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Comparing four modalities of fetal assessment and their impact on perinatal outcome in cases of asymmetrical IUGR

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Abstract
Objectives: We aim to compare the diagnostic value of cerebroplacental ratio, rBPP, modified biophysical profile (MBP) and non- stress test (NST) in predicting fetal outcome in cases with asymmetrical IUGR.
Methods: The study was conducted from June2020 to June 2021 after approval of Alexandria university Ethics Committee, Alexandria, Egypt.
After signing an informed consent, pregnant patients with asymmetrically growth retarded fetuses just before delivery were clinically examined and subjected to Doppler ultrasonography assessing cerebroplacental ratio(CPR), modified biophysical profile testing (MBPP), non- stress test (NST) and rapid biophysical profile (rBPP).
Results: Results of CPR were statistically significant (Neonatal acidaemia; $X^{2=}$ 12.379, p= 0.001*, Apgar at one minute; $X^{2=}$ 9.114, p= 0.004*and Apgar at five minutes; $X^{2=}$7.593, p= 0.014*). rBPP was statistically significant only inone minute apgar score but not with acidaemia but all its normal cases had normal CPR.
Conclusion: The CPR is a good predictor of adverse neonatal outcomes in cases of IUGR. RBP may be a good, inexpensive and less time-consuming alternative for evaluating antepartum fetal well-being.

Keywords: IUGR, CPR, rBPP, nonstress test, fetal outcome.

Introduction
Intrauterine growth restriction (IUGR) or fetal growth restriction (FGR) is defined as an estimated fetal weight (EFW) and/or abdominal circumference (AC) at one point in time during pregnancy being below 3rd percentile or EFW and/or AC below the 10th percentile for gestational age with deranged Doppler parameters [1]. IUGR has two main types:

- type I: symmetrical intrauterine growth restriction
- type II: asymmetrical intrauterine growth restriction

Asymmetrical intra- uterine growth retardation (IUGR) accounts for 70-80% of all IUGR cases [2]. This fetus suffers from decreased oxygen or nutrient supply caused by placental insufficiency during the third trimester of pregnancy which can be assessed by Doppler ultrasonography decreasing the risk of neonatal morbidity and mortality [3, 4].
Nonstress tests and/or biophysical profile scoring are also recommended tests for standard fetal surveillance [5, 6].
Tongsong *et al*., proposed the rapid biophysical profile (rBPP) which consists of amniotic fluid index measurement (AFI) and observation of sound-provoked fetal movement (SPFM) [7]. This new test could predict adverse perinatal outcome with a 98.18% accuracy [8].
The present study was conducted to compare the diagnostic value of rBPP, cerebroplacental ratio using Doppler ultrasonography, modified biophysical profile (MBP) and non- stress test (NST) in predicting fetal outcome in pregnant women with asymmetrical IUGR.

Material and Methods
The study was conducted from June2020 to June 2021. It was approved by the Ethics Committee of Alexandria faculty of medicine, Alexandria, Egypt. Pregnant patients with asymmetrically growth retarded fetuses were gathered from the delivery ward just before delivery.

All patients met the following criteria: single fetus with asymmetrical IUGR and no structural malformations, gestational age over 32 weeks.

After signing an informed consent to participate in the study, they were clinically examined and subjected to Doppler ultrasonography assessing cerebroplacental ratio (CPR), modified biophysical profile testing (MBPP), non- stress test (NST) and rapid biophysical profile (rBPP).

