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Original Article

Effectiveness of Cerebroplacental Ratio Estimation Early in Labor as A predictor of Adverse Perinatal Outcomes in Full-term Low-risk Pregnancy

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ABSTRACT

Objective of the Study: To test the efficacy of the cerebroplacental ratio [CPR] in the prediction of early labor fetal distress and adverse neonatal outcomes in full-term [FT] low risk pregnancy.

Patients and Methods: One hundred fifty pregnant women met the inclusion and exclusion criteria were subjected for the estimation of umbilical artery [UA] and middle cerebral artery [MCA] pulsatility indices [PI]. CPR is calculated by dividing MCAP/UA. All of these measures have been converted to multiple medians [MOMs]. The findings of CPR MOM were Correlated with the following; traces of cardiotocography; cesarean section [CS] for fetal distress; 5 min APGAR scoring; cord PH; and NICU admission. The ROC curve was used to test CPRMOM's predictive performance of adverse perinatal outcomes.

Results: Out of 150 patients, 18 [12%] showed abnormal CPR MOM<1. All adverse perinatal outcomes were significantly higher among participants with reduced CPR MOM <1 compared to those with normal one, P value =0.000. There was negative significant correlation between CPRMOM and both of emergency CS, [r=-0.293, P<0.001] and NICU admission [r=-0.302, P<0.001]. ROC curve showed that CPRMoM is good negative predictor, in both CS due to fetal distress, and NICU admission at cut off values, ≤0.97 and ≤0.84 with sensitivity, 72.7 % and 75.0 %, specificity, 91.4 % and 92.3 % with AUCs, 0.778 and 0.827, P = 0.005, and < 0.001 respectively.

Conclusion: Reduced CPRMOM < 1 considers a good predictor for both of CS due to fetal distress and NICU admission; however normal CPR doesn't perfectly rule them out. Reduced CPR MOM is a poor predictor for each of initial non reassuring CTG, APGAR score at 5 min and lower umbilical PH. Nevertheless, normal CPRMOM considers as good predictor for normal fetuses.

Keywords: Doppler Ultrasound; Cerebroplacental Ratio; Cardiotocography; Adverse Perinatal Outcomes

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* Main subject and any subcategories have been classified according to the research topic.

INTRODUCTION

Labor proceedings is most challenging period for the fetoplacental unit [1], during uterine contraction the placental perfusion is decreased up to 60% [2]. Fetal hypoxia during labor is most leading cause of adverse perinatal outcome [3] It can lead to various neurodevelopmental disabilities ranging from school difficulties to dyslexia, attention deficit hyperactive disorders, vision or hearing impairment and mental disorders as cerebral palsy [4]. Unfortunately, current data has been found that intrapartum hypoxia and adverse perinatal outcome, more likely developed in uncomplicated pregnancies [5]. It was found that about 70% of still birth, 80% of fetal distress occur in appropriate for gestational age [AGA] [5]. So, the available screening policy depends on history of disease and intrapartum events do not define high risk cases that prone to intrapartum hypoxia. Therefore, perinatal care should determine the fetuses with hypoxia rather than small fetuses [6].

Despite wide spread use of intrapartum electronic fetal monitoring [EFM], however, there is controversy about the feasibility of its use. It shown that EFM has low specificity in predicting of fetal acidosis and has not avoid or even reduce the perinatal death [7]. Moreover, there is evidence that use of EFM increase the rate of unnecessary CS and operative vaginal delivery [8]. Many studies found that CPR evaluate both limited placental function and consequently fetal circulatory accommodation [9]. A low CPR suggests that COP is redistributed to the cerebral circulation, coinciding with an adverse perinatal outcome [10].

AIM OF THE WORK

Aim of this work was to evaluate the role of CPR Doppler in predicting intrapartum fetal distress and adverse perinatal outcome in FT low risk pregnancy in early labor.

