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Original Article

Cerebroplacental doppler ratio in prediction of adverse perinatal outcome in term normal pregnancy

Gynecology and Obstetrics

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ABSTRACT

Background: The cerebroplacental ratio (CPR) may be able to detect fetus that do not develops fully at term and predict poor pregnancy outcomes. In third-trimester studies of high-risk pregnancies, low CRP due to increased umbilical artery (UA) or fetus middle cerebral artery pulsatility index (MCA-PI) has been linked to poor pregnancy outcomes. .

Objective: To assess the predictive utility of doppler CPR for screening of full-term (37 week - 40 week) normal un-complicated pregnancies with a bad outcome.

Methodology: This observational hospital based cross sectional study was conducted on 500 women normal uncomplicated full-term pregnancy (37- 40 weeks), giving birth at Al-Zahraa university hospital and Elsinbelaween general hospital from June 2021 to June 2022. All women were subjected to measurement of abdominal ultrasound, femur length (FL), abdominal circumference (AC), gestational age, complete, cardiotocography (CTG) to assess fetal, and umbilical and placental doppler for middle cerebral artery (MCA) and umbilical artery (UA).

Results: MCA systolic / diastolic (S/D) ratio was inversely correlated with pCO_2, while UA-S/D ratio was positively correlated with pCO_2 and negatively correlated with all other parameters except neonatal death and neonatal intensive care unit admission.

Conclusion: In full-term normal pregnancy, the CPR is an excellent predictor of unfavorable perinatal outcome.

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INTRODUCTION

One of the key problems of contemporary obstetrics is the prediction of a negative pregnancy outcome. The cerebroplacental ratio (CPR) has been studied as a possibly reliable method for identifying fetuses who do not attain their full development potential at term and hence for predicting unfavorable pregnancy outcomes [1].

Elevated resistance to flow, as expressed by a rising pulsatility index (PI) in the umbilical artery (UA), and reduced PI in the fetus middle cerebral artery (MCA), have been linked to fetal hypoxemia and acidemia in investigations of fetus blood gained by cordocentesis from small for gestational age (SGA) embryos [2].

The cerebroplacental ratio (CPR) was found to be a good predictive of negative pregnancy outcomes in SGA embryos than MCA-PI or UA-PI alone. A reduced CPR is linked to enhanced rates of perinatal mortality, caesarean section for fetus's compromise in labor, newborns acidosis, 5-minute Apgar scores <7, and newborns intensive care unit (NICU) stay>24 hours [3]. The notion that the CPR might predict bad perinatal outcomes not just in SGA but also in adequately grown for gestational age (AGA) babies has reignited interest in the index [4].

In a regularly tested of 30,870 women with singleton pregnant women able to attend for a regular visit to the hospital at 30-34 weeks' conception, there was a connection between CPR and birth weight Z score, umbilical cord blood pH, and admittance to the NICU, but the efficiency of screening by CPR was poor, with detection rates (DRs) of 5% e11 percent and a false-positive rate (FPR) of 5%.[5].

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One reason for the screening's unsatisfactory results might be because the perinatal negative outcomes at term were too far removed from the gestation age at which CPR was evaluated [6]. Another research of 6178 singleton fetuses regularly tested at 35-37 weeks' pregnancy found substantial relationships between CPR and markers of bad pregnancy outcomes, although CPR screening efficiency was low, with a DR of 6% e15 percent at an FPR of 6% [7].
Vasodilation and lower resistance in the cerebral vasculature are related with greater UA-PI, reduced MCA-PI, and low CPR, resulting in elevated UA-PI, reduced MCA-PI, and low CPR. [8]. Our aim was to see how accurate Doppler (CPR) was in identifying unfavorable pregnancy outcomes in full-term, uncomplicated pregnancies (37week- 40week).

