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ORIGINAL ARTICLE

Clinical and Ultrasound Predictors of Adverse Neonatal Outcome at Diagnosis of Late Onset Fetal Growth Restriction Low Resources Settings

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ABSTRACT

Background: Fetal growth restriction (FGR) is associated with high incidence of perinatal morbidity and mortality. Early diagnosis of fetuses at risk will allow for close monitor and timely delivery accordingly; which remains challenging mainly in late onset FGR where some cases remain unrecognized during pregnancy because of normal Doppler findings. The aim of this study was to determine different clinical and ultrasound predictors of adverse neonatal outcomes at the time of diagnosing late onset FGR.

Methods: Analysis of medical records at Ain Shams University Maternity Hospital was conducted to evaluate singleton pregnancies complicated by late-onset FGR. Different clinical and sonographic parameters obtained at time of FGR diagnosis were evaluated as possible predictors of composite neonatal morbidity in low resources settings.

Results: One hundred fifty-one non-anomalous singleton pregnancies with late-onset FGR were evaluated, the composite neonatal morbidity were significantly associated with hypertensive disorders. The estimated fetal weight ≤3 percentile at the time of late-onset FGR diagnosis had a sensitivity of 87.7% and specificity of 51.06 % in predicting composite neonatal morbidity. Amniotic fluid index to head-to-abdomen circumference ratio (AHC/AC) had the highest area under the ROC curve (AUC) of 0.727; p-value <0.0001. At the cut-off ≤0.06, AHC/AC was 77.19 % sensitive and 62.77% specific in predicting composite neonatal morbidity.

Conclusion: The findings of the current study suggest that EFW and AC percentiles, AFI, and AHC/AC ratios at the time of late onset FGR diagnosis have acceptable predictive value for composite neonatal morbidity.

Keywords: Amniotic fluid index; fetal growth restriction; low resources; neonatal outcomes; neonatal morbidity.

INTRODUCTION

Fetal growth restriction (FGR) represents one of the most prevalent complications during pregnancy, which is considered a leading cause of many adverse perinatal outcomes.[1] The main goal of screening, early diagnosis and management protocols of FGR is to provide adequate monitoring, thereby minimizing the risk of stillbirth and neonatal morbidity and mortality.[2]

Late onset FGR diagnosed at or beyond 32 weeks of gestation; occurs in up to 10% of all pregnancies. However, it remains a diagnostic challenge and can go undetected due the lack of routine late pregnancy ultrasound in current clinical practice, together with the inaccuracies in the clinical evaluation of fetal size.[3]

Most of the pregnancies diagnosed with suboptimal fetal growth result in a physiologically normal fetus but small for gestational age (SGA). Differentiating SGA from those with pathological growth restriction remains a significant challenge.[4]

It was reported that abnormal Doppler findings can predict adverse perinatal outcomes in SGA fetuses. Compared to fetuses with appropriate growth for gestational age, those who were constitutionally SGA have higher rates of poor perinatal and long-term outcomes. Therefore, the development of new strategies for accurate identification of high-risk SGA fetuses is of crucial importance.[5]

The low- and middle-income countries (LMICs) are considered resource constrained settings for the routine use of ultrasound. This limitation is mainly due to the lack of affordable equipment, insufficient trained personnel, and other issues related to the equipment maintenance. Moreover, the advanced ultrasound technologies that include Doppler and color flow capabilities are limited within LMICs. [6] Therefore, the International Federation of Gynecology and Obstetrics (FIGO) emphasizes the need for tailored guidelines considering the unique characteristics of antenatal care in low-resource settings.[7] The inclusion of the clinical characteristics into the risk assessment, alongside ultrasound findings, can refine risk stratification and decision-making for SGA fetuses.[5]

The aim of this study was to determine the accuracy of different clinical and ultrasound parameters (mainly AHC/AC) in predicting composite neonatal morbidity in pregnancies complicated by late onset FGR.