PATIENTS AND METHODS

This was a prospective observational study carried out at Department of Obstetrics & Gynecology, Al-Zharaa University Hospital, Cairo, Egypt, from september 2019 - May 2020 on 150 women with singleton full term low risk pregnancies, coming to obstetric word with true labor pain, were in early labor

and anticipating for vaginal deliveries. Low risk pregnancies mean absence of maternal disease, pregnancy complications with normal fetal growth which detected by U/S. Early labor is defined by presence of at least 3 contractions in 10 minutes each one lasting 45 second, dilated cervix 3-4 cm and 70% effaced.

Inclusion criteria: healthy pregnant women, aged 18-40 years, average BMI, with singleton vertex presentation, gestational age at 37-41 weeks [detected by LMP and confirmed by early scan], appropriated normal fetal growth [determined by U/S growth scan performed at 30-36 weeks] were included. While patients with; BMI < 17 or > 40 [in early booking of antenatal care or after delivery]; multiple pregnancies; preexisting chronic disease; pregnancy induced disease; patients with fetal anomalies; or fetal growth restriction; patients with previous scar or cervical dilatation > 5 cm were excluded.

Informed consent was taken from all participants before enrolling this study, the latter is approved as ethical committee of Faculty of Medicine of girls, Cairo, Al-Azhar University. On admission, all participants were subjected to; full details history; complete examination and abdominal U/S to fulfill inclusion and exclusion criteria. Transabdominal color Doppler U/S is applied to measure blood flow in both [UA] and [MCA]. This done between the uterine contractions in absence of fetal movement, using angle of insonation close to 0° between Doppler beam and direction of blood flow in each vessel [International U/S using an automated Standard trace of at least three consecutive waveforms. Plustile artery indices used to assess impedance flow. CPR defined as MCAPI divided by UAPI, Doppler indices, including the CPR, were converted into multiples of the medians [MOMs] for adjusting to the gestational age CPR was considered abnormal if < 1.0 MOM or less than 5th percentile [10, 11]

Electronic monitoring of fetal heart by CTG was done. The results of stress test categorized regarding ACOG Practice Butlletin [12]. Diagnosis of intrapartum fetal distress based on abnormal CTG trace [non reassuring CTG] is defined by presence of at least three recurrent late or variable decelerations in 10 minutes, Bradycardia and or sinusoidal pattern [12]. Mode of delivery and indication of CS were recorded.

After delivery, either spontaneous vaginal delivery or CS, the baby was treated with dryness, warmth, gentle suctioning and tactile stimulation if needed. Neonatal resuscitation was performed for the baby that didn't show normal vitals for the age, according to Neonatal Resuscitation Program [13]. APGAR scoring within 5 min, cord blood PH, NICU admission and neonatal deaths were recorded. Fetal birth weight in grams is converted into centile [14]. Correlation is established between CPR and adverse perinatal outcomes. The latter is defined by presence of non-reassuring CTG, CS due to fetal distress, APGAR score < 7, cord PH < 7.1. NICU admission more than 24 h and neonatal death. ROC curve is used to detect the cut off value, sensitivity, specificity of CPR in prediction of fetal distress and adverse perinatal outcomes.

Sample size: Sample of about 150 pregnant women, it was calculated using the Cochran formula for cross-sectional studies: $n = Z^2 P[1-P]/d^2$; Where **n** is the sample size, **Z**= 1.96 which is the standard normal variate [at 5% type I error], **p** =expected proportion of adverse fetal outcome due to low CPR based on previous studies, **d** = absolute error or precision it's considered 5%. It was about 139 with non-response rate of 5%. So, the total sample size was 150.

RESULTS

Demographic data of the participants are summarized in table [1] The Mean of UA-PI MOM was 0.95±0.09, mean MCA-pl MOM was 1.1±0.18 and mean CPR MOM was 1.16±0.2. We considered the cut level of CPR MOM <1 was abnormal level. Out of 150 patients, 18 [12%] showed abnormal CPR MOM<1. Initial non-reassuring tracing of stress test CTG was recorded in 16 women [10.7%] [Table 2]. No cases of stillbirth were recorded. There were 128 women [86%] underwent to SVD while twenty-two women were delivered by C.S [14.7%]. The causes of CS in participants attributable to 1-Suspected fetal distress reported in 12 women [8%]; and 2-Arrested Partogram in the remaining 10 cases [6.7 %].