PATIENT AND METHODS

This observational hospital based cross sectional study was conducted on 580 pregnant women with normal uncomplicated full-term pregnancy, of them 80 cases were dropped out so we studied 500 cases. They were recruited from gynecology and obstetrics departments of both Al-Zahraa university hospital - Cairo - Egypt, and Elsinbelaween general hospital - Aldakahlia - Egypt, during the period from June 2021 to June 2022. Pregnant women with singleton, normal a full-term pregnancy were included in the study. Women with extreme age, hypertension, diabetes mellitus, anemia, severe congenital abnormalities, a euploidy, multiple pregnancy, and premature delivery <37-weeks' gestation were excluded from the study.

Ethical approval was gained according to the recommendations of Ethics Unit at Al-Azhar University's Faculty of Medicine in Cairo, Egypt. The clinical steps and possible adverse events were plainly demonstrated for all candidates. Informed consent was obtained from each patient.

Detailed history taking with special emphasis on gravity, parity, menstrual history, obstetric history, and history of any medical problems. Full clinical examination including fundal level, lie and presentation of the fetus was done.

Abdominal ultrasound was done for bronchopulmonary dysplasia (BPD), femur length (FL), and abdominal circumference (AC) before delivery to asses gestational age. Complete biophysical profile including cardiotocography (CTG) were perform to asses fetal wellbeing. Finally umbilical and placental doppler were recorded including middle cerebral artery (MCA) and umbilical artery (UA) measuring indices and ratio correlated normal values at this age. Ultrasonography and doppler measurements were done using Philips system (Philips 5000, PHILIPS Egypt, Cairo, Egypt).

The fetal MCA was located using color Doppler imaging by insonation angle as close to 0^{o} as possible. The plane used for measuring MCA was the trans-thalamic plane which contains the thalami and cavum septum pellucidum. The MCA was seen pulsating at the level of origin of the circle of Willis. For UA the measurement was made in the free cord. Due to difficulty with measuring the cord at the fetal end in many growth-restricted fetuses, measurement in a free loop was acceptable. Care was taken to apply minimal pressure of the transducer to the maternal abdomen and fetal head, as fetal head compression can alter fetal intracranial pressure and hence the arterial flow velocity waveforms obtained from the MCA and UA. The following indices were measured umbilical artery plasticity index (UA-PI), umbilical artery resistance index (UA-RI), umbilical artery systolic / diastolic (UA-S/D), ratio, middle cerebral artery plasticity index (MCA-PI), middle cerebral artery resistance Index (MCA-RI), middle cerebral artery systolic / diastolic (MCA-S/D) ratio. A minimum of three separate readings were averaged before the final values were obtained.

The FL was measured using a longitudinal view of the fetal thigh closest to the probe and with the femur as close as possible to the horizontal plane. The angle of insonation of the ultrasound beam was approximately 90◦ with the full length of the bone visualized, un-obscured by shadowing from adjacent bony parts, and the femur had to fill at least 30% of the monitor screen. The intersection of the calipers was placed on the outer borders of the edges of the femoral diaphysis (outer to outer) ensuring clear femoral edges. For Abdominal circumference (AC) measurements transverse section through the upper abdomen. Adverse neonatal outcomes were NICU admission and neonatal death.

Blood gas analysis including pO_2 and pCO_2 was performed with analyzing umbilical artery blood sample as we used invasive method. Invasive blood gas analysis, required an arterial puncture, which was done directly at the umbilical artery and required more expertise.

Statistical analysis

The data was analyzed using the Statistical Package for the Social Sciences version 20. (SPSS Inc., Chicago, IL, USA). The mean, standard deviation (SD), and range of quantitative data were employed to characterize them. Number and percentage were utilized to describe qualitative characteristics. Independent t test was used for assessing parametric quantitive variables. When assessing qualitative variables chi- square test was used and Fisher's exact test was used instead when the frequencies were less than five. The correlation between two normally distributed variables was evaluated utilizing person correlation coefficients. A p- value of 0.05 was considered significant with 95% confidence.

RESULTS

Most of cases (52.6%) aged between 21-25 years and 30.6% of cases were para-2. The mean ± SD of pregnancy age at delivery was 38.5 ± 1.1 weeks. The mean ± SD of Apgar score at 1 minute was 7.5 ± 2.3, while it was 7.9 ± 1.9 at 5 minutes. The mean ± SD of UA-PI was 1.22 ± 0.48, while that of UA-RI was 0.66

± 0.15, MCA-PI have a mean± SD of 1.73 ± 0.70, while that of MCA-RI was with mean± S/D of 0.93 ± 3.24 (table 1).

