CEREBROPLACENTAL RATIO IN REDUCED FETAL MOVEMENTS: EVIDENCE FOR WORSENING FETAL HYPOXEMIA

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Running Head: CEREBROPLACENTAL RATIO IN REDUCED FETAL MOVEMENTS

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Keywords:

cerebroplacental ratio, reduced fetal movements, doppler ultrasound, fetal hypoxemia

ABSTRACT

Objective: To investigate the fetal cerebroplacental ratio (CPR) in women presenting with reduced fetal movements (RFM).

Methods: This is a retrospective cohort study conducted over a 7-year period at a Fetal Medicine Unit at a tertiary referral centre. 4500 singleton pregnancies presenting with RFM after 36 weeks' gestation and 1527 control pregnancies at a similar gestation without RFM were analysed. Fetal biometry and Doppler parameters were recorded and converted into centiles and multiples of the median (MoM). The CPR was defined as the ratio between the middle cerebral artery (MCA) pulsatility index (PI) and the umbilical artery (UA) PI. Maternal and pregnancy characteristics were obtained from hospital records.

Results: The MCA PI MoM (median 0.95; IQR 0.84-1.09 vs 0.97; 0.86-1.11, $p<0.001$) and the CPR PI MoM (median 0.97; IQR 0.83-1.15 vs 0.99; 0.85-1.16, $p=0.018$) were significantly lower in pregnancies with RFM when compared to controls. Women presenting with multiple episodes of RFM, defined as ≥ 2 episodes, demonstrated significantly lower CPR PI MoM (median 0.90; IQR 0.81-1.12 vs 0.96; 0.84-1.08, $p=0.021$) compared to single episodes. Logistic regression analysis demonstrated a significant association between maternal age (OR 0.96, 95%CI 0.93-0.99), non-Caucasian ethnicity (OR 0.72; 95% CI 0.53- 0.97), estimated fetal weight (EFW) (OR 1.01; CI 1.00-1.02), CPR PI MoM (OR 0.24; 95% CI 0.12-0.47) and the risk of recurrent RFM.

Conclusion: Pregnancies complicated by multiple episodes of RFM show significantly lower CPR PI MoM and MCA PI MoM when compared to single episodes and controls. This is likely to represent evidence of worsening fetal hypoxemia in women presenting with recurrent RFM.

INTRODUCTION

Pregnancies complicated by reduced fetal movements (RFM) are associated with an almost twofold increased risk of late stillbirth compared to women experiencing strong and frequent fetal movements.[1] Up to 55% of women diagnosed with an intrauterine fetal death have presented with RFM days before the actual fetal demise. [2-5] As a risk marker in pregnancy, RFM is relatively common. Approximately 6-10% of all pregnant women experience at least one episode of RFM in the third trimester.[6]

The assessment and management of RFM have recently become the focus of on-going prospective studies with an overall aim of reducing the increased stillbirth rate in this population.[7] Pregnancies complicated by RFM have also been associated with a higher incidence (15.6%) of small-for-gestational age (SGA) babies when compared to women without RFM (7.6%).[8] Women presenting with recurrent episodes of RFM in particular, have been shown to give birth to SGA infants more frequently.[8] This association between fetal size and reduced fetal activity may be indicative of a common underlying pathophysiology of uteroplacental insufficiency.[9-12] Fetal size was previously considered to be the most important factor in determining fetal well-being. However, recent studies have challenged this assumption giving consideration to other factors like cerebroplacental ratio (CPR). [13,14]
The CPR - the ratio of middle cerebral artery (MCA) to umbilical artery (UA) Doppler pulsatility indices – is a marker of fetal cerebral blood-flow redistribution.[15] A lower CPR has been shown to be more strongly associated with adverse perinatal outcome, such as intrapartum operative delivery for fetal compromise and admission to the neonatal unit compared to birth weight (BW).[14,16] The CPR is also a better predictor of adverse perinatal outcome than either biophysical profile or Doppler assessment of the UA or MCA alone[17]. Therefore, the assessment of CPR should be considered as an important tool during the third trimester ultrasound assessment.[14,18,19]

Given the association between RFM and adverse perinatal outcome, we hypothesise that the CPR may be altered in cases presenting with RFM. The aim of this study was to evaluate the CPR in women presenting with RFM at or beyond 36 weeks of gestation.

