REFERENCE VALUES OF FETAL PEAK SYSTOLIC BLOOD FLOW VELOCITY IN THE MIDDLE CEREBRAL ARTERY AT 12-41 WEEKS OF GESTATION IN JOS ,NORTH CENTRAL,NIGERIA.

[1]Ulu U O, [2]Udoh B E, [3]Agwu K K

[1]Department of Radiology, Jos University Teaching Hospital, Jos, Plateau State, Nigeria
[2]Department of Medical Radiography and Radiological Sciences, University of Calabar, Cross Rivers State, Nigeria
[3]Department of Radiography and Radiological Sciences, Faculty of Health Sciences and Technology, University of Nigeria, Enugu State, Nigeria

ABSTRACT

OBJECTIVES
The objectives of this prospective cross sectional study are (i) to establish new reference values of peak systolic blood flow velocity measurement in the fetal middle cerebral artery (MCA-PSV) following validated methodological guidelines (ii) to correlate peak systolic velocity with gestational age and (iii) to establish regression prediction model of MCA-PSV for our population.
Patients and Methods Cross-sectional data were obtained from 480 low risk pregnant women and cross validated by 120 high risk pregnant women between 12 and 41 weeks' gestation. Reference ranges for MCA-PSV were constructed and for each measurement linear regression models were fitted separately to the mean and standard deviations (SD) as a function of gestational age.A comparison was made between the reference ranges produced in our study and those of Caucasians.

RESULTS
Tables of mean values of peak systolic velocity and percentile with regression equations of MCA-PSV are resented, with suggested limits of 2.5th as lower borderline and 97.5th values representing the upper borderline of normal. Foetal middle cerebral artery peak systolic velocity demonstrated simple continues increase and strong positive correlation with gestational age. Calculated values of z were higher than critical values for PSV of subjects and Caucasian values; $p<0.05$

CONCLUSIONS
We have constructed reference ranges for MCA-PSV of gestation 1241week period and because the methodological flaws of published study have been eliminated, cross validated by a control group including larger sample size drawn from our population we therefore consider this to be useful for clinical practice.

KEY WORDS: Infant mortality, Doppler ultrasound, peak systolic velocity, reference values, pregnancy

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INTRODUCTION

High infant and maternal mortality rates in Nigeria continue to be issues of high concern[1,].These could be due to inadequate or insufficient options for foetal monitoring. Most causes result from haemodynamic challenges such as anaemic disorders, complications of prematurity and child birth such as low birth weight, birth asphyxia and cardiovascular diseases [2-3]. Some traditional methods of assessing fetal wellbeing like amniocentesis and cordocentesis expose the fetus to the risk of infections, haemorrhage, pre-term labour and miscarriages [4]. The foetus mobilizes a spectrum of compensatory homeostatic responses in these conditions including flow redistribution to vital organs like the adrenals, heart and the brain in a phenomenon called 'brain sparing effect' [5,6].

Routine ultrasound provides anatomical information but lacks physiologic data. Arterial Doppler of fetal vessels provides non-invasive assessment of foetal circulation. Middle cerebral artery is one of the paired arteries that supply blood to the cerebrum [7].

It is a vessel of choice because it is the most favourably positioned vessel in the brain and demonstrates high resistive indices [8-10].To the best of the researcher's knowledge, this work has not been carried out in this locality.

Corresponding Author: Dr Ulu O Ulu,
Radiology Department, Jos University Teaching Hospital,
PMB 2076, Jos, Plateau State.
Email: edwinulu@gmail.com.
Phone: +2348069694854

MATERIALS AND METHODS

Four hundred and eighty pregnant women aged between 17 and 42 years from a referral centre in Jos were prospectively examined using Aloka SSD-3500 ultrasound machine, manufactured by Aloka Corporation of Japan. It has pulsed wave Doppler facility with frequency range of 2.5MHz to 10MHz. The study was approved by the Ethics Committee of Jos University Teaching Hospital (reference: JUTH/DCS/AMD/127/XIX/5306 of 2nd July, 2012). Informed consents were obtained from subjects who met the inclusion criteria and convenient sampling was adopted to recruit the subjects who gave their consent and were willing to participate in the study. The study was carried out between November, 2012 and February, 2014. The biometrics and biophysical profile scores of foetuses between 12 to 41 weeks of singleton gestation were obtained using real time ultrasound according to the technique standardized by Sanders[11]. The foetal middle cerebral artery was also scanned using Doppler according to the technique developed by Nicolades and Abdel-Fattah to establish waveform values[12.] These values were categorized into peak systolic velocity, end diastolic velocity, pulsatility index, resistivity index and systolic-diastolic ratio. Mean values of the indices were used to construct percentile values. Pearson's correlation and regression models were used to determine the relationships between foetal gestational age and peak systolic velocity. Z-test was used to compare the means values of the peak systolic velocity in low and high risk pregnancies and also to compare mean values of subjects with Caucasian values. Level of significance was accepted at $p < 0.05$

