East African Medical Journal Vol. 94 No. 5 May 2017
UMBILICAL ARTERY DOPPLER ABNORMALITIES AND ASSOCIATED FACTORS IN WOMEN WITH PRE-ECLAMPSIA AT MULAGO HOSPITAL- A CROSS SECTIONAL STUDY
P. Gimei , MBChB, Resident, Department of Obstetrics and Gynecology, Makerere University, R.B. Busingye, MBChB, MMED, MSc, Department of Obstetrics and Gynecology, Mulago National Referral Hospital. PO Box 7051, Kampala, Uganda, E. Nakabembe , MBChB, MMED, Department of Obstetrics and Gynecology, Makerere University. PO Box 7072 Makerere Hill, Kampala, Uganda and R.K. Byanyima , MBChB, MMED RAD, MBA, Department of Radiology, Mulago National Referral Hospital. PO Box 7051, Kampala, Uganda.

Request for reprints to: P. Gimei , MBChB, Resident, Department of Obstetrics and Gynecology, Makerere University

UMBILICAL ARTERY DOPPLER ABNORMALITIES AND ASSOCIATED FACTORS IN WOMEN WITH PRE-ECLAMPSIA AT MULAGO HOSPITAL- A CROSS SECTIONAL STUDY

P. Gimei, R.B. Busingye, E. Nakabembe and R.K. Byanyima

ABSTRACT

Background: **Umbilical artery (UA) Doppler velocimetry detects foetuses at risk of asphyxia from IUGR before changes in the CTG and biophysical score are evident. This has made it a primary fetal surveillance tool in pre-eclampsia in developed countries with resultant reduction in perinatal mortality by 29%. Iatrogenic preterm deliveries related to pre-eclampsia are a key contributor to neonatal intensive care admissions at Mulago hospital due in part to limited use of UA Doppler velocimetry to optimize delivery because of high patient load.**

Objective: **The objective was to determine the prevalence and factors associated with UA Doppler abnormalities in women with preeclampsia from 28 weeks of pregnancy so as to identify a subpopulation who would require routine UA Doppler velocimetry to improve perinatal outcomes in a resource limited context.**

Study design: **This was a cross-sectional analytical study. Maternal age, Gestational age, Parity, and Blood pressure were recorded. Degree of proteinuria, Platelet count, serum creatinine and liver transaminases were analysed and UA Doppler sonography was performed to determine the RI, S/D ratio, AEDV and RF patterns. These data were entered into EPIDATA 3.1 and exported to STATA version 12 for analysis. Bivariate and Multivariate analysis were deployed to identify factors associated with Doppler abnormalities.**

Study Setting: **The study was conducted on the labour and maternal-fetal medicine wards of Mulago National Referral hospital, Kampala Uganda between June and September 2014.**

Subjects: **A total of 155 women with pre-eclampsia between 28 and 42 weeks of pregnancy were consented/assented and recruited for the study. Critically ill**

patients and those in active phase of labour or premature rupture of membranes were excluded.

Results: **The overall prevalence of UA Doppler abnormalities was 31.6%. High RI, high S/D ratio, AEDV and RF were found in 25.8%, 31.6%, 7.7% and 4.5% of the population respectively. Key factors associated with UA Doppler abnormalities were gestational age below 35 weeks (AOR=8.1, 95% CI: 2.91-22.76, P<0.001), severe pre-eclampsia with heavy proteinuria (AOR=7.3, 95% CI: 2.82-18.87, P<0.001), and multiparity (AOR=5.3, 95% CI: 1.52-18.53, P<0.001). Severe pre-eclampsia comprised 61% (n=95) of the study population. Maternal age and pre-eclampsia with light proteinuria had no association with UA Doppler abnormalities.**

Conclusion: **UA Doppler abnormalities are very common in pre-eclampsia. Gestational age below 35 weeks and heavy proteinuria are the key associated factors of these abnormalities.**

INTRODUCTION

Pre-eclampsia constitutes 8.2% of the admissions per day to the labour ward and contributes 10% of the still births and over 20% of admissions to the NICU of Mulago Hospital (1). Perinatal concerns in women with pre-eclampsia relate to risks of placental abruption, IUGR, and perinatal morbidity and mortality related to preterm birth (2)which are dependent on disease severity and gestational onset of disease(3).