MATERIALS AND METHODS

This was a retrospective cohort study of data obtained in a single tertiary referral centre between January 2008 to October 2015. An electronic database search (Viewpoint 5.6.8.428, Wessling, Germany) was conducted in the Fetal Medicine Unit at St George's Hospital, London in order to identify cases (pregnancies presenting with RFM) and controls (uncomplicated pregnancies without history of RFM). Pregnant woman who present with RFM are routinely offered an ultrasound assessment. This examination routinely encompasses measurement of the fetal UA and MCA Doppler. The inclusion criteria for cases were singleton pregnancies presenting with RFM at or beyond 36 weeks' gestation, where an ultrasound assessment of the fetal biometry, UA and MCA Doppler was performed. The number of episodes of RFM beyond 36 weeks' gestation was recorded. Recurrent RFM was defined as two or more episodes. Every visit to the fetal medicine unit for the purpose of RFM was considered an episode. In cases of recurrent RFM the ultrasound assessment preceding delivery was selected for evaluation. The control group consisted of singleton pregnancies who attended the department for presentation scan, scan for placental location and assessment of fibroids during the study time period and routine ultrasound assessment beyond 40 weeks of gestation, which included recording of the UA and MCA Doppler. Multiple pregnancies and those affected by congenital anomaly or aneuploidy were excluded in both groups.

Pregnancies were dated according to the crown-rump length measurement in the first trimester in accordance with national guidelines.[20] When the first ultrasound examination was performed after 14 weeks' gestation the pregnancies were dated according to the head circumference measurement.[21] Routine fetal biometry was measured during the ultrasound assessment according to the departmental protocol and the estimated fetal weight (EFW) was calculated.[22] The UA Doppler waveform was recorded in a free loop of cord using colour Doppler and the pulsatility index (PI) was calculated using a standard protocol.[23] The MCA Doppler waveform was produced using colour Doppler adjacent to the circle of Willis where the vessel passes the sphenoid wing. The PI of the MCA was subsequently calculated according to a standard protocol.[24] The CPR was calculated as ratio between the MCA-PI and the UA-PI[15] as part of the study protocol and was not calculated at time of the ultrasound assessment. All Doppler studies were performed during fetal quiescence maintaining a Doppler angle of less than 30° within the vessel.

In order to correct for gestational age all Doppler indices as well as the CPR ratio were converted into multiples of the median (MoM) using published reference ranges.[25,26] EFW and BW values were converted into centiles.[27] Maternal characteristics including maternal age, ethnicity (Caucasian, Asian, Black, Mixed and Other), body mass index (BMI) and parity (parous/nulliparous if no previous pregnancies beyond 24 weeks' gestation) were recorded. Ethnicity was self-reported. Data on pregnancy outcome were collected from the hospital obstetric and neonatal records. These included pregnancy outcome, mode of delivery, gestation at birth, fetal sex, BW and admission to the neonatal intensive care unit. SGA was defined as BW less than the 10^{th} centile after correcting for gestational age at delivery. Stillbirth was defined as fetal demise after 24 completed weeks of pregnancy. Perinatal mortality included stillbirth and neonatal death within the first 28 days after delivery. Although data integrity was aimed to be as high as possible, less than 10% missing data was achievable for all parameters.

Statistical analysis

The Kolmogorov- Smirnov tests of normality as well as histograms were used to assess the distribution of the data. Continuous Data were expressed as median and interquartile range (IQR). Continuous variables that were not normally distributed were compared using Mann Whitney U Test. Categorical variables were described as numbers (%) and differences between the groups were assessed using the Chi Squared test. Logistic regression analysis was performed to evaluate the association between maternal characteristics, Doppler parameters, SGA, EFW centile and the presence of multiple RFM. Subgroup analysis was performed for single versus multiple episodes of RFM, as well as for appropriate for gestational age (AGA) versus SGA fetuses in the RFM group versus the control group. P value <0.05 was considered statistically significant. Statistical software (SPSS 24.0; SPSS Inc, Chicago, IL) was used to perform the statistical analysis.

RESULTS

During the study period we identified 4973 pregnant women who presented with one or more episodes of RFM at or beyond 36 weeks' gestation. Of those 159 were external referrals delivered elsewhere and therefore detailed neonatal outcome data was not available. We excluded a further 286 patients for whom fetal Doppler assessment was not performed as part of the ultrasound examination and a further 28 cases of fetal anomalies or chromosomal disorders. All 4500 eligible women experiencing RFM were compared with 1527 controls. The maternal and pregnancy characteristics, ultrasound findings and pregnancy outcome of the two study groups are presented in Tables 1 and 2. Compared to control pregnancies, women presenting with RFM were significantly younger (p<0.001), more likely to be from an Asian background (p<0.001) and delivered significantly earlier (p<0.001) than the control group (Table 1).