RESULTS

The mean age and parity of subjects were 27.93±5.17 years and 2.31±1.46 respectively. The mean values of the foetal middle cerebral peak systolic velocity were obtained as follows: peak systolic velocity- 15.36 ± 2.50cm/s at 12weeks, 17.10±2.77 at 16 weeks,20.46±3.66 at 20 weeks, 23.90 ± 3.42cm/s at 24 weeks,31.71±2.33 at 28 weeks, 36.78±4.73 at 32 weeks,39.91 ± 6.71cm/s at 36 weeks and 40.79. ±5.66 at 40 weeks of gestation Results show simple continuous increase in mean values of peak systolic velocity of foetuses with gestational age. Pearson's correlation of middle cerebral artery peak systolic velocity with foetal gestational age shows significant positive correlation ($r=0.924, p=0.000$),Regression prediction model was obtained and expressed mathematically as follows: peak systolic velocity= 0.866GA+5.160. the slope and constant of the equation of the study was different with other published works. No two population equation was similar. Significant differences in mean values of peak systolic velocity were noted between subjects and others reported in literatures, $p<0.05$.

DISCUSSIONS

Arterial Doppler ultrasound velocitometer of fetal vessels has become established method of antenatal monitoring allowing non-invasive assessment of fetal circulation and provides important information on the hemodynamics of the vascular area under study. This has become relevant because each vessel has its specific Doppler signature, and so physiological and pathological changes of vessels can be recognized by the evaluation of the Doppler spectrum. Pulsed wave Doppler is used to identify vessels, assess their direction, velocity and pattern of blood flow. The common indices measured include peak systolic velocity (PSV), end diastolic velocity (EDV), pulsatility index (PI), resistivity index (RI) and systolic/ diastolic ratio [13-15.] Application of Doppler in pediatrics are increasing, gray scale sonography is routinely performed to evaluate high risk pregnancies. Although this provides anatomic information, it lacks the ability to provide physiologic data. Duplex Doppler ultrasound on the other hand has the potential to provide physiologic information concerning the middle cerebral artery blood flow and resistance [16].

Multilevel modeling was used to calculate the mean values and subsequently constructed the percentile curves of the Doppler indices according to gestational age in order to determine the limits of normal at the 2.5^{th}, 5^{th}, 35^{th}, 50^{th}, 90^{th} and 95^{th} percentiles suitable for use for foetal surveillance in the locality. The 97.5^{th} percentile was considered as the upper border of normal for the peak systolic velocity and 2.5^{th} percentile as the lower border of normal. The percentile values of the foetal middle cerebral artery peak systolic velocity increased steadily throughout gestation. Values obtained were similar to published work by Tarzamni et al[17] but with slight differences in values especially towards the end of pregnancy. Kurmanavicius et al and Mari et al[18,19] especially before the 24^{th} weeks of gestation but consistently lower in the last weeks of gestation.

Study methodology was expected to cause some degree of differences in the results of this study and those of others. The study by Mari et al [19] was retrospective and included only 135 subjects at 15-42 gestational weeks which according to Royston [20] is too small a number to construct a reliable reference values. The study by Kurmanavicius et al[18] on the middle cerebral artery peak systolic velocity had few observations in the last weeks of gestation while Kacherwar et al[21] used only 90 observations. Contributory to the variability of velocities and indices aside low number of observations could be the different sites of middle cerebral artery measurements (ie distal part of the vessel rather than the recommended proximal site. Also environmental and

genetic diversity could have contributed to these differences as was reported by Abdel-Fattah [12] and Kacherwar et al[21].

Comparison of the regression curve equation of this study with other studies shows differences both in constant and slope ;and further demonstrated that no two population equations are the similar[15,21].