The rBPP testing was performed by a single operator. It has 2 items each has 2 points; amniotic fluid index (AFI) and fetal response to acoustic stimuli. (AFI) was evaluated using a Voluson E8 (General Medical System, Healthcare, Zipf, Austria) machine, equipped with a convex multifrequency transducer (RAB 4-8) and through a real-time two-dimensional ultrasound, amniotic fluid index measurement (AFI) was calculated by dividing the uterus into four quadrants using the linea nigra for the right and left divisions and the umbilicus for the upper and lower quadrants. We measured the maximum vertical amniotic fluid pocket diameter in each quadrant not containing cord or fetal extremities; the sum of these measurements in centimeters was considered the AFI. Values over 5 cm were considered normal (score 2) (Table 1). An acoustic stimulus in the form of a ringing bell applied for 3 seconds over the cephalic pole was used to stimulate fetal movement. Detection of fetal movement by ultrasound within 15 seconds after stimulation was considered normal (score 2) (Table I). In absence of fetal movement, the test was repeated up to 3 times.

After 15 minutes rest, MBPP was assessed in terms of fetal heart rate, fetal breathing status, fetal movements, fetal muscle tone (the ability of the fetus to bend the legs and hands and its physical response to collision), and the level of amniotic fluid (four quadrants measurement). Scores from 8 to 10 indicate the fetal proper wellbeing. Scores 6 indicate that the fetus should be re-evaluated within next 12-24 hours. Scores 4 or lower indicate serious complications (Table II) [9, 10, 11].

We performed transabdominal color Doppler ultrasound with a 4–8 MHz transabdominal convex probe and General Electric Voluson (GE Healthcare, Chicago, IL, USA) device during fetal quiescence. At least five reproducible waveforms were analyzed for each fetus at each examination. For both the UA and MCA values, an average of three consecutive automated measurements was recorded for each of the indices. We chose a mid-segment of a free loop of umbilical cord as the site of insonation for recording the UA-PI as described by Acharya *et al*. [12] An angle of insonation <15° and as close to zero as possible was used. Measurements of the MCA indices were performed as previously reported by Mari *et al*. [13] We obtained an axial section of the fetal brain at the level of the cavity of the septum pellucidum and thalamus. Color flow Doppler was used to identify the circle of Willis. The vessel nearest to the transducer was studied with an angle of insonation close to 0° between the ultrasound beam and the direction of blood flow. The proximal one-third of the MCA was sampled close to its origin from the internal carotid artery.

Umbilical and cerebral artery Doppler were assessed and CPR was calculated as the ratio of middle cerebral artery (MCA) to umbilical artery (UA) pulsatility index (PI) values, a ratio more than one is considered normal [14]. NST was performed using the tocodynamometer, it involved 20 minutes fetal heart rate (FHR) monitoring while assessing the number, amplitude, and duration of accelerations that usually correlate with fetal movement. We monitored the fetal heart rate using the Doppler ultrasound transducer, and a tocodynamometer was applied to detect uterine contractions or fetal movement [15]. The patient was asked to record fetal activity by using an event marker.

A normal test result was defined as one in which two or more accelerations peak at 15 bpm or more above baseline, each lasting 15 seconds or more, and all occurring within 20 minutes of beginning the test [16].

Lacking sufficient fetal heart rate accelerations over 40 minutes was considered a nonreactive NST [15].

After delivery, neonates were clinically assessed by the same neonatologist and one minute as well as five minutes Apgar scores were calculated. a 2 mL sample of blood from the umbilical vein was obtained in 3 mL plastic syringes to calculate the pH and pCO_2. Blood samples were analyzed automatically 5 to 10 minutes after birth by the Radiometer.

Statistical analysis

The Data was collected and entered into the personal computer. Statistical analysis was done using Statistical Package for Social Sciences (SPSS/version 22) software.

The statistical test used as follows:

Arithmatic mean, standard deviation, for normally distributed data, comparison between two categorized parameters Chai square test was used. The level of significant was 0.05.

Results

We gathered 29 cases of pregnant females with asymmetrical fetal IUGR, their age ranged from 22 to 35 years with a mean of 27.31years, gravidity from G1 to G6 and parity from P0 to P4, Gestational age at the time of examination ranged from 32 weeks to 37 weeks with a mean of 35.28 (Table III). Fetal assessment was done by four methods Doppler (assessing the CPR), NST, MBPP, rBPP.