There were statistically significant difference between neonatal outcome as regard basal UA-PI and UA-RI (p = 0.001), and there was statistically significant variations between neonatal outcomes as regard basal UA-S/D ratio. UA-PI, UA-RI and UA-S/D ratio were significantly higher in patients with poor outcome (table 2).

There was no statistically significant variations between neonatal outcomes regarding basal MCA doppler indices. There was no significant difference between poor and good outcomes group regarding MCA-PI, MCA-RI and MCA- S/D ratio (table 3).

The UA-S/D ratio was positively correlated with mode of delivery and pCO_2, while it was negatively correlated with neonatal birth weight, Apgar at 1 minute, Apgar at 5 minutes, pH, pO_2, and base excess (table 4**).** The MCA-S/D ratio was negatively correlated pCO_2 (table 5).

Table (1): Demographic characteristics and clinical history of the study cases

Items	n =500
Age:	
- 21-25 years	263 (52.6%)
- 26-30 years	124 (24.8%)
- 31-35 years	113 (22.6%)
Parity:	
- Primi	106 (21.2%)
- Para-1	148 (29.6%)
- Para-2	153 (30.6%)
- Para-3	75 (15.0%)
- Para-4	18 (3.6%)
Mode of delivery:	
- Vaginal	268 (53.6%)
- Cesarean	232 (46.4%)
Gestational age at delivery (weeks) (mean ± SD)	38.5 ± 1.1
Neonatal birth weight (g) (mean ± SD)	3681 ± 799
Apgar score at 1 minute (mean ± SD)	7.5 ± 2.3
Apgar score at 5 minutes (mean ± SD)	7.9 ± 1.9
UA-PI (mean ± SD)	1.22 ± 0.48
UA-RI (mean ± SD)	0.66±0.15
UA- S/D ratio (mean ± SD)	3.27 ±3.40
MCA-PI (mean ± SD)	1.73 ±0.70
MCA-RI (mean ± SD)	0.93±3.24
MCA- S/D ratio (Mean ± SD)	5.97 ±5.97
CPR ratio (mean ± SD)	1.65±0.74

UA-PI: Umbilical artery plasticity index, UA-RI: Umbilical artery resistance index, UA-S/D ratio: Umbilical artery systolic / diastolic ratio, CPR ratio: Cerebroplacental ratio, *: Significant P value (<0.05)

Table (2): Basal umbilical Doppler finding and its relation to neonatal outcome

Items	Poor outcome (n = 93) Mean ± SD	Good outcome (n = 407) Mean ± SD	Stat. test	p-value
UA - PI	1.58±0.58	1.15±0.43	t = 3.9769	0.001*
UA -RI	0.76±0.10	0.64±0.15	t = 3.2660	0.001*
UA -S/D ratio	5.68±8.24	2.86±1.04	t = 2.9704	0.005*

UA-PI: Umbilical artery plasticity index, UA-RI: Umbilical artery resistance index, UA-S/D ratio: Umbilical artery systolic / diastolic ratio,*: Significant P value (<0.05)

Table (3): Basal middle cerebral artery Doppler finding and its relation to neonatal outcome

Items	Poor outcome (n = 93) Mean ± SD	Good outcome (n = 407) Mean ± SD	Stat. test	p-value
MCA-PI	1.71±1.01	1.73±0.64	t = 0.1228	0.902
MCA-RI	0.75±0.39	0.96±3.49	t = 0.2477	0.606
MCA-S/D ratio	8.02±10.16	5.62±4.87	t = 1.8738	0.053

MCA-PI: Middle cerebral artery plasticity index, MCA-RI: middle cerebral artery resistance Index, MCA-S/D ratio: middle cerebral artery systolic / diastolic ratio

Table (4): Correlation between umbilical artery S/D ratio and parameters of neonatal outcome