Z-test comparison of mean values of the middle cerebral artery peak systolic velocity of this study and other studies showed that the critical value of Z was higher than the calculated values of Z(1.96;$p<0.05$). This is in complete agreement with other reports by Tarzamni et al. and Kacherwar [18,21] who have showed that the use of the peak systolic velocity, pulsatility index, and resistivity index depend on appropriate reference ranges and is thus, population-specific. Meyberg [22] and his team in recognition of this stressed that knowledge of the reference range Doppler parameters helps to discriminate between a normal fetal situation and disease conditions; and therefore, recommended that each perinatal centre should develop their data.

CONCLUSIONS

It is concluded that foetal middle cerebral artery peak systolic velocity showed simple continuous step-wise increase attaining high values between the 34^{th} -38^{th} weeks of gestation and demonstrated statistically significant positive linear relationship with foetal gestational age. Relationship between peak systolic velocity and gestational age yielded important prediction model. Significant differences exist in the mean values of MCA- peak systolic velocity and regression curves equations of subjects and Caucasian values. This nomogram could serve as a useful guide in determining the limits of normality of foetal foetal peak systolic velocity of the middle cerebral artery in this locality. As the procedure is non-invasive and reproducible it will help reduce the number of risky and invasive diagnostic procedures such as amniocentesis and cordocentesis and could be used to diagnose foetal anaemia. It could serve as a tool in foetal surveillance for early and appropriate intervention such as in timing for intrauterine foetal transfusion, and also in the evaluation of a foetus when there is doubt of the well-being and thus predict status of an unsuspected foetal disorder.

CONFLICT OF INTEREST

There was no conflict of interest.

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Table 1: Age distribution of subjects

Age of subjects(Years)	Number of subjects	Percentage (%)
15-20	85	18.6
21-25	98	21.5
26-30	151	33.1
31-35	85	18.6
36-40	36	7.9
41 and above	1	0.22
TOTAL	456	100

Table 1 shows the age distribution of subjects. The data shows that 33.1% of subjects were between the age range of 26 and 30 years. Subjects above 41 years of age represent 0.22% of study population.

Table 2: Percentile values of the foetal middle cerebral artery peak systolic velocity at different foetal gestational age.

	Percentiles Suggested Limits of Normal										
GA (Weeks)	No of subjects	2.5th	10th	35th	50th	75th	90th	95th	97.5th	Lower	Upper
12	9	11.30	11.30	12.50	15.50	15.80	16.10	17.50	17.50	11.10	17.80
13	10	14.40	14.48	16.43	16.85	17.20	17.86	17.90	17.90	12.32	18.00
14	15	11.81	12.92	15.76	16.45	17.85	18.75	18.75	18.75	12.50	18.99
15	10	13.54	13.71	15.46	16.49	17.69	18.63	18.70	18.70	13.31	19.02
16	13	16.70	17.30	18.72	19.33	20.59	21.99	22.08	22.08	15.78	22.11
17	25	17.67	19.70	20.08	21.08	22.80	23.10	23.60	23.60	17.66	23.90
18	13	17.90	20.49	21.32	21.45	21.45	22.62	22.89	23.89	17.70	24.08
19	15	17.98	19.44	21.09	21.65	22.02	24.29	24.29	26.80	17.75	26.82
20	14	17.81	18.70	21.89	22.08	23.90	24.62	24.62	26.10	17.80	26.87
21	15	18.59	22.62	23.64	24.50	24.55	26.00	26.00	26.00	18.00	26.90
22	18	18.70	21.65	22.03	22.20	22.76	22.98	22.98	26.07	18.11	26.95
23	23	21.20	21.91	23.42	23.47	23.91	25.54	25.54	26.90	20.24	26.97
24	19	21.40	21.40	22.93	23.32	23.90	24.94	24.94	26.98	20.95	27.22
25	25	22.43	22.75	24.84	25.09	25.78	25.78	26.94	27.40	21.22	27.50
26	20	25.00	25.05	25.82	25.98	26.73	26.99	28.44	28.60	23.87	28.50
27	11	25.70	25.73	26.68	28.75	29.50	29.98	30.00	30.00	24.07	30.50
28	23	25.88	28.23	30.98	31.98	33.60	34.92	35.17	35.20	25.00	35.60
29	15	26.76	29.76	32.05	32.97	33.40	34.38	35.05	35.05	25.88	35.90
30	13	27.90	29.29	30.89	31.80	33.09	35.17	35.87	36.11	26.22	36.11
31	18	27.40	27.89	36.45	37.62	39.90	39.90	39.90	39.90	26.50	39.98
32	13	29.00	31.88	36.02	36.11	33.66	38.99	41.00	41.00	28.92	41.43
33	12	35.76	35.77	35.89	35.99	36.19	38.80	38.88	38.88	30.76	42.07
34	10	31.90	31.97	33.36	33.70	35.56	38.62	38.81	38.81	31.07	42.76
35	15	28.97	29.48	35.04	36.51	38.92	39.02	39.07	39.07	32.87	43.75
36	12	33.70	35.35	39.16	40.35	41.61	43.88	45.90	45.90	33.11	44.78
37	11	32.70	33.08	37.50	39.50	40.50	41.30	41.50	41.50	32.00	44.79
38	13	33.16	34.50	39.10	39.70	42.40	46.48	47.50	47.50	32.50	47.80
39	12	34.00	36.73	39.06	39.87	40.91	42.28	42.60	42.60	33.76	38.98
40	10	38.47	38.54	39.78	40.79	41.31	41.95	41.97	41.97	36.87	45.33
41	13	35.32	36.08	36.77	38.45	43.75	48.40	45.80	48.40	34.87	50.44

