REFERENCE VALUES OF DOPPLER RESISTANCE INDICES OF FETAL MIDDLE CEREBRAL ARTERY IN A NIGERIAN POPULATION.

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ABSTRACT

Background. *Nigeria records high infant and maternal deaths. Most causes result from haemodynamic challenges and complications of prematurity. Some traditional methods of assessing fetal well being like amniocentesis and cordocentesis vis-a-visbilirubin delta level in amniotic fluid level assessments expose the fetus to the risk of infections, pre-term labour and miscarriages.*

Methodology. *This was a prospective cross-sectional study of six hundred pregnant women aged between 17 and 47 years using Aloka SSD-350 ultrasound machine to establish reference values of the fetal middle cerebral artery Doppler waveform resistance indices for fetuses aged between 12 to 41 weeks of gestation. The foetal biometrics and biophysical profile scores of subjects obtained were used to establish foetal gestational age and also to determine the suitability of subjects for inclusion into the study. Foetal middle cerebral artery was scanned using Doppler ultrasound to establish waveform values which were categorized into peak systolic velocity (PSV), end diastolic velocity, pulsatility index and resistivity index.*

Results: *The mean values of pulsatility index obtained were as follows: 1.09±0.28 at 12 weeks of gestation, 1.12±0.18 at 16 weeks gestation, 0.93±0.16 at 20 weeks gestation, 1.22±0.22 at 24 weeks of gestation, 1.15±0.22 at 28 weeks gestation, 0.95±0.19 at 32 weeks gestation, 0.90±0.20 at 36 weeks of gestation and 0.88±0.10 at 41 weeks of gestation while mean values of resistivity index were as follows: 0.72±0.35 at 12 weeks of gestation, 0.68±0.18 at 16 weeks gestation, 0.71±0.08 at 21 weeks of gestation, 0.75±0.04 at 24 weeks of gestation, 0.74±0.08 at 25 weeks of gestation, 0.73±0.07 at 31 weeks of gestation, 0.71±0.11 at 33 weeks of gestation, 0.64±0.07 at 36 weeks of gestation, and 0.61±0.03 at 41 weeks of gestation. Calculated values of Z were higher than the critical values for Doppler parameters of subjects and Caucasian values; p=0.05.*

Conclusion. *It is concluded that the mean value of the fetal middle cerebral arterial pulsatility index and resistivity index showed parabolic pattern, demonstrating inverse relationships with gestational age. As this procedure is non-invasive, reproducible and population –specific, these parameters could serve as useful guide and early warning signs for the surveillance of foetal distress especially in intrauterine growth restriction and foetal anaemic disorders for our locality.*

Key words: *Reference values, Resistivity index, Doppler ultrasound, middle cerebral artery.*

INTRODUCTION

Background of study

Globally about 1,500 women die daily because of complications during pregnancy or child birth. Africa and Asia account for 95% of these deaths each year. Nigeria's maternal mortality rate is estimated at 440 maternal deaths per 100,000 live and ranked among the highest in the world. It is also estimated that 15% of all deaths across the globe occur in children under the age of 5 years and a child dies every 45 seconds[1].

The most common causes worldwide of infant mortality are dehydration from diarrhoea and pneumonia. Other major causes of infant mortality include: malnutrition, malaria, congenital malformation, infection and sudden infant death syndrome (SIDS). Studies conducted in Nigeria showed that 29% of infant mortality resulted from birth asphyxia, 24% from severe infection such as pneumonia and diarrhoae, 24% from complications of prematurity (low birth weight) and 7% by tetanus [1].

The World health organization (WHO) in its 2005 World Health Report "Make Every Mother and Child Count", reported that the major causes of maternal deaths are: severe haemorrhage (25%), infections (13%), unsafe abortions (13%), eclampsia (12%), obstructed labour (8%), complicated pregnancy 20% and other indirect causes (8%). A few of such indirect causes are malaria, anemia, HIV/AIDS and cardiovascular diseases. It is further reported that lack of access to skilled Medicare during child birth is a factor to high infant and maternal death rate. The tragedies of these preventable deaths, high maternal and infant mortality come with a high cost to the rest of the society [5].