METHODS

This study was conducted at Ain Shams University Maternity Hospital after the approval of Faculty of Medicine Ain Shams University Ethical Research Committee (FMASU ERC) (FMASU MS 254/2021). Analysis of medical records of singleton pregnancies complicated by late onset FGR was performed. Estimated fetal weight and /or abdominal circumference below the 10th percentile cutoff were the universally accepted standard for defining FGR. Those with fetal structural or chromosomal abnormalities (identified through postnatal examination by expert neonatologist or prenatal ultrasound examination), suspected infectious causes (diagnosed during pregnancy or postnatally), and records with unreliable gestational age (GA) were excluded. We extracted the medical records and all the demographic, clinical, ultrasound parameter measured at diagnosis of FGR were collected and evaluated for respect to their ability to screen for various adverse neonatal outcomes.

This study represents a secondary analysis of data originally collected to validate the international consensus-based definition of FGR involving various biometric and Doppler parameters. The current FIGO guidelines for diagnosing FGR in high income countries can be difficult to implement in resource-constrained settings. Firstly, the poor adherence to scheduled antenatal (ANC) visits limited the physician's ability to perform serial assessments of fetal size to detect a drop in percentile. Secondly, the limited access to Doppler ultrasound in the private sector where the majority of ANC visits occurs. Thirdly, there is a huge preference in emergency situations for the umbilical artery resistance index (RI) compared to the pulsatality index (PI). The PI can take slightly longer to calculate than the RI or systolic/diastolic ratio because of the need to measure the mean height of the waveform.

Thus, we evaluated the role of different clinical and ultrasound parameters other than Doppler in predicting adverse neonatal outcomes. In order to improve risk stratification of SGA into phenotypes, we included maternal and placental clinical characteristic that were evaluated by Ruiz-Martinez et al. [5] They included hypertensive disorders, gestational diabetes, chronic maternal conditions, use of assisted reproductive techniques, bleeding in $2^{nd}/3^{rd}$ trimesters, and spontaneous preterm birth, but we excluded congenital anomaly phenotype.

The reviewed ultrasound parameters encompassed various fetal biometric measurements and their corresponding ratios, including abdominal circumference (AC), biparietal diameter (BPD), head circumference (HC) and femur length (FL). All measurements followed the standardized protocols and ultrasound scan guidelines. The HC/AC and FL/AC ratios were calculated by dividing the HC and FL by AC and multiplying by 100, respectively.[8] Amniotic fluid volume was

measured using the amniotic fluid index (AFI). Oligohydramnios was defined as AFI ≤ 5 cm.[9]
Other calculations included amniotic-head circumference -to-abdominal circumference ratio (AHC/AC) which is the ratio of AFI to HC: AC ratio = AFI / (HC/AC), the amniotic-femur length -to-abdominal circumference ratio (AFL/AC) which is the ratio of AFI to FL: AC ratio = AFI / (FL/AC).
We calculated the amniotic-head circumference-to-abdominal circumference ratio (AHC/AC) from the medical records to predict adverse neonatal outcomes. This builds upon the recommendations of the American College of Obstetricians & Gynecologists (ACOG) of using serial ultrasound measurements of fetal biometry and amniotic fluid volume for assessing fetal growth restriction (FGR).[10]
Moreover, the fetal hypoxemia or acidemia can trigger aortic arch and carotid body chemoreceptor reflex cardiovascular redistribution resulting in decreased renal perfusion. This makes AF volume a good indicator of long-term placental dysfunction cardiovascular redistribution and a main contributor of BPP and modified BPP which are the most accurate predictor of current fetal status in FGR.[11] The HC/AC was found to be associated with adverse pregnancy outcomes as preterm birth, lower birthweight, fetal distress, and neonatal morbidity.[12] Lastly, the amniotic fluid volume assessment, fetal biometry, and fetal body proportions are simple measures that can be utilized in any resource setting where Doppler is lacking.
The main outcome of the study was the ability of clinical and ultrasound parameters measured at FGR diagnosis to predict the composite neonatal morbidity that includes one or more of the following: the need for neonatal intensive care unit (NICU) , Apgar score < 7 at 5 minutes of age, neurologic abnormality including (intracerebral hemorrhage, periventricular leukomalacia, or seizures), respiratory morbidity including pulmonary hypertension or respiratory distress syndrome (RDS), necrotizing enterocolitis,, neonatal anemia, , and/or neonatal death. The secondary outcome measures were SGA neonate, urgency and mode of delivery.