Perinatal deaths occurred in the RFM group only (n=7, Table 2). Women who presented with RFM had significantly lower MCA PI MoM (p<0.001), CPR MoM (p=0.018) and a higher proportion of fetuses with CPR less than the 5th centile (p=0.002) compared with the control cohort. Furthermore, the RFM group had significantly lower EFW (p=0.019) and BW (p<0.001) centiles, as well as more SGA fetuses (p<0.001), when compared to controls. Hypertensive disorders in pregnancy (HDP) were almost twice as common in women presenting with RFM (5.9%) compared to the control group (3.4%) (p<0.001) (Table 2).

In the subgroup analysis according to the fetal size (SGA vs AGA), there was no significant difference in the MCA PI MoM (p=0.149), CPR PI MoM (p=0.421) and CPR less than the 5th centile (p=0.266) in the SGA fetuses with and without RFMs (Table S1). In contrast, AGA fetuses in the RFM group showed significantly lower MCA PI MoM (p=0.002) and significantly higher rates of CPR less than the 5th

centile when (p=0.015) compared to AGA fetuses in the control group (Table 3). A further subgroup analysis compared single versus recurrent episodes of RFM demonstrating significantly lower median MCA PI MoM (p=0.021) and CPR MoM (p=0.003) values in recurrent compared to the single episode of RFM cohort (Table 4). There was no significant difference in the EFW centiles (p=0.109), BW centiles (p=0.270) and the proportion of SGA fetuses (p=0.870) between the pregnancies with single and those with recurrent RFM cohorts. A comparison between the controls and the cases according to the number of episodes of RFM is shown in Supplementary Table S2. Women who presented with recurrent episodes of RFM had significantly lower MCA PI MoM (p<0.001), CPR MoM (p<0.001) and a higher proportion of fetuses with CPR less than the 5^{th} centile (p=0.001) compared with the control cohort. Furthermore, the multiple episode RFM group had significantly lower BW (p<0.001) centiles, as well as more SGA fetuses (p=0.003), when compared to controls. The incidence of HDP was also significantly higher in women presenting with recurrent RFM compared with the control group (p=0.011).

The logistic regression analysis showed a significant association between maternal age (odds ratio (OR) 0.91, 95% confidence interval (CI) 0.88-0.94; p=0.002), non-Caucasian ethnicity (OR 0.61; 95% CI 0.43- 0.86; p=0.004), CPR PI MoM (OR 0.15; 95% CI 0.07-0.36; p<0.001), EFW centile (OR 1.14; 95% CI 1.05-1.24; p=0.002) and SGA (OR 2.16; CI 1.12-4.18; p= 0.022) with the risk of multiple episodes of RFM.

DISCUSSION

Main findings

The findings of this study demonstrate that RFM are associated with fetal Doppler changes such as low MCA PI and CPR, reflecting fetal hypoxemia secondary to placental insufficiency. These changes were more evident in the pregnancies with multiple episodes of RFM, where the fetuses had significantly lower CPR and MCA PI compared to those with a single episode of RFM.

Interpretation of the study findings

Our results are consistent with those of O'Sullivan et al[28], who demonstrated that women presenting with multiple episodes of RFM are at higher risk of placental insufficiency and delivering SGA neonates – supporting the causal association between RFM and SGA through utero-placental insufficiency. This hypothesis is consistent with data from recent studies evaluating second trimester uterine artery Doppler assessment as well as maternal serum PAPP-A levels in a cohort of pregnancies with RFMs. These changes are suggestive of placental dysfunction in affected pregnancies.[9,10] Warrander et al.[11] examined placental structure in women presenting with RFM and described reduced villous vascularity and trophoblast area in the terminal villi leading to impaired placental function and decreased oxygen/nutrient supply to the fetus.