GA= gestational age

The 2.5th percentile values represent the range of borderline lower limits of normal; the 2.5th -97.5th values represent the range of normal values whereas the 97.5th percentile values the range of borderline upper limits of normal.

Table 3: Comparison of regression equations of subjects with Caucasians.

	Country	Equation
Kurmanaviscius et al.,2001	Switzerland	Y=2.127X+4.762
Teixeira et al.,2000	England	Y=1.0511X+20.138
Kachewar et al.,2013	India	Y=1.1131X+10.381
Ebbing et al.,2007	Norway	Y=1.903X+8.2639
Zimmerman et al.,2002	USA	Y=1.6971X+6.9546
Andrei et al.,2012	Hungary	Y=2.04872X-20.535
Tan et al.,2009	Singapore	Y=1.506X+11.05
Present study	Nigeria	Y=0.866X+5.160

Table 3 shows the regression curve equation of the fetal middle cerebral artery peak systolic velocity of different populations. The table shows that the regression curve equation of study was different both in constant and slope to Caucasians and further demonstrated that no two population equations are the same.

Table 4: Z-test comparison of Means and standard deviations (SD) values of MCA-PSV of subjects with a Caucasian study at selected weeks of gestation.

	20 weeks GA PSV(cm/s)	24 weeks GA PSV(cm/s)	30 weeks GA PSV(cm/s)	38 weeks GA PSV(cm/s)
Iran	n=41;20.00±12.23	n=45;27.92±11.38	n=46;46.42±11.16	n=57;56.97±15.91
Present study	n=14;20.46±3.66	n=19;23.90±3.42	n=13;30.15±6.11	n=13;42.40±6.32
Calculated value of Z	0.214	2.15	6.70	5.30
Critical value of Z	1.96	1.96	1.96	1.96

Table 4 shows the Z-test analysis of means and standard deviations (SD) values of the fetal middle cerebral artery peak systolic velocity at the 20th, 24th, 30th and 38th weeks of gestation. Results show that calculated values of Z was significantly greater than the critical value of Z at the 24th ,30th and 38th weeks of gestation.