Pre-eclampsia/eclampsia is the commonest cause of indicated preterm delivery(4). Objective fetal surveillance is therefore critical to optimizing perinatal outcomes especially when conservative management is considered. Umbilical artery Doppler indices become abnormal before change in the biophysical score and therefore a better predictor of fetal acidosis than biophysical score alone (5, 6). Resistive index above 0.7 and SD ratio above 3.0 have a high discriminatory value for IUGR (7). This has made umbilical artery Doppler velocimetry a good preliminary investigation in fetal surveillance in high risk pregnancies (8)

Routine use of umbilical artery Doppler velocimetry in pre-eclampsia and other high risk conditions of pregnancy has reduced perinatal morbidity and mortality in these conditions by 29% in developed countries (9). Perinatal morbidity and mortality related to pre-eclampsia however, remains high in developing countries(10). This may be in part due to inadequate fetal surveillance and therefore limited conservative management of women with pre-eclampsia. Routine use of this investigation to improve perinatal outcomes in high risk pregnancies in resource limited settings is hampered by high patient load, high cost of the investigation and limited technical skills.

The aim of this study was to determine the prevalence of Umbilical artery Doppler abnormalities in pre-eclampsia as well as identify a sub-population of pre-eclampsia women most in need of this investigation as resources improve to improve perinatal outcomes in a resource limited context as Mulago Hospital.

METHODS

This was a cross -sectional analytical study conducted between June and September 2014 on the labour ward (ward 5C) of the Department of Obstetrics and Gynecology, Mulago National Referral Hospital-Kampala.

The study population was women with pre-eclampsia and having live singleton

foetuses in the third trimester (28-42 weeks of pregnancy) admitted to the labour ward of Mulago hospital.

The blood pressure was measured using a calibrated aneroid sphygmomanometer and proteinuria assessed by dipstick using LABOQUICK brand .The women who were in the active phase of labour, those with premature rupture of membranes and the critically ill were excluded from the study.

A sample size of 150 patients was derived from the Kish and Leslie formula (11) using a prevalence of 10.95% of umbilical artery Doppler abnormalities in high risk pregnancies at Mulago Hospital (12). Umbilical artery Doppler abnormality in this study was defined as resistive index >0.7, systolic/diastolic (S/D) >3.0 or absence of end-diastolic flow or presence of reversed flow.

A total number of 155 women with pre-eclampsia who met the eligibility criteria were consented and consecutively recruited. Blood samples were drawn for complete blood count, renal and liver function tests and were analysed in the same laboratory using haematology analyser model MEK 8222K and clinical chemistry machine COBUS 6000 respectively. The women were then asked to provide on spot urine samples for assessment for proteinuria by dipstick and the results were recorded in real time on the data collection tool. Thereafter, ultrasound for biometry, umbilical artery Doppler sonography and biophysical score assessment using a VOLUSON 730 PRO nr 21043 machine was done. For quality control purposes, measurement of blood pressure and proteinuria was done by the same person while the ultrasonography was performed by the same team of a Radiologist and Principal Investigator.

Bivariate analysis was conducted between degree of hypertension, level of proteinuria, maternal age, parity, gestational age and umbilical artery Doppler abnormality to identify factors with significant association ($P<0.05$). Factors with $p<0.05$ were subjected to multivariate logistic regression to identify factors that were independently associated with Doppler abnormality.

RESULTS

Participant characteristics

A total of 155 women were enrolled into the study. The women's age ranged from 15-40 years with a median age of 27 years [Inter Quartile Range (IQR): 22-31]. The parity ranged from 0 to 8 with a median parity of one (IQR: 0-3). The gestational age ranged from 27-42 weeks and a median gestational age of 34 weeks (IQR: 31-37). Severe preeclampsia was diagnosed in 61% of the women and only six (6) women had significantly deranged laboratory tests (Table 1).

Table 1
Demographic and clinical features of 155 women with pre-eclampsia at Mulago hospital

Variable		n (%)
Maternal Age in yrs, n (%)		
	15-19	13(8.4)
	20-29	93(60.0)
	30-35	37(23.9)
	36-40	12(7.7)
Parity		
	Primigravida	53(34.2)
	multigravida	102(65.8)
Gestational age		
	≤ 31 weeks	42(27.1)
	32-34 weeks	43(27.7)
	35-37 weeks	40(25.8)
	≥38weeks	30(19.4)
Systolic blood pressure (mmHg) , median(IQR)		142(136-154)
Diastolic blood pressure (mmHg), median(IQR)		96(88-101)
urine protein (degree), median(IQR)		3(1-3)
Fundal length(cm) ,median(IQR)		34(28-36)
Type of preeclampsia, n (%)		
	Mild	60(38.7)
	Severe	95(61.3)
Platelet count,	n (%)	
	Normal	152(98.1)
	Low(<100x10^3)	3(1.9)
AST	n (%)	
	Normal	149(96.1)
	High	6(3.9)

4.2 Prevalence of UA Doppler abnormalities

High S/D ratio was central to all the other abnormalities. Therefore, the overall prevalence of UA Doppler abnormalities was 31.6%.