Interestingly, all 7 perinatal deaths occurred in the AGA group. Furthermore, AGA fetuses with RFM demonstrated significantly lower MCA PI and CPR compared to those without RFM. This observation suggests placental dysfunction inducing RFM resulting in a reduction in subsequent growth rate accompanied by redistribution of fetal blood flow. In contrast, compared to the controls, the SGA group had lower Doppler indices (MCA PI and CPR) irrespective of whether they presented with RFM or not. These data question the received wisdom of fetal size or growth being the major contributing factor to fetal wellbeing. A recent study by Man et al[29] demonstrated that the actual rate of SGA in stillborn fetuses might be overestimated by the fact that fetuses continue to loose weight after their demise and continue to loose weight until they are born.[29] Our results are in keeping with the findings of Morales-Rosello et al[25], who reported low CPR in AGA fetuses as being indicative of placental insufficiency, and failure to achieve fetal growth potential and fetal hypoxemia. Furthermore, the logistic regression analysis showed a significant association between higher EFW centiles and increased recurrent RFM. This finding may be explained by intervention bias (SGA babies with a single episode of RFM might have prompted delivery) or because our population was mainly Caucasian, and have previously been shown to have bigger babies and more likely to present with RFM[8].

Clinical and Research Implications

There is now a wealth of consistent published data showing that CPR is more strongly and independently associated with adverse perinatal outcomes, such as the need for emergency operative delivery for presumed fetal compromise, low cord pH, admission to the neonatal unit, stillbirth and perinatal death, compared to BW centile.

Although, according to the Guidelines of the Royal College of Obstetrics and Gynecology (RCOG)[30] and the American College of Obstetrics and Gynecology[31], fetal Doppler evaluation is not essential during ultrasound assessment for RFM, our data suggests that there may be value in using fetal Dopplers in this evaluation. In addition it is also important to note that these guidelines predate the recent studies on CPR not taking the recent study findings into account.

In the current study, the subsequent development of HDP was demonstrated to be almost twice as high in women presenting with RFM compared to normal pregnancies. This finding suggests a causal relationship between RFM and SGA with HDP – potentially through the common aetiology of utero-placental insufficiency. This finding needs to be evaluated further in large prospective trials.

Strength and limitations

The main strengths of this study include the large number of women, comprehensive Doppler assessment and the adjustment of fetal Doppler, EFW and BW centiles for gestational age. Furthermore, sensitivity analyses were conducted to look at the effects of fetal size and number of episodes of RFM on the study outcomes. The limitations include the retrospective study design, more advanced gestation of the control group and the un-blinded nature of the groups, raising the potential for intervention bias, such as intervention by a clinician or offering induction of labor. However, the CPR values were not calculated before the analysis for this study. The healthcare professionals providing the clinical care were therefore effectively blinded to these values.

CONCLUSION

The findings of this study report the presence of fetal hypoxemia due to placental insufficiency in fetuses presenting with RFM. This is even more apparent in women presenting with recurrent episodes of RFM – despite the latter group having similar BW and prevalence of SGA to the single RFM cases. The additional finding that fetal deaths were observed only in the AGA fetuses with RFM, questions the relative importance of fetal size in the assessment of fetal well-being at term. The association between RFM and subsequent development of HDP deserves further attention.

ACKNOWLEDGEMENT

None.

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Accepted Article

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Table 1. The maternal and pregnancy characteristics in the two study groups

	Controls (n=1527)	Cases (reduced fetal movements) (n=4500)	P value
Maternal age in years, median (IQR)	32.0 (25.0-35.0)	31.0 (27.0-34.0)	<0.001
BMI in kg/m^2, median (IQR)	24.5 (22.0-28.78)	24.6 (21.9-28.3)	0.405
Ethnicity			<0.001
Caucasian, n (%)	1001 (65.6)	2673 (59.4)	
Afro-Caribbean, n (%)	213 (13.9)	535 (11.9)	
Asian, n (%)	249 (16.3)	1071 (23.8)	
Nulliparous, n (%)	671 (43.9)	1903 (42.3)	0.527
GA at ultrasound in weeks, median (IQR)	37.86 (36.29-41.43)	39.14 (37.86-40.29)	0.350
GA at delivery in weeks, median (IQR)	41.14 (39.71-41.86)	40.43 (39.57-41.14)	<0.001