Within the whole sample we had;

- 18 Cases with normal CPR (MCA PI/UA PI more than one) and 11 cases with abnormal CPR (MCA PI/UA PI less than one) (Table III).
- 10 cases had normal MBPP, 10 cases had abnormal result and the test was equivocal in 9 cases (Table III).
- 6 Cases with reactive NST, 14 cases were non- reactive, 5 cases showed late deceleration, 3 cases with variable deceleration and only one case with early deceleration (Table III).
- 3 Cases had normal, ***rBPP*** 17 cases were equivocal and 9 cases had abnormal test (Table III).
- 23 Cases had neonates with normal ***cord blood sample*** and 6 cases had neonatal acidaemia. (Table III).
- 18 Neonates had normal ***Apgar score at one minute***, and 11 had abnormal score (Table III).
- 25 Neonates had normal ***Apgar score at five minutes,*** and 4 had abnormal score (Table III).

As regards fetal outcome

Cases with normal CPR had no neonatal acidaemia, abnormal Apgar at one minute was reported in 3 neonates and all neonates had normal Apgar score at five minutes. Cases with abnormal CPR (less than one) had neonatal acidaemia in 6 neonates, abnormal Apgar score at one minute in 8 neonates and abnormal five minutes Apgar score in 4 neonates. These results were statistically significant (Neonatal acidaemia; $X^{2=}$ 12.379, p= 0.001*, Apgar at one minute; X^2= 9.114, p= 0.004*and Apgar at five minutes; $X^{2=}$7.593, p= 0.014*) (Table IV, Figure 1).

Cases with normal rBPP had no fetal acidaemia but cases with abnormal rBPP had 4 neonates with fetal acidaemia and cases

with equivocal rBPP had 2 neonates with fetal acidaemia which was statistically nonsignificant ($X^{2=}$ 0.879, p=0.644) (Table V).
All neonates of cases with normal rBPP had normal one minute and five minute Apgar score but cases with abnormal rBPP had 10 neonates with abnormal one minute and only 3 of them had abnormal five minute Apgar scoring and cases with equivocal rBPP had only one neonate with abnormal one minute as well as five minute Apgar score. These results were statistically significant for Apgare score at one minute; $X^{2=}$7.735, p=0.021*(Table V, Figure 2) but not for Apgare score at five minutes where $X^{2=}$ 0.747, p= 0.688 which was statistically nonsignificant) (Table V).
All cases with normal NST had no neonatal acidaemia, normal one minute as well as five minute Apgar scores. Cases with nonreactive NST had neonatal acidaemia in 5 neonates and abnormal Apgar score at one minute in 8 neonates reduced to 4 at five minutes scoring. We had 5 cases with late deceleration resulted in only one neonate with mild acidaemia and 3 neonates with abnormal one minute Apgar score who became normal at five minute Apgar scoring. These results were statistically nonsignificant (Neonatal acidaemia; $X^{2=}$4.536, p=0.338, one minute Apgar score; $X^{2=}$ 9.340, p=0.063 and five minute Apgar score; $X^{2=}$4.971, p= 0.290) (Table VI).
MBPP was normal in 8 cases 2 of them had their neonates with acidaemia, 4 neonates with abnormal one minute Apgar score and only one neonate with abnormal five minute Apgar score. Cases with abnormal MBPP had fetal acidaemia in 2 neonates, abnormal one minute Apgar score in 4 neonates and abnormal five minute Apgar score in only one neonate. Cases with equivocal MBPP had fetal acidaemia in 3 neonates, abnormal one minute Apgar score in 2 neonates and abnormal five minute Apgar score in 2 neonates. These results were statistically nonsignificant (Neonatal acidaemia; $X^{2=}$ 0.019, p= 0.991, one minute Apgar score; $X^{2=}$0.117, p= 0.943, five minute Apgar score; $X^{2=}$ 0.780, p=0.677) (Table VII).
When comparing fetal monitoring methods, we found that results of CPR were matching with those of rBPP but not those of MBPP or NST. All cases with normal rBPP had normal CPR and those with either abnormal or equivocal rBPP had abnormal CPR which was statistically significsnt; $X^{2=}$ 10.86, p= 0.004*) (Table VIII).
On the other hand, results of CPR were not statistically significant when related to other methods (MBPP; $X^{2=}$3.515, p= 0.172, NST; $X^{2=}$ 2.917, P= 0.189) (Table VIII).