STATISTICAL ANALYSIS

Data were collected, tabulated and subjected to the proper statistical analysis using SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA). Normally distributed numerical variables were presented as mean and standard deviation (SD) and intergroup differences were compared using the independent-samples t test.
Categorical data were presented as number and percentage and differences were compared using Fisher's exact test or the chi-squared test. Receiver-operating characteristic (ROC) curve analysis was used to examine the predictive value of the different sonographic parameter for prediction of composite neonatal morbidity.

RESULTS

A total of 245 pregnancies were evaluated during the study period; multiple gestations, pregnancies complicated with fetal death or congenital anomalies, or incomplete data regarding the clinical, sonographic and neonatal outcome were excluded, thus the records of 151 cases were analyzed.
Basic clinical criteria were presented in table 1; our cohort did not include any cases of assisted reproductive techniques, and only one case of 3rd trimester bleeding.as shown in **table 1**
Obstetric and neonatal outcomes in the studied group are shown in table 2

Our cohort was divided into two groups according to the presence of composite neonatal morbidity. Parity and FL/AC ratio was not significantly different between both groups, while ultrasonographic parameters significantly differed between both groups as shown in **table 3**
Plotting of ROC curve analysis for predicting composite neonatal morbidity using different sonographic parameters revealed that; the (AHC/AC) ratio had the highest area under the ROC curve (AUC) of 0.727; p-value <0.0001). The best cut-off criterion was ≤ 0.06, and had a sensitivity of 77.19 % and specificity of 62.77%. On the other hand, the EFW percentile had fair predictive value with an area under the ROC curve (AUC) of 0.700; p-value <0.0001). The

best cut-off criterion is ≤3 percentile which had a sensitivity of 87.7% and specificity of 51.06 %. As shown in table 4 and **figure 1**

Logistic regression analysis for AHC/AC ratio as predictor for composite adverse neonatal outcome after adjustment for other variables; AC, HC/AC ratio and AHC/AC ratio were the only predictors for adverse neonatal outcome with p value 0.041, 0.023, and0.001 respectively as shown in table **table 5**

Table (1): Basic demographic and clinical characteristics of the study group

Variable	
Age (Mean ± SD)	**28.53± 6.19**
Parity **Primigravida (n, %)** **Multiparous (n, %)**	 **46 (30.5%)** **105(69.5%)**
GA at diagnosis of FGR (Mean ± SD)	**37.35±2.13**
GA at labor (Mean ± SD)	**37.76±1.85**
Pregnancy induced disorder (n, %)	
SPET **non severe PET** **Gestational HTN** **Antepartum hemorrhage** **Intra amniotic infection** **GDM**	**40 (26.4%)** **6 (3.9%)** **7 (4.6%)** **3 (2%)** **2 (1.4%)** **1 (0.7%)**
Chronic medical disorder (n, %)	
APAS	**2 (1.3%)**
Asthma	**3 (2%)**
Chronic HTN	**8 (5.4%)**
Epilepsy	**2 (1.3%)**
Chronic Hepatitis B	**1 (0.6%)**
Hypothyroidism	**4 (2.7%)**
PGDM	**3 (2%)**
Others	**7(4.7%)**
Previous placental mediated disorders	
Previous SGA (n, %)	**2 (1.3%)**
Previous pre-eclampsia (n, %)	**6 (4%)**
Previous stillbirth (n, %)	**10 (6.6%)**

Table (2): Obstetric and neonatal outcomes in the study group

Variables	Number
Mode of delivery	
LSCS	118 (78.1%)
VD	33 (21.9%)
Indication of termination	
spontaneous labor	32(21.2%)
SPET	41(27.2%)

Variables	Number
term IUGR	70(46.4%)
fetal distress	6(4%)
Other	2(1.3%)
Urgency of termination	
Elective	77 (51%)
Emergency	74 (49%)
Time of delivery	
Term	92(60.9%)
Preterm	59(39.1%)
Spontaneous PTL	18 (11.9%)
Neonatal outcomes	
Birth weight (Mean ± SD)	2211.67± 515.4
BW percentile Median (IQR)	2 (1-7)
SGA neonate	122 (80.8%)
Composite ANO	57(37.7%)
RDS	53(35.1%)
NEC	1(0.7%)
Neonatal death	5 (3.3%)
NICU admission	55(36.4%)