Abnormal APGAR score<7 at 5 min. was recorded in 10 newborns [6.7%], 13 newborns [8.7%] had lower umbilical pH [< 7.1]. Eight neonates [5.3%] required more than 24 h NICU admission. The mean birth weight of newborns was 33410± 331.2 in grams and 51.5±33.6 percentile. Newborn weights were ranged from 21st - 89th percentile i.e, all of them were appropriate for gestational age [AGA] [table 3]. All adverse perinatal outcomes were significantly higher among participants with reduced CPR MOM <1 compared to those with normal CPR MOM >1 [Table 4]. Pearson correlation Coefficient used to find relation between CPR and adverse perinatal outcomes It revealed that was negative significant correlation between CPR MOM and both of CS due to fetal distress [r=-0.293, P<0.001] and NICU admission [r =-0.302, P<0.001. On other hand there was no correlation between CPR and each of initial non reassuring CTG, APGAR score at 5 min and umbilical PH as follows; [r=0.085, p=0.300]; [r 0.116, p 0.157] and [r=0.023, p=.0.780] respectively. Also, no relation was found between the birth weight and CPRMOM, r=0.021and p= 0.798 [Table 5]. ROC curve analysis showed that abnormal CPR MoM was a good negative predictor marker than positive one in case of CS due to fetal distress at cut off value ≤0.97 with sensitivity of 72.7 and specificity, 91.4, PPV,40.0, NPV,97.4 with AUC 0.778 and P value = 0.005 and NICU admission at cut off value ≤0.84 with sensitivity of 75.0 and specificity, 92.3, PPV of 35.3, NPV of 89.5 with AUC 0.827 and P value<0.001. While CPR was considered a poor predictor in initial pathological CTG, lower APGAR score [<7] and low umbilical pH [<7.1] as follows; at cut off values of, ≤ 0.97, ≤ 0.85and ≤ 1 with AUCs of 0.538,0.534 and 0.500 with sensitivity of 39.3%, 45.2% and 42.9 % and specificity of 90.2%, 90.6% and 76.2%, positive predictive values [PPVs] of 35.0%, 27.8 % and 8.1% and negative predictive values [NPVs] of 91.5%, 95.4% and 96.5% respectively with p values >0.05. No neonatal deaths were recorded, [table 6; Figures 3-7]

Table [1]: Demographic profile of the studied group.

		N =150
Maternal age [years]	Mean ± SD; Range [max. -mini.]*	27.14 ± 3.4; [37-19]
Maternal BMI [kg/m²]	Mean ± SD; Range	25.66 ± 1.97; [32.48-23.56]
Gestational age [weeks]	Mean ± SD; Range	38.63 ± 1.61; [41-37]
Parity	Mean ± SD; Range	1.06 ± 0.96; [3-0]

* Range [max. -mini.]*= Max= maximum, Mini= minimum

Table [2]: Intrapartum assessment of fetal parameters [doppler U/S and CTG] among the studied group.

		N =150	
UA PI [MoM]	Mean ± SD; Range	95±0.09; 0.78-1.21	
MCA PI [MoM]	Mean ± SD; Range	1.10±0.18; 0.76-1.60	
CPR *	Mean ± SD; Range	1.88±0.33; 1.05-2.77	
CPR [MoM]	Mean ± SD; Range	1.16±0.20; 0.65_1.68	
		No.	%
CPR [MoM] classification	Abnormal <1	18	12
	Normal >1	132	88
CTG results: **	Non reassuring	16	10.7
	Reassuring	134	89.3

* UA PI = Umbilical artery pulsatility index, MCA PI =Middle cerebral artery pulsatility index, CPR Cerebroplacental ratio, **CTG=cardiotocography

Table [3]: Perinatal outcome assessment among the studied group.