Table 2
UA Doppler indices among 155 women with pre-eclampsia

Outcome		n (%)
RI	High	40(25.8)
	Normal	115(74.2)
S/D ratio		
	High	49(31.6)
	Normal	106(68.4)
AEDV		
	Present	12(7.7)
	Absent	143(92.3)
RF		
	Present	7(4.5)
	Not present	148(95.5)

Table 3
Bivariate associations between abnormal UA Doppler outcome and selected factors among 155 women with preeclampsia

Variable		N	Abnormal UAD	Normal UAD	OR (95%CI)	P value
Maternal Age						
	15-19 yrs	13	4(30.8)	9(69.2)	1	
	20-29yrs	93	27(29.0)	66(71.0)	0.92(0.26-3.26)	0.879
	30-35yrs	37	15(40.5)	22(59.5)	1.53(0.39-6.02)	0.536
	36-40yrs	12	3(25.0)	9(75.0)	0.75(0.12-4.53)	0.753
Parity						
		53	8(15.1)	45(84.9)	1	
		102	41(40.2)	61(59.8)	3.78(1.57-9.13)	0.002
Gestational age						
	≤ 31 weeks	42	28(66.7)	14(33.3)	1	
	32-34 weeks	43	15(34.9)	28(65.1)	0.27(0.10-0.69)	0.004
	35-37 weeks	40	4(10.0)	36(90.0)	0.05(0.01-0.25)	<0.001
	≥38weeks	30	2(6.7)	28(93.3)	0.04(0.01-0.26)	<0.001
Blood pressure						
	High	115	35(30.4)	80(69.6)	1	
	Very high (≥160/110)	40	14(35.0)	26(65.0)	1.23(0.57-2.64)	0.594
Urine protein						
	Light	71	9(12.7)	62(87.3)	1	
	Heavy	84	40(47.6)	44(52.4)	6.26(2.58-15.20)	<0.001
Type of Preeclampsia	Mild	58	6(10.3)	52(89.7)	1	
	Severe	97	43(44.3)	54(55.7)	6.90(2.53-18.8)	<0.001

Table 4
Multivariate Logistic analysis between Abnormal UA outcome and selected factors among 155 women with Pre-eclampsia

Variable		AOR(95%CI)	P value
Maternal Age			
	15-19 yrs	1	
	20-29 yrs	0.41(0.07-2.31)	0.312
	30-35yrs	0.24(0.03-1.71)	0.154
	36-40yrs	0.39(0.03-4.32)	0.440
Gestational age			
	<35 weeks	8.1(2.91-22.76)	<0.001
	≥ 35 weeks	1	
Urine protein			
	Light	1	
	Heavy	7.3(2.82-18.87)	<0.001
Blood pressure			
	High	1	
	Very High	0.8(0.29-1.96)	0.574
Parity			
	Primigravida	1	
	multigravida	5.3(1.52-18.53)	<0.001

AOR is the Adjusted Odds Ratio; CI is Confidence Interval

DISCUSSION

This was a cross-sectional analytical study of women with pre-eclampsia and live singleton foetuses from 28 weeks of gestation who underwent UA Doppler sonography at Mulago Hospital during a four months period between June-September 2014.

A total of 155 women were recruited. The median maternal age was 27 years (IQR: 22-31) and a median parity of one (IQR: 0-3). This may be due to the fact that the majority of obstetric patients in Uganda are in the age range of 20-28 years and have had at least one pregnancy carried beyond 28 weeks of gestation. The median gestational age was 34 weeks (IQR: 31-37). Severe pre-eclampsia was diagnosed in 61.3% of the women and 86.7 % of these had heavy proteinuria. The number of women who had significant abnormalities in LFTs, RFTs or CBC was very low (six women) so these results were not considered in the diagnosis of severe pre-eclampsia since all of these also had heavy proteinuria.