Items	UA-S/D ratio	
	r	p value
Mode of delivery	0.089	0.048*
Neonatal birth weight	-0.217	< 0.001*
Apgar at 1 minute	-0.252	< 0.001*
Apgar at 5 minutes	-0.236	< 0.001*
pH	-0.114	0.011*
pO_2	-0.140	0.002*
pCO_2	0.058	0.019*
Base excess	-0.112	0.012*
Neonatal ICU admission	-0.035	0.433
Neonatal death	0.051	0.258

UA-S/D ratio: Umbilical artery systolic / diastolic ratio, pO_2: partial pressure of oxygen, pCO_2: partial pressure of Carbone dioxide, ICU: Intensive care unit, *: Significant P value (<0.05)

Table (5): Correlation between middle cerebral artery S/D ratio and parameters of neonatal outcome

Items	MCA-S/D ratio	
	r	p value
Mode of delivery	-0.049	0.279
Neonatal birth weight	0.086	0.055
Apgar at 1 minute	-0.017	0.709
Apgar at 5 minutes	0.053	0.238
pH	0.058	0.196
pO_2	0.041	0.366
pCO_2	-0.094	0.036*
Base excess	0.058	0.197
Neonatal ICU admission	0.040	0.367
Neonatal death	-0.013	0.767

MCA-S/D ratio: middle cerebral artery systolic / diastolic ratio, pO_2: Partial pressure of oxygen, pCO_2: Partial pressure of carbon dioxide, ICU: Intensive care unit, *: Significant P value (<0.05)

DISCUSSION

The CPR is utilized to identify and measure the fetus response to oxygen shortage while still in the womb. The impedance in fetus circulation steadily lowers as the gestation progresses. Nonetheless MCA-RI readings should be greater than UA-RI values in uncomplicated pregnancies, implying that CPR (the proportion of MCA-RI to UA-RI), should be greater than 1–1.1 [9].

In our study, mean ± SD of MCA-PI was 1.73 ± 0.70 and that of UA-PI was 1.22 ± 0.48, which relatively near to the results reported by Ale et al., [10] who found that the median MCA-PI was 1.15±0.19 and that of UA-PI was 0.83 ±0.16 and. Also in study by Khalil et al., [11] who studied 7944 pregnancies, and reported that the median MCA-PI was 1.31 and the median UA-PI was 0.82.

In our study, mean± SD of MCA-RI was with mean± SD of 0.93±3.24, while that of UA-RI was 0.66±0.15, which in agreement with Ropacka-Lesiak et al., [9] who stated that As the pregnancy proceeds to term, there is less resistance in the embryonic circulation. The resistance in the MCA, on the other hand, should be greater than in the UA. In an uncomplicated gestation, CPR should be more than 1-1.1. Also, in another study by Zamora et al., [12] , doppler variables were at 287 and 300 days of pregnancy. They found that as the pregnancy progressed, the UA-RI values declined while the RI values of the fetus grew. While in previous study by Sayan et al., [13] revealed that The UA-RI values in the research group's protracted pregnancies were higher in those hospitalized to ICU and low in those not admitted to ICU. In addition, the RI median value in the MCA in protracted pregnancies was considerably lower in those admitted to ICU compared to those not hospitalized to ICU, indicating that the brain has a protective mechanism in place. CPR might be utilized to detect fetuses at risk of hemodynamic pathology before delivery, since CPR is a sign of placental hypoperfusion and diminished placental effective reserve[14].

In our study, the mean ± SD of UA-PI in poor outcome group was 1.58±0.58 and in good outcome group was 1.15±0.43, which near to the results in the study done by Fiolna et al., [2] who studied 1,902 singleton pregnancies and found the mean ± SD of UA-PI of

poor outcome group was 1.07 and that of good outcome group was1.03. Also in study by Melekoglu R et al.,[15] who studied 317 pregnancies identified with LOFGR at 37–40 weeks of pregnancy the mean ± SD of UA-PI of infants with poor outcome was 1.04, while that of infants with good outcome was o.93. There was statistical significant difference between neonatal outcomes in the study as regard basal UA-PI similar to other report [16]. Also, the meta-analysis done by Vollgraff et al., [17] as UA-PI was significantly linked to major neonatal outcome. In other study, there was no difference in UA blood flow impedance, and UA doppler was not a good indicator of poor perinatal outcomes [18]. This discrepancy may be due to the different criteria used for UA doppler measurement and the research population under concern [19] embryos with stunted growth with standard UA doppler US images had reduced perinatal death (0.3% vs. 1.4 %; p =.01) and a reduced rate of overall negative events, described as a composite of intraventricular bleeding, periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, BPD, sepsis, or death (1.3 % vs. 11.5%; p < .0001).