Over the ages several methods have evolved that are used to assess and monitor fetal and maternal well being. These methods range from physical examination, rectal examination to biochemical analysis of fetal fluids in terms of amniocentesis and cordocentesis [6] Some of these methods of assessing fetal wellbeing like amniocentesis and cordocentesis expose the fetus to the risk of boosting antibody concentration which has led to miscarriage and pre-term labour[7]. However, cordocentesis is still best reserved for monitoring cases in which severe fetal anemia is suspected and intrauterine transfusion is likely to follow[8].

In recent years however, two methods have been developed to assess and monitor fetal and maternal well being following advances in medicine and technology. They are fetal biophysical profile scores using real-time sonography and fetal multivessel Doppler velocity waveform analysis. Both methods are non invasive and provide insight into facets of fetal responses [9]. Although real-time sonography provides anatomic information, it lacks the ability to provide physiologic data as studies have shown that the ultrasonographic fetal biometric measurements are weaker predictors of fetal conditions than Doppler measurements[10,11].

Studies have shown that the advantages of studying the MCA rather than other vessels is that it allows measurements of velocity without angle correction, because in the axial plane , the angle of insonnation of the MCA is close to zero degree ,improving reproducibility and the association of increased blood flow velocity in the fetal middle cerebral artery with fetal anaemia is the most promising of non-invasive tests that has been reported[12].

In a study to establish reference ranges and standard percentile-curves for Doppler indices resistance index(RI) and systolic /diastolic ratio of the fetal middle cerebral artery color Doppler measurements in a perinatal centre, Meyberg et al [13] showed that the increase in the diastolic component in the middle cerebral artery of the last third of the pregnancy demands reference ranges by using percentile curves; and further stressed that knowledge of the reference range helps to discriminate between a normal fetal situation and disease. Meyberg and his team therefore, recommended that because of the different absolute ranges values shown in literature, each perinatal centre should develop their data.

This recommendation for population-specific Doppler range resistance indices defines the basis for this study. It is hoped that by providing population specific values racial bias will be reduced and the values obtained can be precisely used for a more objective and effective maternal prenatal care.

MATERIALS AND METHODS

Study population

Six hundred pregnant women aged between 17 and 42 years with single gestation who presented at the Antenatal unit and sent for ultrasound for biophysical profilewere recruitedrecruited. This study was approved by the Ethics Committee of Jos University Teaching Hospital. Informed consents were obtained from subjects who met the inclusion criteria and convenient sampling was adopted to recruit the subjects who were willing to participate in the study.

METHODOLOGY

Technique : The technique standardized by Sanders [14] was adopted to measure the biophysical profiles of subjects as follows: The subject lay in a recumbent or semi recumbent position with a slight lateral tilt on the couch. The maternal abdomen was scanned using a 5.5MHz transducer after a coupling gel has been generously applied until the foetus was clearly seen and the foetal skull shown in a transverse position. The biparietal diameter was measured on the transverse section of the fetal skull showing circular skull outline, a short midline echo, cavum septum pellucidum, basal cistern and thalami. Measurements were from the inner border of the skull to the outer body on the opposite side as skull as shown in figure 5. Abdominal circumference – this was measured on the foetal abdomen at the level of the portal sinus and the liver, showing the umbilical vein, aorta ,adrenal gland, stomach and the spine and the femoral length was measured along the axis showing femoral head and the condyles. These were used to calculate the gestational age and the foetal weight.

The technique developed by Nicolaides et al and standardized by Mari et al 1998 & Abdel-Fattaah was used in the measurement of the fetal middle cerebral arterial Doppler waveform velocities.

Doppler scans were done with the subjects lying in a recumbent or semi recumbent position with a slight lateral tilt; this was to minimize the risk of the subject developing supine hypotension syndrome due to caval compression. Sample volume of 2-3mm was used.