Table (3): Univariate analysis of factors affecting adverse neonatal outcome

Variable	Composite ANO absent (N=94)	composite ANO present (N=57)	P value
Parity			**0.185**
Primiparous	**25 (26.6%)**	**21 (36.8%)**	
Multiparous	**69 (73.4%)**	**36 (63.2%)**	
Phenotypes			**0.03**
HTN disorders	**27 (28.72%)**	**30(52.6%)**	
Spontaneous PTL	**11 (11.7%)**	**6(10.5%)**	
chronic medical disorders other than HTN disorders	**6(6.4%)**	**3(5.3%)**	
Antepartum hemorrhage	**3(3.2%)**	**0(0.0%)**	
Gestational DM	**0(0.0%)**	**1(1.8%)**	
GA at diagnosis			**0.000**
<36 weeks	**10(10.6%)**	**25(43.9%)**	
≥36 weeks	**84(89.4%)**	**32(56.1%)**	
EFW (mean ±SD)			**0.000**
	2439.39 ± 321.92	**1940.08± 509.25**	
AC (mean ±SD)			**0.000**

Variable	Composite ANO absent (N=94)	composite ANO present (N=57)	P value
	295.68 ±15.52	269.73 ± 28.23	
EFW less than 3rd percentile			**0.000**
	46(48.9%)	48(84.2%)	
AC less than 3rd percentile			**0.000**
	21(22.3%)	31(54.4%)	
HC/AC ratio (mean ±SD)			**0.020**
	106.62 ± 5.35	109.21 ± 8.173	
FL /AC ratio (mean ±SD)			**0.182**
	23.35 ± 1.48	23.76 ± 2.23	
AHC/AC ratio (mean± SD)			**0.000**
	0.084±0.04	0.052±0.03	
AFL/AC ratio (mean± SD)			**0.000**
	0.385±0.19	0.244±0.15	
Oligohydramnios			**0.017**
	25(26.6%)	26(45.6%)	
Urgency of delivery			**0.042**
Elective	54(57.4%)	23(40.4%)	
Emergency	40(42.6%)	34(59.6%)	
Mode of delivery			**0.002**
CS	66(70.2%)	52(91.2%)	
VD	28(29.8%)	5(8.8%)	

Table 4: Receiver-operating characteristic (ROC) curve analysis for prediction of ANO using different sonographic parameters

	Cut off	AUC	P value	sensitivity	specificity
EFW percentile	≤3	0.700	<0.0001	87.72	51.06
AC percentile	≤4	0.717	<0.0001	71.93	63.83
HC/AC	>107.52	0.631	0.0079	68.42	56.38
FL/AC	>23.96	0.584	0.0941	50.88	68.09
AHC/AC	≤0.06	0.727	<0.0001	77.19	62.77
AFI	≤7	0.719	<0.0001	78.95	56.38

Table (5): logistic regression analysis for predictors of composite adverse neonatal outcome

		B	S.E.	Wald	df	Sig.	Exp(B)
	AC percentile	-0.010	0.064	0.023	1	0.881	0.990
	AC	-0.171	0.083	4.173	1	**0.041**	0.843
	EFW	0.004	0.003	1.727	1	0.189	1.005

	AHC/AC ratio	-20.473	5.996	11.656	1	**0.001**	0.000
	HCAC	-0.154	0.068	5.160	1	**0.023**	0.857
	FLAC	-0.473	0.331	2.044	1	0.153	0.623
	EFW percentile	-0.164	0.162	1.034	1	0.309	0.848
	Constant	67.721	28.911	5.487	1	0.019	