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

Table 2. Ultrasound findings and pregnancy outcome in the two study groups

	Controls (n= 1527)	**Cases (reduced fetal movements) (n=4500)**	**P value**
Pregnancy outcome			0.455
Live birth, n (%)	1527 (100)	4088 (91.0)	
IUD, n (%)	0	4 (0.1)	
NND, n (%)	0	3 (0.1)	
UtA mean PI MoM, median (IQR)	0.65 (0.55-0.76)	0.65 (0.56-0.78)	0.118
UA PI MoM, median (IQR)	1.06 (0.95-1.19)	1.07 (0.95-1.20)	0.089
MCA PI MoM, median (IQR)	0.97 (0.86-1.11)	0.95 (0.84-1.09)	<0.001
CPR MoM, median (IQR)	0.99 (0.85-1.16)	0.97 (0.83-1.15)	0.018
CPR <5th centile (%)	60 (3.9)	272 (6)	0.002
EFW centile, median (IQR)	59.56 (42.36-76.10)	57.97 (38.37-75.55)	0.019
BW centile, median (IQR)	55.73 (30.57-79.52)	45.80 (23.72-70.26)	<0.001
SGA, n (%)	80 (5.2)	380 (8.4)	<0.001
HDP, n (%)	52 (3.4)	265 (5.9)	<0.001

IUD: intrauterine death; NND: neonatal death; UtA: uterine artery; pulsatility index: PI; UA: umbilical artery; MCA: middle cerebral artery; CPR: cerebroplacental ratio; EFW: estimated fetal weight; BW: birth weight; SGA: small for gestational age; HDP: hypertensive disorders in pregnancy.

Table 3. Ultrasound findings and pregnancy outcome in the two study groups in the pregnancies with appropriate for gestational age (AGA) neonates

	AGA – Controls (n=1429)	**AGA – Cases (reduced fetal movements) (n=3676)**	**P value**
Pregnancy outcome			0.432
Live birth, n (%)	1429 (100)	3676 (99.8)	
IUD, n (%)	0	4	
NND, n (%)	0	3	
UtA mean PI MoM, median (IQR)	0.65 (0.55-0.76)	0.65 (0.56-0.76)	0.739
UA PI MoM, median (IQR)	1.06 (0.95-1.19)	1.05 (0.94-1.18)	0.259
MCA PI MoM, median (IQR)	0.96 (0.86-1.09)	0.96 (0.84-1.08)	0.002
CPR MoM, median (IQR)	0.99 (0.86-1.16)	1.00 (0.86-1.17)	0.059
CPR <5th centile, n (%)	52 (3.6)	194 (5.3)	0.015
EFW centile, median (IQR)	61.35 (45.95-77.25)	59.37 (43.24-73.79)	0.202
BW centile, median (IQR)	56.93 (34.05-80.21)	50.05 (29.98-71.05)	<0.001
HDP, n (%)	49 (3.4)	228 (6.2)	<0.0001

IUD: intrauterine death; NND: neonatal death; UtA: uterine artery; pulsatility index: PI; UA: umbilical artery; MCA: middle cerebral artery; CPR: cerebroplacental ratio; EFW: estimated fetal weight; BW: birth weight; SGA: small for gestational age; HDP: hypertensive disorders in pregnancy.

Table 4. Comparison between the controls and the cases according to the number of episodes of reduced fetal movements (RFM)

	Controls (n=1527)	**RFM- single episode (n=4115)**	**P value**	**RFM- multiple episodes (n=385)**	**P value**
Pregnancy			0.413		
Live birth, n (%)	1527 (100)	3727 (91)		361 (94)	
IUD, n (%)	0 (0)	4 (0.1)		0	
NND, n (%)	0 (0)	3 (0.1)		0	
UtA mean PI MoM, median (IQR)	0.65 (0.55-0.76)	0.65 (0.56-0.77)	0.128	0.66 (0.55-0.80)	0.545
UA PI MoM,	1.06 (0.95-	1.07 (0.95-	0.096	1.08 (0.94-	0.329
MCA PI MoM,	0.97 (0.86-	0.96 (0.84-	0.001	0.95 (0.81-	<0.001
CPR MoM, median	0.99 (0.85-	0.98 (0.83-	0.061	0.94 (0.80-	<0.001
CPR <5th centile, n	60 (3.9)	242 (5.9)	0.004	30 (7.8)	0.001
EFW centile,	59.56	57.93 (38.29-	0.012	61.85 (39.63-	0.640
BW centile,	55.73	45.73 (23.64-	<0.001	46.75 (24.18-	0.001
SGA, n (%)	80 (5.2)	346 (8.4)	<0.001	34 (8.8)	0.003
HDP, n (%)	52 (3.4)	241 (5.9)	<0.001	24 (6.2)	0.011

IUD: intrauterine death; NND: neonatal death; UtA: uterine artery; pulsatility index: PI; UA: umbilical artery; MCA: middle cerebral artery; CPR: cerebroplacental ratio; EFW: estimated fetal weight; BW: birth weight; SGA: small for gestational age; HDP: hypertensive disorders in pregnancy.