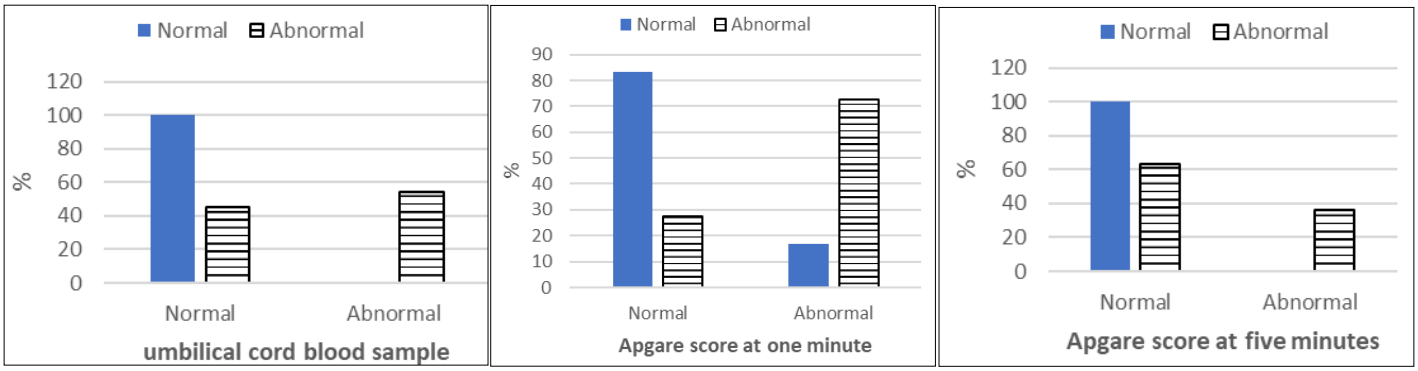

Fig 1: Relation between CPR and fetal outcome parameters.

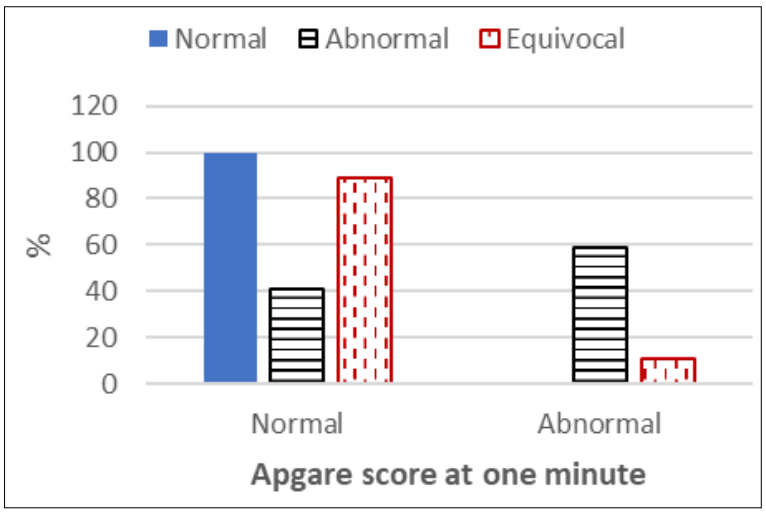

Fig 2: Relation between rBPP finding and fetal outcome parameters.

