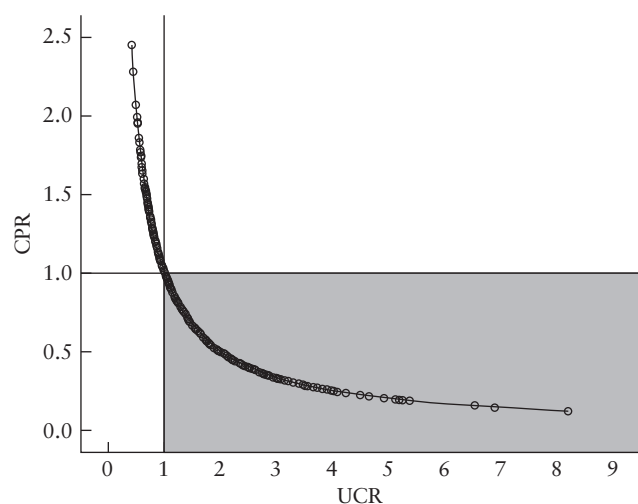
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Figure 2 Cerebroplacental ratio (CPR) *vs* umbilicocerebral ratio (UCR) at study inclusion in 374 patients from TRUFFLE study. Shaded area defines abnormal test with cut-off at 1.0 for either CPR or UCR. Reproduced from Stampalija *et al.*[4].

Table 1 Adjusted odds ratios (OR) with 95% confidence limits for 2-year infant survival without neurodevelopmental impairment of umbilicocerebral ratio (UCR) Z-score calculated based on reference ranges of Arduini and Rizzo[6] and of cerebroplacental ratio (CPR) Z-score calculated based on reference ranges of Arduini and Rizzo[6] and Baschat and Gembruch[7]

	OR (95% confidence limits)	P
UCR Z-score (Arduini and Rizzo)	0.88 (0.78–0.99)	0.04
CPR Z-score (Arduini and Rizzo)	1.58 (0.92–2.71)	0.10
CPR Z-score (Baschat and Gembruch)	1.49 (0.89–2.49)	0.13

Model was adjusted for gestational age and birth weight to 50th percentile ratio.

CPR would change from 0.5 to 0.25 (0.25 integer units) and UCR would change from 2 to 4 (2 integer units) between the two Doppler examinations. In other words, the change in UCR would be eight times greater than that in CPR.

The clinical utility of a variable is dependent on its ability to identify arterial Doppler abnormality, rather than normality; hence, in the context of an abnormal UA-PI and/or MCA-PI, UCR appears to discriminate better than does CPR. Furthermore, the compression of CPR in the abnormal range reduces its statistical power in comparison to UCR. This was demonstrated in the TRUFFLE study, in which UCR Z-score, but not CPR Z-score, at inclusion to the trial was associated significantly with the primary study outcome of 2-year infant survival without neurodevelopmental impairment, after adjustment for gestational age at delivery and birth weight (Figure 1 and Table 1).

Of course, when comparing Doppler parameters across gestation, it is helpful to adjust the values for the effect of gestational age. This can be achieved by using percentiles, multiples of the median or Z-scores; in the latter, the parameter is described as positive or negative in relation to the mean value for that gestational age and divided by SD. In the TRUFFLE study, Z-scores were calculated based on a cross-sectional study of 1556 low-risk pregnancies examined between 20 and 42 weeks' gestation[6]. To adjust for the skewness of the UCR distribution, the SD used for Z-score calculation was calculated only from the high percentile values (50th–95th percentiles) using the chart provided by Arduini and Rizzo[6] (Figure S1). CPR Z-scores were not transformed directly from the UCR value. After transformation of UCR to 1/CPR, the SD of CPR values was recalculated from the low CPR percentiles (5th–50th percentiles). In addition, to assess whether the skewed distributions of UCR and CPR with opposite direction might have caused bias in our Z-score calculation for CPR, we recalculated the Z-scores using reference data for CPR[7]. In agreement with our results for CPR Z-scores calculated based on Arduini and Rizzo, these CPR Z-scores were not significantly associated with the primary endpoint of the TRUFFLE study (Table 1).

Kalafat and Khalil assessed statistical differences between CPR and UCR in a cohort of 7758 appropriately grown and 1405 small-for-gestational-age near-term fetuses[1]. These cohorts were not fully described or referenced, and were retrieved from a retrospective database. Nevertheless, based on these data, the authors showed that the distribution of UCR is skewed with a tail to the right (abnormal) side, while the CPR distribution is not. The authors argue that, because Z-score calculation depends on SD and normal distribution, the skewed distribution of UCR could cause bias, while CPR can be used appropriately in statistical analysis. This was demonstrated by Q–Q plots, which showed linearity for CPR but not for UCR in their dataset. Due to these concerns regarding the Z-score distribution of UCR and CPR, we assessed CPR and UCR Z-scores in the TRUFFLE dataset using Q–Q plots (Figure S2). This showed a linear pattern for both parameters. Additionally, we tested whether linearity to the log odds assumption held by including the product of UCR Z-score and the natural logarithm of this parameter in the regression analysis. This showed that the interaction of these two variables was not statistically significant ($P = 0.62$).

Hence, we disagree with the criticisms of Kalafat and Khalil in relation to UCR and the statistical procedures that were used in the secondary analysis of the TRUFFLE data. It is because the UCR distribution is more skewed in the abnormal range that differentiation of Doppler deterioration is seen more clearly using this ratio rather than CPR.

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SUPPORTING INFORMATION ON THE INTERNET

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

Figure S1 Plot of cerebroplacental ratio (CPR) 50th (p50) and 5th (p5) percentiles and of umbilicocerebral ratio (UCR) p50 and 95th percentiles (p95) against gestational age in 1556 normal fetuses, according to Arduini and Rizzo[6]. CPR was calculated as 1/UCR.

Figure S2 Q–Q plots of cerebroplacental ratio (CPR) Z-score using reference chart from Baschat and Gembruch[7] (a) and reference chart from Arduini and Rizzo[6] (recalculated) (b), and of umbilicocerebral ratio (UCR) Z-score using reference chart from Arduini and Rizzo[6] (c).