		N =150		%	
Mode of delivery*	NVD	128		86	
	CS	22		14	
Causes of CS		No.=22/150		%	
	Persistent pathological CTG	12		8	
	CPD or failure to progress	10		6.6	
Umbilical artery pH	Mean ± SD; Range	7.22 ± 0.05; [7.05-7.29]			
Umbilical pH classification (n,%)	Acidemia [<7.1]	13		8.7	
	Normal [≥7.1]	137		91.3	
APGAR score at 5 min	Low [< 7]	10		6.7	
	Normal [>7]	140		93.3	
Birth weight [gm]	Mean ± SD; Range	3410± 331.2; [2.750-4200]			
Birth weight [centile]	Mean ± SD; Range	51.5±33.6; 21 st - 89 th			
NICU admission (n,%)	Yes	8		5.3	
	No	142		94.7	

Table [4]: The frequency of abnormal CPR MOM in cases with adverse perinatal outcomes.

	Abnormal CPR [N=18]	Normal CPR [N=132]	X ²	P value
Abnormal CTG	7	9	17.1	<0.001*
Normal	11	123		
C.S due to fetal distress	8	4	36.9	0.000
Normal or CS due to arrested partogram	10	128		
Low umbilical PH<7.1	7	6	23.6	0.000
Normal	11	126		
Low APGAR<7	5	5	14.6	0.000
Normal	13	127		
NICU admission	6	2	31.8	0.000
No	12	130		

Table [5]: Correlation between CPR and adverse perinatal outcomes.

	CPR MOM	
	r	p
Birth Weight	0.021	0.798
APGAR score	0.116	0.157
CTG	0.085	0.300
Umbilical PH	0.023	0.780
CS according to fetal distress	-0.293	<0.001*
NICU	-0.302	<0.001*

Table [6]: ROC curve analysis of CPR MoM to predict CS due to fetal distress and neonatal outcomes.

	CPR MoM							AUC
	Cut off	Sensitivity	Specificity	PPV	NPV	Std error	P value	
CS according to fetal distress	≤0.97	72.7	91.4	40.0	97.7	0.098	0.005*	0.778
APGAR score	≤0.85	45.5	90.6	27.8	95.4	0.121	0.777	0.534
CTG	≤0.97	39.3	90.2	35.0	91.5	0.088	0.663	0.538
NICU	≤0.84	75.0	92.3	35.3	98.5	0.083	<0.001*	0.827
Umbilical pH	≤1	42.9	76.2	8.1	96.5	0.142	0.997	0.500