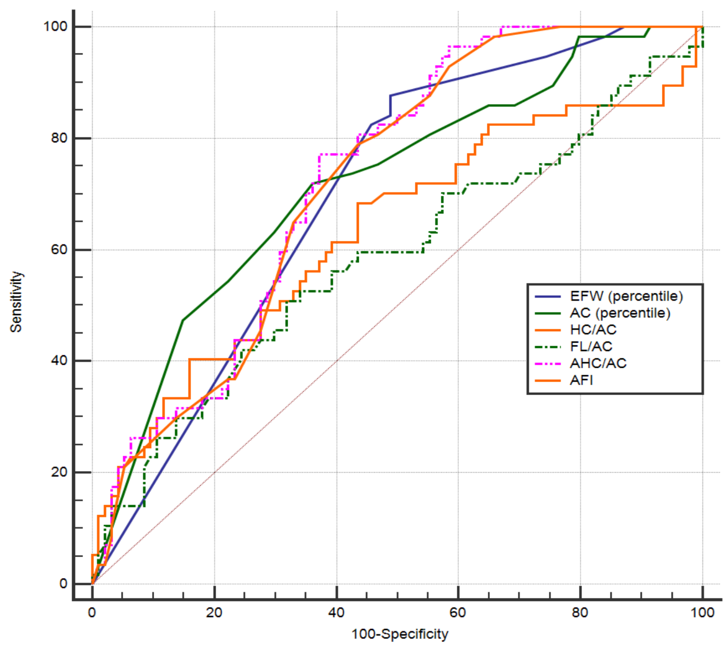

Figure 1: ROC curve analysis for prediction of composite neonatal morbidity using different sonographic parameters

DISCUSSION

Being a major pregnancy related concern; FGR is one of the highest ranked causes of stillbirth, neonatal mortality, and morbidity. Thus, establishing standard consistent definitions and treatment protocols for FGR is crucial to improve neonatal outcomes.[2]

FIGO defines FGR differently for low- and high-resource settings (HRS). In low resource settings (LRS), FGR is diagnosed by fetal weight below the 10th percentile for GA, while it is defined by the application of Doppler technologies and growth curve in HRS.[7] Applying HRS definitions to LRS can be misleading considering the huge differences between the two settings regarding the rates of adverse pregnancy outcomes. Therefore, we evaluated the clinical and ultrasound parameters that can predict composite neonatal morbidity and can be adopted easily in LRS.

The use of estimated fetal weight <10th percentile for GA has a limited accuracy for predicting adverse perinatal outcomes.[13] Adding other clinical and ultrasound parameters can augment its accuracy.

Ruiz-Martinez et al. reported nine clinical phenotypes linked to different perinatal outcomes in SGA. Therefore; considering a combination of different clinical and ultrasound characteristics can improve risk assessment in SGA fetuses, potentially leading to better management decisions. [5] In their study, those with second or third-trimester hemorrhage were associated with the worst perinatal outcome represented by higher rates of cesarean deliveries for fetal acidosis.[5]

The current study found that in singleton pregnancies with late-onset FGR with no congenital defects, hypertensive disorders were significantly linked to composite neonatal morbidity. The EFW ≤3 percentile at the time of diagnosis of late-onset FGR strongly predicted composite neonatal morbidity (87.7% sensitivity, 51.06% specificity).

Several studies reported that the biometry measures are more effective in identifying SGA and predicting poor newborn outcomes. Moreover, they are easier to use in clinical practice. In late-onset FGR, EFW below the 3.95th percentile was the only ultrasound measure independently linked to poor perinatal outcomes.[14] Furthermore, there were significant differences in EFW z-score at diagnosis between FGR with and without adverse perinatal outcomes (P=0.023).

On the other hand, Caradeux and colleagues[15], found no significant differences in EFW z-score at last ultrasound or EFW z-velocity between FGR with and without adverse perinatal outcomes.

Regarding the timing of ultrasound examination, the assessment performed at 36 weeks' gestation was more accurate than that at 32 weeks' gestation in identifying FGR and predicting poor outcome.[16-18] Similarly, we found 32 (56.1%) of cases with composite neonatal morbidity were diagnosed at 36 weeks' gestation or higher.

In this study, oligohydramnios was significantly associated with composite neonatal morbidity. 26 (45.6%) of cases with composite neonatal morbidity had AFI ≤ 5. However, plotting of ROC curve analysis revealed that the AFI had fair predictive value with AUC of 0.719; p-value <0.0001. The best cut-off criterion is ≤7 which had a sensitivity of 78.95% and specificity of 56.38 %.