Table I: RBP scoring

rBPP	Normal	Abnormal
Sound provoked fetal movement	Response	
AFI	> 5 cm	≤ 5 cm
Total	4	0

Score = 4 Normal fetus
Score = 0-2 Fetal hypoxia

Table 2: MBPP

MBPP	Normal	Abnormal
Fetal breathing movements (FBM)	One or more episodes of FBM > 30 sec in 30 min	Absent or no episode of FBM > 30 sec in 30 min
Gross body movements	Three or more discrete body/limb movements in 30 min (episodes of active continuous movement considered as single movement)	Two or less episodes of body/limb movements in 30 min
Fetal tone	One or more episodes of active extension with return to flexion of fetal limb(s) or trunk; opening and closing of hand considered normal tone	Either slow extension with return extension with return to flexion to partial flexion or movement of limb in full extension or absent fetal movement
Reactive fetal heart rate	Two or more episodes of acceleration of > 15 bpm and of > 15 sec associated with fetal movement in 20 min	Less than 2 episodes of acceleration of FHR or acceleration of < 15 bpm in 40 min
Amniotic fluid volume	> 5 cm	
Interpretation	Score = 8-10 Score = 6 Score = 0- 4	Normal fetus Fetal hypoxia is suspicious Fetal hypoxia

Table 3: Basic demographic and clinical data of the studied group.

	No	%
Age		
<25	10	34.48
25-30	18	62.07
>30	1	3.45
Range	22-35	
Mean±SD	27.31±3.85	
Gravidity		
Range	1-6	
Mean±SD	2.86±1.30	
Parity		
Range	0.0-4.0	
Mean±SD	1.41±1.05	
Gestational age at the time of termination		
Range	32-37	
Mean±SD	35.28±1.60	
CPR,		
Normal	18	62.07
Abnormal		
MBPP	11	37.93
Normal	10	34.48
Abnormal	10	34.48
Equivocal	9	31.03
NST		
Normal	6	20.69
Non reactive	14	48.28
LD	5	17.24
VD	3	10.34
ED	1	3.45
RBP		
Normal	3	10.34
Equivocal	17	58.62
Abnormal	9	31.03
Umbilical cord blood sample		
Normal	23	79.31
Acidaemia	6	20.69
Range	6.90-7.60	
Mean±SD	7.31±0.20	
Apgare score at one minute		
Normal	18	62.07
Abnormal	11	37.93
Range	5.00-10.00	
Mean±SD	7.62±1.70	
Apgare score at five minutes		
Normal	25	86.21
Abnormal	4	13.79
Range	5.00-10.00	
Mean±SD	8.34±1.14	

Table 4: Relation between CPR and fetal outcome

	CPR				X^2 p
	Normal		Abnormal		
	No	%	No	%	
Umbilical cord blood sample					
Normal	18	100.0	5	45.5	12.379
Abnormal	0	0.0	6	54.5	0.001*
Apgare score at one minute					
Normal	15	83.3	3	27.3	9.114
Abnormal	3	16.7	8	72.7	0.004*
Apgare score at five minutes					
Normal	18	100.0	7	63.6	7.593
Abnormal	0	0.0	4	36.4	0.014*

Table 5: Relation between RBP finding and fetal outcome parameters.

	RBP						X2 p
	Normal		Abnormal		Equivocal		
Umbilical cord blood sample	No	%	No	%	No	%	0.879
Normal	3	100.0	13	76.5	7	77.8	0.644
Abnormal	0	0.0	4	23.5	2	22.5	N.S.
Apgare score at one minute							
Normal	3	100.0	7	41.2	8	88.9	7.735
Abnormal	0	0.0	10	58.8	1	11.1	0.021*
Apgare score at five minutes							
Normal	3	100.0	14	82.4	8	88.9	0.747
Abnormal	0	0.0	3	17.6	1	11.1	0.688 N.S.