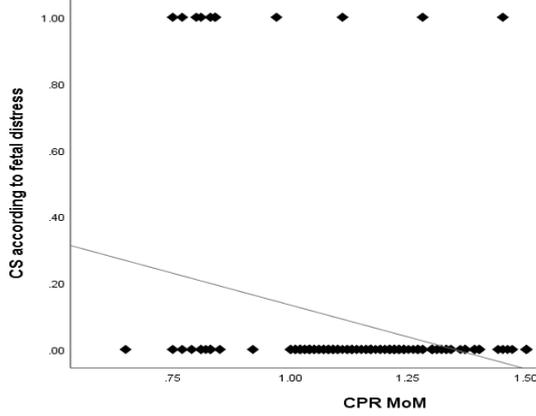


Figure [1]: Correlation between CPR and CS according to fetal distress

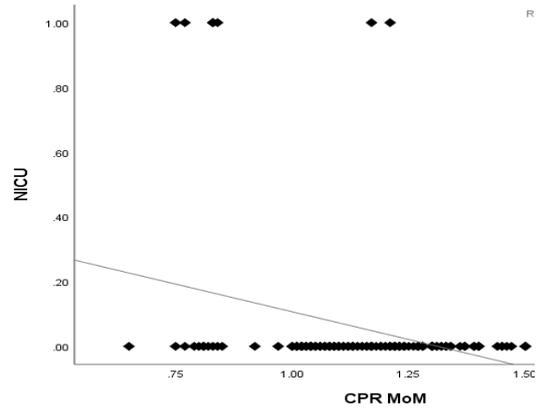


Figure [2]: Correlation between CPR and NICU

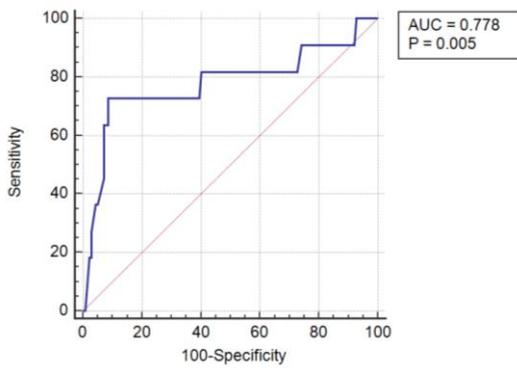


Figure [3]: ROC curve analysis of CPR to predict CS according to fetal distress

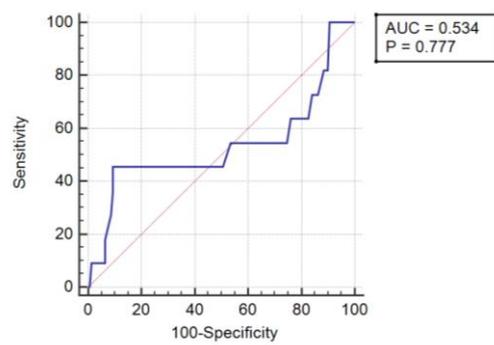


Figure [4]: ROC curve analysis of CPR MoM to predict Low APGAR score

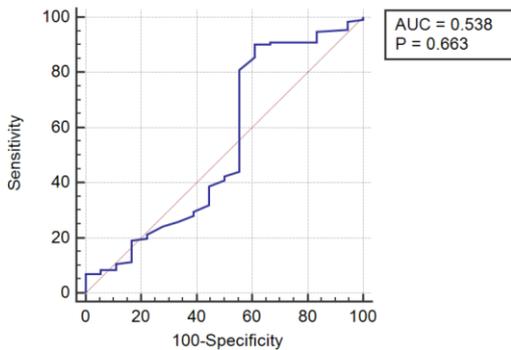


Figure [5]: ROC curve analysis of CPR MoM to predict Pathological CTG

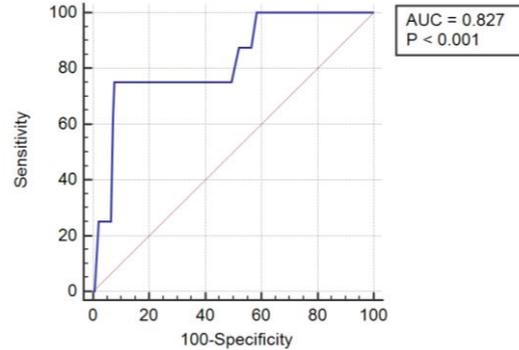


Figure [6]: ROC curve analysis of CPR MoM to predict NICU

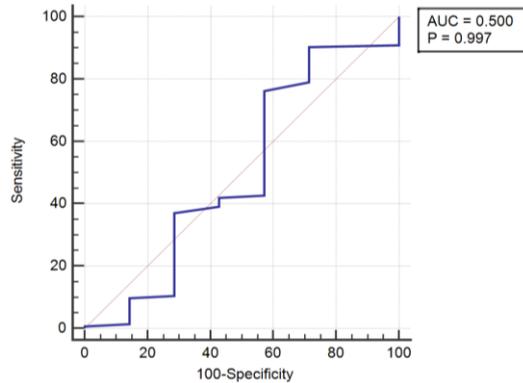


Figure [7]: ROC curve analysis of CPR MoM to predict lower Umbilical pH

DISCUSSION

This study is based on the concept that early labor is the optimal time to challenge placental reserve. During Uterine contractions, the uterine blood flow is diminished up to 60%, and this reduction perfusion may affect greatly the undetectable cases of suboptimal placental perfusion including low risk babies Janbu and Nesheim [15]. CPR reflects the hemodynamic alteration and redistribution of blood flow more precisely than the umbilical or cerebral flow when each used separately.