The prevalence of high RI and high S/D ratio was 25.8% and 31.6% respectively. According to the study by Nguku, etal (2006), an abnormal RI was found in 33.9% of the women with pregnancy induced hypertension. The prevalence of abnormal RI in this study was lower perhaps because we excluded women between 26 and 27 weeks of amenorrhea. According to Kofinas, etal (1990), high S/D ratio was observed in 26.5% of the 68 patients they studied who had chronic hypertension or pre-eclampsia. The prevalence of high S/D ratio in our study of 31.6% (95% CI: 24.2-39.0; P=0.103) is comparable to the findings in Kofinas' study.

AEDV was noted in 7.7% of the women that were studied. This agrees with other studies which have found it to be 4-8%(13). However, it's almost twice the prevalence observed by Komuhangi (2009) who did a similar study among several high risk pregnancy categories within the same environment. The difference could be related to the fact that our study looked purely at pre-eclampsia and included more women with severe pre-eclampsia.

RF was found in 4.5% of the women that were studied and all of them had severe pre-eclampsia with heavy proteinuria. This is in sharp contrast to an estimated prevalence of 0.5% reported by various sources (13) (12). The explanation could be due to the large number of patients with severe pre-eclampsia and heavy proteinuria in the sample population.

In the multivariate analysis, gestational age below 35 weeks, heavy proteinuria, and multiparity were independently associated with Doppler abnormalities. In a study by Kofinas (1990), gestational age of 33.5 ±1.03 weeks was strongly associated with high S/D ratio. This study found that gestational age below 35 weeks was independently associated with abnormal Doppler indices and this agrees with Kofinas. Pre-eclampsia that manifests before 34 weeks (early onset) has been found to be very severe (14) and this could explain why Doppler abnormalities are frequent below this gestational age.

Our study found that heavy proteinuria was also independently associated with UA Doppler abnormalities. This is in contrast with Kofinas' study which did not find an association between the degree of proteinuria and high S/D ratio. Earlier evidence suggested that heavy proteinuria was a marker of severe disease (15) even though more recent evidence refutes this (16). Therefore, with the findings of our study, should heavy proteinuria still be retained as a marker of severe pre-eclampsia?

This study did not find an association between severity of blood pressure and UA Doppler abnormalities. This is in contrast to the study by Nguku which found a positive

association between high blood pressure and high resistive index (17). This discrepancy could not be explained as it is common knowledge that the more severe the hypertension, the higher the risk of having IUGR. This finding therefore warrants further study.

Multiparity was also found to be independently associated with Doppler abnormalities in our study. Although primiparity was initially thought to be associated with severe pre-eclampsia (18), recent evidence shows that multiparity is more associated with severe pre-eclampsia or early onset disease (19). The association between multiparity and UA Doppler abnormalities in our study therefore concurs with these findings. However, no other study was found that studied parity as a predictor of Doppler abnormalities.

Maternal age was not associated with Doppler abnormalities. This also requires cautious interpretation because its long been known that extremes of age (below 18 & more than 40 years) are associated with severe disease (20) and presumably more severe Doppler abnormalities. Our sample population had few patients in these two age categories for sufficient analysis of the association between extremes of age and UA Doppler abnormalities.

STUDY LIMITATIONS

The very sick and non-ambulant patients could not be studied for ethical and technical reasons respectively. Therefore, the prevalence of abnormal UAD abnormalities that was obtained may have been an under-estimate for the pre-eclampsia population.

A single spot urine examination for protein was used in this study yet proteinuria is not constant. The error was minimized by performing a repeat urine examination before the ultrasound investigation.

A single scan was performed in the third trimester to assess the estimated gestational age. This carries an error of ±3 weeks so the obtained gestational ages could not be very accurate. However, the error was minimized by taking the average of several biometry measurements (head circumference, bi-parietal diameter & femur length).

CONCLUSIONS

According to this study, a third of the women with pre-eclampsia had UA Doppler abnormalities.

Gestational age below 35 weeks, severe pre-eclampsia with heavy proteinuria and multiparity were independently associated with UA Doppler abnormalities.

RECOMMENDATIONS

Based on these findings, women with severe pre-eclampsia with heavy proteinuria and gestational age <35 weeks should have routine UA Doppler sonography to guide decisions as to when to deliver.

Pre-eclamptic women with heavy proteinuria and clinical signs of IUGR regardless of gestational age should also be prioritized for this investigation.