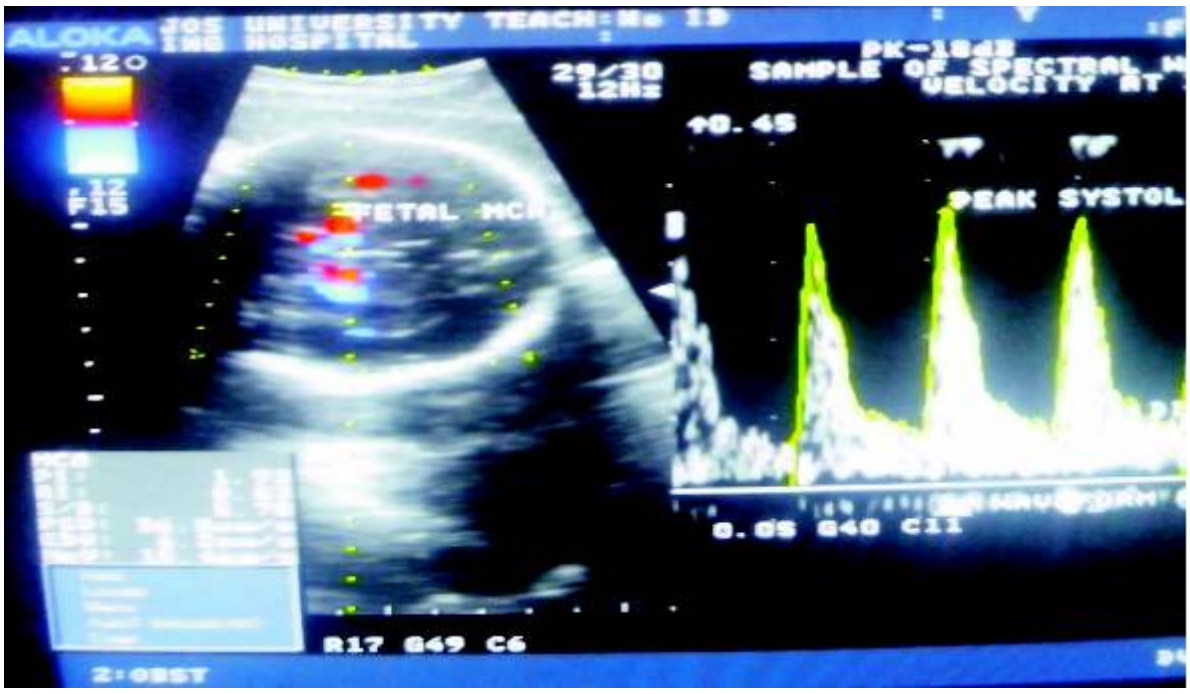

Figure 1 Transverse view of the fetal head at the level of the circle of Willis, and Doppler flow waveform of the normal middle cerebral artery at 31 weeks' gestation,