Our study considered the cut level of CPR MOM < 1 was abnormal level. Therefore, we analyzed our results regarding this cut level. The current study revealed that 18 participants [12%] had abnormal CPR, this was in accordance with Dall'Asta et al. [16] who conducted study on 572 low risk FT pregnant women in labor and they found that abnormal CPR MOM was 9.6%. Gruettner et al. [17] conducted retrospective research included 2,270 women with singleton low risk pregnancies, regarding the adverse outcome that based on CPR estimation. The authors revealed the rate of abnormal CPR among their participants was 5.5. The authors didn't measure CPR intrapartum, but they measured it 8 weeks before delivery. Electronic fetal surveillance is still considered to be the most popular intrapartum fetal surveillance tool currently used [16]. Although there was a debate about the efficiency of non-reassuring stress CTG in prediction of adverse neonatal outcome Devane et al. [18]. Ultimately, CTG is a commonly recognized intrapartum fetal surveillance technique aimed at detecting fetuses with hypoxia during labor. Initially, the current research revealed 10.7% experienced non reassuring CTG and we showed that higher frequency of abnormal CTG among the women that had lower CPR compared to those with normal CPR, 36.8% VS 6.8%. Our study revealed that, there was no correlation between CPR MOM and pathological CTG. Our patients that had pathological CTG were subjected to conservative measure i.e, change of maternal position to boost placental circulation, short term oxygen mask, stop oxytocin infusion if used. Subcutaneous 0.25mg terbutaline given if there was uterine hyper stimulation and cervical examination to exclude, 1-Cord prolapse, 2-Descent of the head. Four women with non-reassuring CTG turned to reassuring CTG after this conservative measure. The remaining women with

abnormal CTG were 12[8%], they underwent to emergency CS. The current study showed higher significant increase in frequency of CS [due to fetal distress which based on persistent abnormal CTG] in women with abnormal CPRMOM <1 [8/18, [44%], compared to those with normal CPR>1[4/132 [3%] with $p=0.000$. This result agrees with Dall'Asta et al. [14] who found that obstetric intervention for suspected fetal distress in labor was frequently higher among cases with reduced CPR MoM compared to cases with normal CPR MOM [9/54 [16.7%] vs 28/508 [5.5%]; $P=0.001$. Similarly, Sengodan and Mathiyalagan [20] found that 25 babies out of 100 full term uncomplicated pregnancy that had CPR<1, 18 of them were delivered by CS and only 7 of them were delivered vaginally [spontaneous vaginal delivery]. We found that was a significant negative correlation between the rate of emergency CS due to Fetal distress and abnormal CPR, $r=-0.293$, $p=0.001$. Although, there were no available articles showing the relationship between mode of delivery and CPR in low risk, however, all of these articles are based on the increase the incidence of CS among patients with abnormal CPR. Our study revealed that abnormal APGAR score after 5min of labor was significantly higher in newborns that had abnormal CPR than those with normal CPR, 5/18[27.8%] Vs 5/132 [3.8%] respectively.

Our study coincides with Gramellini et al. [21] who found that Apgar score <7 at 5 min was significantly higher in newborns with abnormal CPR compared to those with normal CPR, 16.6% versus 2.7% [$p<0.001$]. Also, Gruettner et al. [15] in accordance with our result, they found a significant lower APGAR scores at 1, 5 and 10 minutes in the group of. Patients with lower CPR compared to the group with normal CPR [$p<0.001$]. On other hand our result was in contrast with of Prior et al. [9] who compared perinatal outcome in 775 AGA fetuses with CPR below or above 0.6765 MoM, the authors showed no significant differences could be found regarding 5-min Apgar score [2.0% vs. 1.2%; $p=0.63$]. The Current study found that a higher frequency of abnormal umbilical PH< 7.1 in newborns that had abnormal CPR than those had normal CPR, 7/18[38.8%]vs6/132[4.5%] respectively], $p=0.000$. Our result consistent with Dall'Asta et al. [16] who reported that reduced CPR MoM was significantly higher in newborns with cord arterial pH < 7.10 compared with those normal one [9.2% vs 2.4%; $P < 0.01$]. Also,