All specialists and Residents in the department of Obstetrics & Gynecology should be trained in doing Doppler ultrasound to offer this investigation to women with pre-eclampsia at their bedside to quickly assess fetal well-being to optimize delivery.

Contributions of the Authors

[1]Was the principal investigator
[2]Senior Supervisor of the PI and contributor of the study topic
[3]Junior Supervisor of the PI and reviewer of manuscript
[4]Offered technical input on Doppler studies and reviewed the manuscript

ACKNOWLEDGEMENTS

Dr. Annette Nakimuli and Dr. Imelda Namagembe of the Department of Obstetrics and Gynecology, Makerere University College of health sciences are particularly appreciated for their key academic input into the academic aspects of the study.

Mr. Ezra Musingye is appreciated for his critical role in the analysis of the data.

SOURCE OF FUNDING

The Belgian Technical Cooperation funded the Principal Investigator to do the study as part of his Master of Medicine program. All parties had no conflict of interest.

REFERENCES

1. Ndayambagye, E.B., Nakalembe, M. and Kaye, D.K. (2010) Factors associated with persistent hypertension after puerperium among women with pre-eclampsia/eclampsia in Mulago hospital, Uganda. BMC pregnancy and childbirth,10:12.
2. Sibai, B.M. et al.(1998). Risk factors for preeclampsia, abruptio placentae, and adverse neonatal outcomes among women with chronic hypertension. New England Journal of Medicine, 339:667-71.
3. Sibai, B.M. Caritis. S. and Hauth, J.(2003). What we have learned about preeclampsia. Seminars in perinatology; Elsevier.
4. Goldenberg, R.L., et al.(2008). Epidemiology and causes of preterm birth. The lancet. ,371:75-84.
5. Turan, S., et al. (2007). Computerized foetal heart rate analysis, Doppler ultrasound and biophysical profile score in the prediction of acid–base status of growth-restricted foetuses. Ultrasound in Obstetrics & Gynecology, 30:750-6.
6. Morris, R. et al. (2011). Fetal umbilical artery Doppler to predict compromise of fetal/neonatal wellbeing in a high-risk population: systematic review and bivariate meta-analysis. Ultrasound in Obstetrics & Gynecology, 37(2):135-42.
7. Maulik D. et al. (1990). The diagnostic efficacy of the umbilical arterial systolic/diastolic ratio as a screening tool: a prospective blinded study. American journal of obstetrics and gynaecology, 162:1518-25.
8. Williams, K.P. et al (2003). Screening for fetal well-being in a high-risk pregnant population comparing the nonstress test with umbilical artery Doppler velocimetry: a randomized controlled clinical trial. American journal of obstetrics and gynecology,188:1366-71.
9. Alfirevic, Z. and Neilson, J. (2009). Doppler ultrasound for fetal assessment in high risk pregnancies.
10. Ngoc ,N.T.N. et al. (2006). Causes of stillbirths and early neonatal deaths: data from 7993 pregnancies in six developing countries. Bulletin of the World Health Organization, 84:699-705.
11. Israel, G.D. (1992). Determining sample size: University of Florida Cooperative Extension Service, Institute of Food and Agriculture Sciences, EDIS.
12. Komuhangi, P. et al. (2013). Umbilical artery doppler flow patterns in high-risk pregnancy and foetal outcome in Mulago hospital. Case Reports in Clinical Medicine, 2:554.
13. Merz, E. (2006). Ultrasound in obstetrics and gynaecology: Thieme.
14. Sibai, B., Dekker, G. and Kupferminc, M. (2005).Pre-eclampsia. The Lancet, 365:785-99.
15. Steegers, E.A. et al.(2010). Pre-eclampsia. The Lancet, 376:631-44.
16. Tranquilli, A.L. et al. (2013). The definition of severe and early-onset preeclampsia. Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health, 3:44-7.
17. Nguku, S., Wanyoike-Gichuhi, J. and Aywak, A. (2006). Biophysical profile scores and resistance indices of the umbilical artery as seen in patients with pregnancy induced hypertension. East African medical journal, 83:96.

18. Duckit , K. and Harrington, D. (2005). Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ, 330:565.
19. Sitras, V. et al. (2009). Differential placental gene expression in severe preeclampsia. Placenta, 30:424-33.
20. Breslin, E. (2013). Pre-eclampsia: predicting onset and poor outcome: University of Warwick.