Table 6: Relation between NST finding and fetal outcome parameters.

	NST										X2 p
	Normal		Non reactive		Late deceleration		Variable deceleration		Early deceleration		
	No	%	No	%	No	%	No	%	No	%	
Umbilical cord blood sample											
Normal	6	100.0	9	64.3	4	80.0	3	100.0	1	100.0	4.536
Abnormal	0	0.0	5	35.7	1	20.0	0	0.0	0	0.0	0.338
Apgare score at one minute											
Normal	6	100.0	6	42.9	2	40.0	3	100.0	1	0	9.340
Abnormal	0	0.0	8	57.1	3	60.0	0	0.0	100	0.0	0.063
Apgare score at five minutes											
Normal	6	100.0	10	71.4	5	100.0	3	100.0	1	100.0	4.971
Abnormal	0	0.0	4	28.6	0	0.0	0	0.0	0	0.0	0.290

Table 7: Relation between MBPP finding and fetal outcome parameters.

	MBPP						X2 p
	Normal		Abnormal		Equivocal		
	No	%	No	%	No	%	
Umbilical cord blood sample							
Normal	8	80.0	8	80.0	7	77.8	0.019
Abnormal	2	20.0	2	20.0	2	22.2	0.991
Apgare score at one minute							
Normal	6	60.0	6	60.0	6	66.7	0.117
Abnormal	4	40.0	4	40.0	3	33.3	0.943
Apgare score at five minutes							
Normal	9	90.0	9	90.0	7	77.8	0.780
Abnormal	1	10.0	1	10.0	2	22.2	0.677

Table 8: Relation between cerebroplacental ratio (CPR) and results of RBP, MBPP and NST

	(CPR)				X^2 p
	Normal (18)		Abnormal (11)		
MBPP	**No**	**%**	**No**	**%**	
Normal	4	22.2	6	54.5	3.515 0.172 N.S.
Abnormal	8	44.4	2	18.2	
Equivocal	6	33.3	3	27.3	
RBP					
Normal	12	66.6	0	0.0	8.114 0.005*.
Abnormal	2	0.11	7	63.6	
Equivocal	4	27.8	4	36.4	
NST					
Normal	6	33.3	0	0	2.917 0.189 N.S
Nonreactive	7	38.8	7	6.36	
LD	2	11.1	3	26.6	
VD	2	11.1	1	5.55	
ED	1	5.55	0	0	

Discussion

Placental insufficiency is the main cause of Intrauterine growth restriction (IUGR), it forces the fetus to preserve oxygen and nutrient supply to the brain (‘brain-sparing') which results in altered cerebral haemodynamics that may persist after birth [17].

A lot of authors recommended calculating the cerebroplacental ratio (CPR) to diagnose brain-sparing [18, 19, 20].

In a retrospective cohort study was done in a single tertiary referral center over a 14-year period from 2000 through 2013 to evaluate the association between fetal cerebroplacental ratio (CPR) and intrapartum fetal compromise and admission to the neonatal unit (NNU) in term pregnancies. 9772 singleton pregnancies were included, the umbilical artery pulsatility index, middle cerebral artery pulsatility index, and CPR were recorded within 2 weeks of delivery. Researchers found that the rates of operative delivery for presumed fetal compromise were significantly higher for appropriate-for-gestational-age fetuses with low CPR multiples of the median (MoM) (22.3%) compared to small-for-gestational-age fetuses with normal CPR MoM (17.3%). Accordingly, they concluded that lower fetal CPR was associated with the need for operative delivery and NNU admission at term regardless of the fetal size [21].