In our study, the mean ± SD of MCA-PI of poor outcome group was 1.71±1.01 that lower than that of good outcome group (1.73±0.64). Acute cerebral redistribution occurs in the fetus in response to uterine contractions, as demonstrated by a lower MCA-PI. This pattern of blood flow centralization is similar to that seen in embryos with stunted growth throughout time. According to certain research, intrauterine pressures as low as 35 mmHg are adequate to obliterate uterine artery end diastolic velocities, leading to decreased placental perfusion. The 'embryo pain' that developed as a consequence of frequent uterine contractions is most likely caused by a lack of oxygen and other substrates being transferred to the placenta throughout labor [20].

In the present study there was no statistical significant difference between neonatal outcomes regarding basal MCA doppler indices that agree with other report by Fattah et al. [18] who documented that women who had a negative result had normal MCA-PI. It has been proposed that the mechanism of embryo compromise in uncomplicated pregnancies is owing to a reduction in nutrient flow throughout the placenta and a reduction in the effectiveness of nutrient uptake by the placenta and the baby, rather than uteroplacental inadequacies with a resultant brain sparing impact [18]. A drop in MCA-PI levels, even before any variations in UA, may be an early indicator of adaptive changes in simple pregnancies without symptoms of impaired placental function. At the same time, it might be a result of primary changes in vascular resistance that occur throughout protracted pregnancies [9]. Devore et al., [1] documented that regardless UA and MCA metrics, the CPR is a better predictive of unfavorable events than the biophysical characteristics and it should be used as a screening tool in embryos enduring 3rd trimester ultrasound. Irregular CPR has been linked to an enhanced risk of perinatal problems, particularly in intrauterine growth retardation (IUGR) embryos from PE gestation. These findings are supported by the fact that placental vascular pathology, which causes hypoperfusion of the fetus, necessitates the activation of the brain spasm effect, which causes abnormalities in the cerebroplacental ratio [21].

In this study there are statistical significant connection between UA-PI and each of Apgar score at 1 minute and at 5 minutes that agree with Jo et al., [22] who studied 404 singleton gestations with small for gestational age embryos at late preterm and term, as well as 184 gestations with full doppler ultrasonography results in the UA and embryo MCA, and found that irregular UA-PI was linked to a low Apgar score (< 7) at 1 minute after birth. Our finding was disagree with Ale et al., study [10] who found no significant change in the Apgar scores at 1 and 5-minute between fetuses with aberrant and normal UA-PI that may be due to the small sample size of their studied cases.

In our study there was no significant difference between MCA-PI and delivery technique. That is in the same way with Li et al., [23] as there were no significant variation in blood flow resistance in MCA across the groups when comparing the incidence of surgical births done in gestations is hampered by fetal discomfort or not.

There was no significant difference in MCA-PI and Apgar at 5 minutes in our research. which in line with Ale et al., [10] who reported that between fetuses with aberrant and normal MCA-PI, there was no significant variation in Apgar scores at 5 minutes. However, this result was disagreed with Stampalija et al., [24] who documented cerebral doppler abnormalities before delivery are linked to a poor short-term neonatal prognosis in fetal growth restriction.

In our research, there was significant connection between UA-PI and neonatal birth weight, pO_2, pH and base excess. Akolekar et al., [6] evaluated the prognostic effect of CPR for a composite poor perinatal outcome in 47211 singleton pregnancies having standard ultrasonography evaluation at 35-37 weeks of gestation. The scientists discovered low probability ratios in both regularly growing and growth-restricted babies, concluding CPR's effectiveness in predicting each unfavorable result was poor, regardless of fetus size or the time among testing and delivering. In the research done by Khalil et al., [11] there was a strong link between UA-PI, MCA-PI, neonatal birth weight, and SGA, which somewhat agrees with our findings. Recent studies by Khalil et al., [25] revealed that low CPR is linked to a variety of negative gestation outcomes, such as surgical delivery due to fetal compromise, neonatal unit hospitalization, stillbirth, and newborn morbidity.