The HC/AC ratio was 109.21 ± 8.173 and 106.62 ± 5.35 in those with and without composite neonatal morbidity, respectively (p-value= 0.02). The (AHC/AC) ratio had the highest AUC of (0.727; p-value <0.0001). At the cut off ≤0.06, it had a sensitivity of 77.19 % and specificity of 62.77%. The HC/AC ratio and FL/AC had AUC of (0.631, p-value 0.0079) and (0.584, p-value 0.0941), respectively.

Although the fetal body proportions measurements are simple, widely available, and affordable, the association between different ratios and composite neonatal morbidity is still controversial, and their accuracy for predicting composite neonatal morbidity in clinical settings remains unclear.[13, 19, 20] Oligohdramnios was associated with adverse perinatal outcomes; it was linked to an increased risk of cesarean delivery due to fetal distress.[21, 22]

In another study oligohydramnios was associated with increased risk of NICU admission by 2.13 times. [23]A recent study assessed the relationship between single deepest pocket and the amniotic-to-umbilical-cerebral ratio and composite neonatal morbidity. Both parameters were significantly lower in the composite neonatal morbidity group. The single deepest pocket was 3.1 ± 1.1 in composite neonatal morbidity compared to 4.0 ± 1.3 in the other group [P = 0.018]. The amniotic-to-umbilical-cerebral ratio was 3.0 ± 1.1 in the composite neonatal morbidity group and 7.1 ± 3.9 in the control group (p < 0.001). The AUC of the ROC curve analyzing the accuracy of the amniotic-to-umbilical-cerebral ratio in predicting composite neonatal morbidity was 0.882.[24]

A recent systematic review on the prognostic accuracy of antenatal Doppler for adverse neonatal outcomes in LIMC reported an inadequacy for the high-quality studies. The existing studies didn't consider different clinical criteria for estimating pregnancy risk. Moreover, using Doppler technology in clinical practice is limited by the lack of access to Doppler equipment and the ability of local healthcare systems to accurately assess the results of the Doppler scan and make clinical decisions, accordingly. [25]

The omission of Doppler evaluation at the diagnosis of late-onset FGR can be justified in clinical practice in LRS because late onset FGR usually represents a milder form of growth restriction that rarely shows Doppler abnormalities in the umbilical artery or ductus venosus studies. Therefore, adding biometric parameters to the umbilical artery Doppler is a better stratification tool for predicting composite neonatal morbidity in late-onset FGR.[7, 25, 27]

A recent study showed that reduced growth velocity in late preterm fetal growth restriction was associated with poor perinatal outcomes, regardless of the signs of cerebral blood flow redistribution.[28]

The primary analysis of PORTO study reported that umbilical artery Doppler abnormalities were related to adverse neonatal outcomes. This association disappeared in the 2ry analysis of data of the growers' group because the UA Doppler abnormalities occurred as a temporary event of an increased UA-PI that eventually recovered in 67% of the cases .[29]

According to Lees and his colleagues, multiple factors should be considered in risk assessment of suspected fetal growth restriction. These factors include fetal size, growth rate, cardiotocography, maternal hypertension, and GA at dianosis.[27]

While our study provides valuable insights into the accuracy of different clinical and ultrasound approaches for predicting adverse neonatal outcomes in pregnancies complicated by late onset fetal growth restriction, it is imperative to acknowledge several limitations. Initially, this was a small, single-site, retrospective study which may limit the generalizability of our findings to broader populations. Additionally, our study was conducted to evaluate the diagnostic accuracy of clinical and sonographic criteria; it is noteworthy that further validation of the sonographic criteria may be necessary in future studies. Nevertheless, the simple and cost-effective assessment employed in the current study will be useful in risk stratification in pregnancies with late onset fetal growth restriction, particularly in resource-limited settings.

CONCLUSION

The results of the current study suggest that EFW and AC percentiles, AFI, and AHC/AC ratios at the time of late onset fetal growth restriction diagnosis have acceptable predictive values for adverse neonatal outcomes.

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Financial disclosures: None

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