In another retrospective study of 2927 term fetuses divided into groups according to birth-weight centile and CPR multiple of the median. At birth, acid–base status was determined by arterial and venous umbilical cord blood pH to determine whether small- and appropriate-for-gestational-age (SGA and AGA) term fetuses with a low cerebroplacental ratio (CPR) have worse neonatal acid–base status than those with normal CPR or not. Researchers found that CPR was better correlated with umbilical cord blood pH (arterial pH, $r^2 = 0.008$, $P < 0.0001$ and venous pH, $r^2 = 0.01$, $P < 0.0001$) than was birth weight (arterial pH, $r^2 = 0.001$, $P = 0.180$ and venous pH, $r^2 = 0.005$, $P < 0.001$). AGA fetuses with low CPR were more academic than were those with normal CPR ($P = 0.0359$ and 0.0006, respectively, for arterial and venous pH). Accordingly, low CPR was considered an important marker of low neonatal pH secondary to placental underperfusion and it can be used in predicting and preventing stillbirth and long-term neurodevelopmental disability [22].

The rBPP which associates SPFM with AFI measurement, the

SPFM reflects the neurologic state of the fetus at the time of the test (acute variable) and the AFI reflects placental function (chronic variable) [6]. Some authors found it to have a low false-positive rate which means that it is extremely safe in case of a normal result.

Somr researchers tested the accuracy of rBPP in 30 IUGR fetuses based on poor outcomes including fetal distress, low Apgar score, admission to the neonatal intensive care unit, and perinatal death. They found that the incidences of negative, equivocal, and positive rBPP were 88.8%, 10.3%, and 0.9%, respectively. Accordingly, the sensitivity of rBPP was 100.0%, its specificity was 89.7%, and it had a positive predictive value of 25%, and a negative predictive value of 100.0%. Accordingly, they concluded that rBPP may be an effective predictor of poor pregnancy outcome in IUGR fetuses and they recommended its use as a back-up test to confirm fetal well-being in pregnancies complicated by IUGR [23].

Others found that rBPP is a highly sensitive test in predicting fetal outcome when compared to other fetal surveillance tests. In a study including pregnant women with insulin-dependent diabetes, rBPP was compared to MBPP, the frequency of normal cases were (88.7%) in the MBPP method and (85.2%) in the rBPP method. Accorddingly, the sensitivity and specificity of rBPP were 56.2% and 90.5% respectively. Researchers concluded that rBPP method compared to MBPP has a better capacity to discriminate non-distressed fetuses from distress-exposed fetuses and they recommended its use as a quick and easy method in crowded centers with limited evaluation tests [24].

Another study was performed in 153 singleton pregnancies to compare the standard (MBPP) to the new rBPP, a positive correlation was found between the two tests ($rs = 0.62$; $p < 0.0001$). Out of the variables, only the NST had a positive correlation with rBPP. The sensitivity, specificity, positive predictive value and negative predictive value of rBPP in predicting adverse outcomes was found to be 71.4%, 87.1%, 35.7%. 96.8% respectively. Accordingly, the authors recommended its use as a primary screening antepartum fetal test in the overcrowded obstetric centers [25].

Standard NST and the new rBPP were used to predict intrapartum fetal distress in a prospective study conducted on a total of 1,069 high-risk singleton pregnancies, rBPP was found to be a reliable predictor of intrapartum fetal distress with higher sensitivity and specificity and better accuracy than the NST [26].

Results of these studies match with ours as we found a statistically significant difference for CPR in predicting fetal outcome assessed by presence of neonatal acidaemia and values of Apgare scoring at one minute and five minutes. As regards rBPP, it was statistically significant only in one minute Apgar score, but when compared with MBPP and NST, it was more accurate as its results were matching with those of CPR, all cases of normal rBPP had normal CPR which means that it is a good positive test.

Conclusion

The CPR better predicted adverse neonatal outcomes in pregnancies complicated by IUGR. This finding may be of particular value in the prediction and prevention of stillbirth and long-term neurodevelopmental disability.

The rBPP may be alternatively used as a primary screening antepartum fetal test in the overcrowded obstetric center. It may suffice as an inexpensive and less time-consuming method of evaluating antepartum fetal well-being.

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