By scanning the maternal abdomen, a transverse section of the fetal head was obtained by ultrasonography using the 5.5-MHz curvilinear probe, and color flow mapping was used to identify the circle of Willis and the Middle Cerebral Artery overlying the anterior wing of the sphenoid bone near the base of the skull. At the level of the lesser wing of the sphenoid bone, the middle cerebral artery was demonstrated as a major branch of the circle of Willis (which runs anterolaterally as shown in figure 4-5. The pulsed wave Doppler gate was then placed on the proximal one-third of the Middle Cerebral Artery and the angle of insonation less than 15° was used. A 125-Hz high-pass filter was used to eliminate signals from slowly moving tissues. Attention was taken to avoid any unnecessary pressure on the fetal head. At least three consecutive waveforms, in the absence of fetal body or breathing movements, were recorded and the highest point of the Doppler waveform was considered as the PSV (cm/s). These values were used to calculate the resistive indices (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 biometrics, biophysical profile scores and Doppler resistive indices parameters, Z-test was used to compare the means values of Doppler indices with combined biophysical profile scores and comparison was also made with Caucasian values. Level of significance was accepted at $p< 0.05$

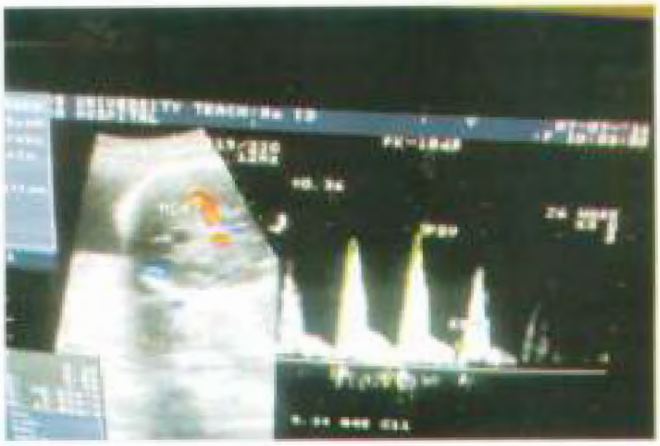

Figure 1: Sonogram showing normal spectral Doppler waveform analysis of the foetal middle cerebral artery at 26 weeks of gestation. The peak systolic velocity and the end diastolic velocity are highlighted in the spectral waveform as PSV and EDV for peak systolic velocity and end diastolic velocity respectively. while the MCA denotes the middle cerebral artery in colour.

Results

Six hundred singleton pregnant women aged between 17years and 42 years were scanned to determine the foetal biometrics and Doppler resistance indices. The mean age of subjects was 27.93±5.17 years with 55.7% of subjects between the ages of 17 and 30 years: mean gravidity was 2.31±1.46.

Variation of the pulsatility index with fetal gestational age shows simple step-wise increase in mean values as follows: 1.09±0.28 at 12 weeks of gestation. 1.20±0.57 at 14 weeks gestation,1.12±0.18 at 16 weeks gestation,0.93±0.16 at 20 weeks gestation 1.17±0.26 at 21 weeks of gestation, 1.27±0.22 at 24 weeks of gestaton,1.09±0.24 at 26 weeks gestion,1.15±0.22 at 28 weeks gestation 1.09±0.22 at 29 weeks of gestation,0.95±0.19 at 32 weeks gestation, 0.90±0.20 at 36 weeks of gestation,0.84±0.33 at 38 weeks of gestaton and 0.58±0.10 at 41 weeks of gestation. These show a parabolic pattern attaining peak values at 24 weeks of gestation and decreased towards end of gestation.A negative correlation was shown to exist between gestational age and pulsatility index($r=-0.421;p<0.05$.The regression curve equation of this relationship was expressed mathematically as follows:pulsatility index (PI)= 1.290Gestational age-0.099