Morales-Rosello et al. [22] evaluated the CPR in AGA fetuses aged 37-41 weeks, and reported that umbilical pH was significantly lower in AGA newborn who had an abnormal CPR than those with a normal CPR. The present study indicated no significant correlation between low CPR value and low umbilical pH at birth, $r=0.023$, $p=0.378$. Similarly, Khalil et al. [5] found that, there was no correlation between abnormal umbilical cord pH and low CPR in AGA. However, some authors were able to demonstrate significant associations between low CPR and low umbilical pH [23,24], this heterogeneity may be attributed to different cut off values used in the previous studies. In addition, in spite of the previous studies conducted on low-risk pregnancy, they were included fetuses that had low birth weight, on contrary our study fortunately was only included fetuses with normal birth weight. The current study showed that newborns with abnormal CPR had higher rate of NICU admission compared to those with normal CPR, 6/18 [33.3%] vs 2/132 [3%] respectively, $p=0.000$. This data consistent with Dall'Asta et al. [16] who reported the rate of NICU admission was increased in newborns with reduced CPR [1.9%] compared with those normal one [1.2%]. Our study revealed negative significant correlation between CPRMOM and NICU admission, $r=-0.302$, $P<0.001$. Stumpf et al. [25] in line with our result they conducted a study to detect the effectiveness of Doppler in predicting fetal compromise, in FT pregnant women at low risk, the authors found a substantial correlation between Doppler parameters and the risk of NICU admission. Flatley and Kumar [26] studied, analogously, the ability of CPR Doppler to predict adverse perinatal outcomes at a low-risk cases. The authors showed that Doppler parameters including CPR had a significant predictor of NICU admission. The current study revealed that no correlation between birth weight and CPR MOM, $r=0.021$, $p=0.798$.

Regarding ROC analysis, CPRMOM was considered a good negative indicator than a positive one in both cases of CS due to fetal distress at cut-off value 0.97 with sensitivity of 72.7% and specificity 91.4% with AUC 0.778 and P value = 0.005, and in cases of NICU admission at cut-off value 0.84 with sensitivity of 75.0% and specificity 92.3% with AUC 0.827 and P value < 0.001. While CPR was considered a poor indicator for cases of initial Pathological CTG, lower APGAR score and umbilical PH [table 6, figure

3,4,5,6,7]. Our result coincides with Prior et al. [27] who reported that abnormal CPR was a better predictor for emergency CS than abnormal UA or MCA. Also, our result in agreement with Mendez-Figueroa et al. [28] who stated the best predictors for recognizing the babies at risk for CS during the labor were the followings, abnormal CPR, fetal weight < third centile and elevated uterine PI.

On other hand, Dall' Asta et al. [16] reported that abnormal CPR MOM in early labor represents poor predictor for all adverse perinatal outcomes with AUC, was 63.7 with ppv18%,12% for fetal distress and adverse neonatal outcomes respectively. Also, they reported that normal CPR MOM considered a good predictor for normal fetuses. Similarly, Sherrell et al. [29] and Khalil et al. [5] and DeVore [10] reported that the CPR is an independent predictor of intrapartum fetal distress, poor acid base state at birth and of NICU admission at term. Nevertheless, previous studies seem in conflict with our results, but this attributable to several factors; 1- Different sample size, relative to our sample size, 2-Different cutoff values used, 3-some of these studies did not use CPR in MOM, 4-other studies were included FGR babies. In term of ability of CPR in prediction of initial pathological CTG, lower APGAR score and lower umbilical PH. We found that though CPR was a poor predictor of these previous adverse outcomes, however due to its high NPP, which exceeded 90%, normal CPR was a good predictor for normal fetuses.

Conclusion: Reduced CPR-MOM < 1 is significantly increased in cases of fetal distress and adverse neonatal outcomes. Reduced CPR considers as a good predictor for both of emergency CS and NICU admission, however normal CPR dose not a perfectly rule them out. Reduced CPR considers a poor predictor for each of initial non reassuring CTG, APGAR score at 5 min and lower umbilical PH; nevertheless, normal CPR is good predictor for normal fetuses. Therefore, we suggest the addition of CPR MOM to the intrapartum fetal surveillance parameters to ameliorate the prediction of jeopardized fetuses for intrapartum hypoxia in low-risk pregnancy.

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