In the present study there was no link in between UA-PI and neonatal ICU admission also in between MCA-PI and neonatal ICU admission. Bligh et al., [26] have

reported capacity of CPR to detect perinatal prognosis regarding fetal distress requiring an emergency caesarean surgery and admission to a neonatal care unit. Monaghan et al., [27] recommended the use of CPR in conjunction with median UA-PI, either with or without fetus biometrics as a secondary measure, to predict stillbirth and perinatal mortality at term.

Our study showed significant negative correlation was found between MCA-S/D ratio and pCO_2. Significant positive correlation was found between UA-S/D ratio with mode of delivery and PCO2. Significant negative correlation was found between UA-S/D ratio with other parameters except for neonatal death and ICU admission there was no significant correlation. The CPR is an excellent predictor of unfavorable perinatal outcome in full-term normal pregnancy.

CONCLUSION

In full-term normal pregnancy the CPR is an excellent prediction of unfavorable perinatal outcome.

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الملخص العربي

نسبة الدوبلر الدماغي الى المشيمي في توقع النتائج العكسية في الفترة المحيطة بالولادة في فترة الحمل الطبيعي

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ملخص البحث

الخلفية: نسبة الدماغ الى المشيمة من الممكن ان تحدد الجنين الذى لا ينمو تماما عند الولادة و توقع مخاطر نتيجة الحمل. في حالات الحمل عالية الخطورة في فترة الثلث الاخير من الحمل، اثبتت الدراسات ربط النسبة المنخفضة للدوبلر الدماغي الى المشيمي الناتج عن زيادة مؤشر النبض في الشريان السري أو انخفاض مؤشر النبض في الشريان الدماغي الأوسط للجنين بارتفاع مخاطر الحمل.

الهدف: تقييم الفائدة التنبؤية لنسبة الدوبلر الدماغي الى المشيمي في حالات الحمل الطبيعي الكامل (37 أسبوعًا - 40 أسبوعًا)،غير المصحوب بمضاعفات في التنبؤ بحدوث نتائج سيئة للحمل.

الطرق: اجريت هذه الدراسة المقطعية على خمسمائة امرأة حامل بحمل طبيعي مكتمل المدة (37-40 أسبوعًا) و الاتي ولدن في مستشفى الزهراء الجامعي ومستشفى السنبلاوين العام في الفترة من يونيو 2021 إلى يونيو 2022. خضعت جميع النساء لعمل موجات فوق الصوتية على البطن، طول عظم الفخذ ، محيط البطن، عمر الحمل، كامل ، تخطيط قلب للجنين، ودوبلر سري ومشيمي للشريان الدماغي الأوسط والشريان السري.

النتائج: ارتبطت نسبة الانقباض / الانبساط للشريان الدماغي الأوسط عكسياً مع الضغط الجزئي لثاني اكسيد الكربون في الدم الشرياني، بينما ارتبطت نسبة الانقباض / الانبساط في الشريان السري إيجابيا مع الضغط الجزئي لثاني اكسيد الكربون في الدم الشرياني عكسيا مع جميع المؤشرات الأخرى باستثناء وفاة حديثي الولادة.

الاستنتاجات: في الحمل الطبيعي المكتمل المدة تعد النسبة ما بين المشيمة الى الدماغ مؤشرًا ممتازًا على النتائج الغير مرغوبة في الفترة المحيطة بالولادة.

الكلمات المفتاحية: النسبة الدماغية المشيمية، الدوبلر، نتائج الجنين، المؤشرات الحيوية.

الباحث الرئيسي:

الاسم: نبيلة أمين محمد، قسم النسا و التوليد، مستشفيي السنبلاوين العام، السنبلاوين، الدقهلية، جمهورية مصر العربية.

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