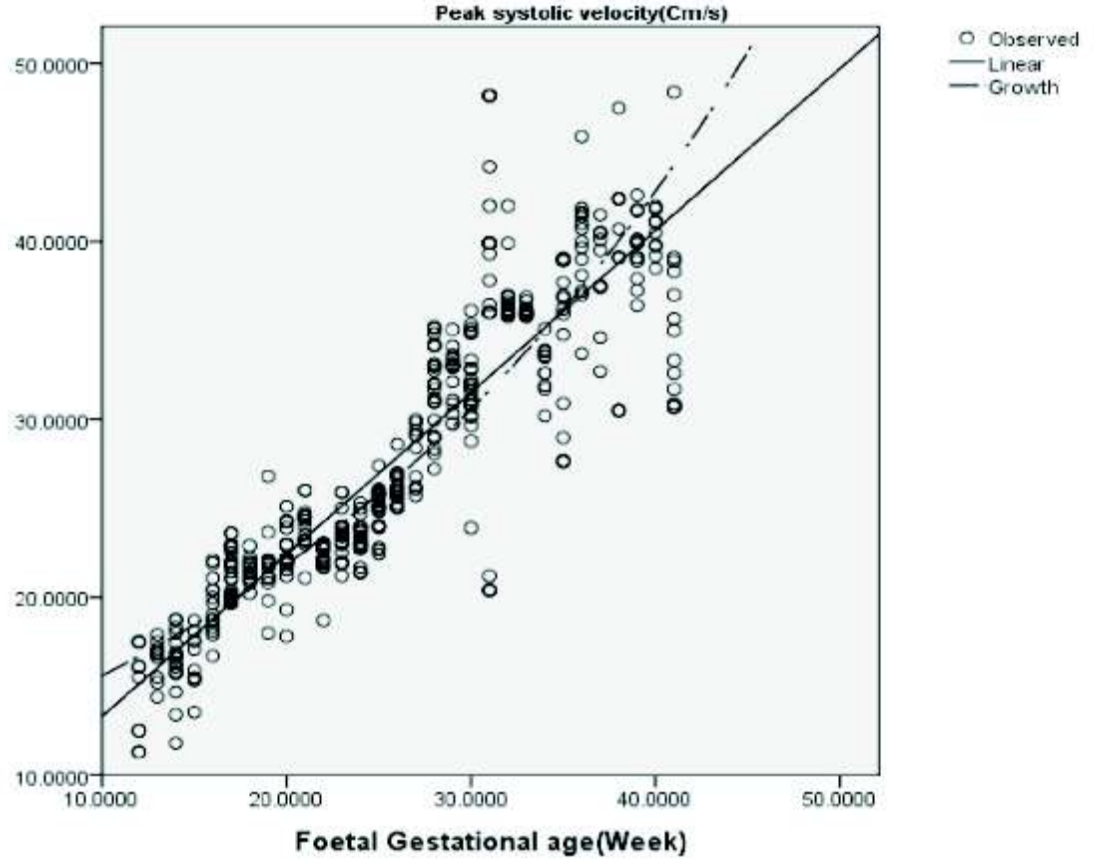

Figure 2: Regression curve of peak systolic velocity (PSV) of the middle cerebral artery (MCA) and gestational age. The figure demonstrates a linear regression curve of fetal middle cerebral artery peak systolic velocity and fetal gestational. Foetal middle cerebral artery peak systolic velocity is related to fetal gestation age with equation; peak systolic velocity= 0.866GA+4.99.

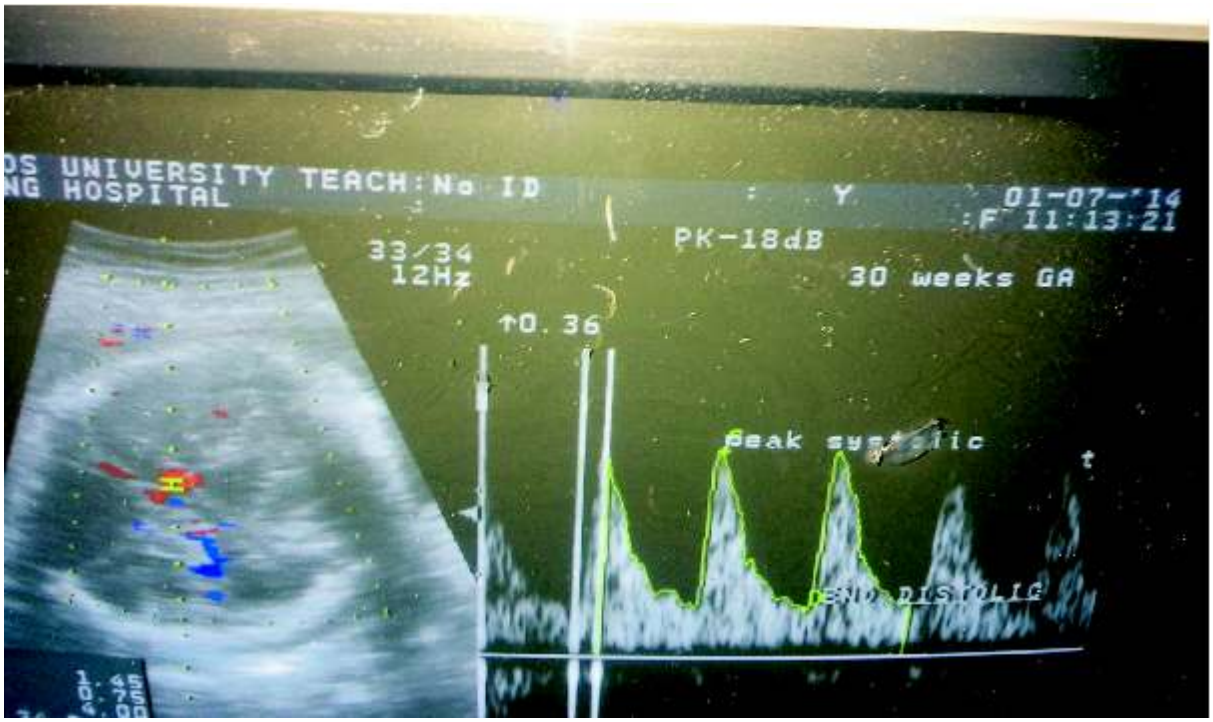

Figure2: Doppler sonogram showing normal spectral Doppler waveform measurement of the foetal middle cerebral artery at 30 weeks of gestation and measurements of Doppler parameters in normal pregnancy. MCA (red colour)= middle cerebral artery, PSV=peak systolic velocity, EDV=end diastolic velocity.

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