Variation of the resistivity index with foetal gestational age shows the following values: 0.72±0.55 at 12 weeks of gestation, 0.68±0.18 at 16 weeks gestation, 0.73 ±0.15 at 17 weeks gestation, 0.73±0.06 at 18 weeks of gestation, 0.71±0.08 at 21 weeks of gestation, 0.75±0.04 at 24 weeks of gestation, 0.74±0.08 at 25 weeks of gestation, 0.75±0.72 at 29 weeks of gestation, 0.73±0.07 at 31 weeks of gestation 0.71±0.11 at 33 weeks of gestation, 0.64±0.07 at 36 weeks of gestation, 0.57±0.13 at 38 weeks of gestation,0.54±0.04 at weeks of gestation and 0.61±0.03 at 41 weeks of gestation. These values demonstrated parabolic pattern, attaining peak values between the 24th and 29th weeks of gestation.A significant though weak negative linear correlation was observed between gestational age and resistivity index r=-0.407 at 0.01 level 2-tailed.The regression curve of this relationship was expressed mathematically as follows: resistivity index=0.860Gestational-0.004

Results further show that Pearson's correlation of pulsatility and resistivity indices with composite biophysical scores such as amniotic fluid index,heart rate, foetal tone show no significant statistical relationship (p>0.05).

Table 1: *Mean and standard deviations of demographic and Doppler waveform findings of subjects.*

Gest.Age (weeks)	No. of subj	Age of subj(yrs)	Parity	PI	RI	S/D ratio
12	9	27.00±9.89	1.50±0.70	1.09±0.28	0.72±0.55	3.47±0.43
13	10	28.00±4.77	1.50±1.00	2.09±1.37	1.22±0.09	4.79±1.39
14	15	27.89±4.86	1.08±0.84	1.05±0.40	0.68±0.18	4.36±2.73
15	10	27.40±4.25	1.90±0.74	1.20±0.57	0.73±0.15	3.69±1.63
16	13	28.50±3.89	1.70±0.68	1.12±0.18	0.76±0.08	4.08±0.93
17	25	27.52±5.02	2.00±1.49	1.04±0.26	0.73±0.09	3.48±0.83
18	13	28.92±4.96	2.20±1.87	1.12±0.24	0.73±0.06	3.79±0.76
19	15	27.26±5.42	2.33±1.79	1.22±0.45	0.73±0.04	3.75±0.75
20	14	20.06±7.10	1.07±0.98	0.93±0.16	0.63±0.06	3.23±0.67
21	15	26.38±4.23	1.94±1.22	1.17±0.26	0.71±0.08	3.55±0.86
22	18	27.81±5.12	2.31±1.49	1.05±0.26	0.66±0.15	3.64±0.92
23	23	27.77±5.95	2.14±1.06	1.10±0.24	0.71±0.12	3.83±0.83
24	19	27.89±3.02	2.53±1.51	1.22±0.22	0.75±0.04	4.13±1.06
25	25	28.30±4.74	2.45±1.63	1.14±0.23	0.74±0.08	3.88±1.19
26	20	28.36±4.44	2.55±1.29	1.09±0.24	0.68±0.14	3.89±1.66
27	11	26.75±4.30	2.66±1.21	1.01±0.22	0.74±0.11	4.39±1.36
28	23	27.38±5.64	2.44±1.36	1.15±0.22	0.69±0.13	3.95±1.07
29	15	27.00±5.30	2.53±1.33	1.09±0.22	0.75±0.72	3.95±0.90
30	13	28.08±5.40	2.80±1.81	1.00±0.22	0.69±0.10	3.63±1.91
31	18	28.17±5.14	2.76±1.92	1.11±0.21	0.73±0.07	4.27±1.81
32	13	27.61±5.26	2.50±1.50	0.93±0.19	0.69±0.06	3.43±0.61
33	12	27.18±4.24	1.80±1.14	1.10±0.24	0.71±0.11	3.81±1.47
34	10	29.70±6.46	3.00±1.51	1.13±0.15	0.70±0.04	3.45±0.51
35	15	25.92±5.74	2.14±1.23	1.07±0.26	0.71±0.08	3.58±1.03
36	12	30.50±1.87	2.67±2.25	0.90±0.20	0.64±0.07	2.75±0.37
37	11	28.36±5.73	2.36±1.96	0.79±0.31	0.56±0.17	2.72±1.13
38	13	31.69±5.02	3.07±2.19	0.84±0.33	0.57±0.13	2.60±0.93
39	12	26.75±5.49	1.89±1.27	0.85±0.27	0.59±0.04	2.49±0.32
40	10	31.00±5.41	2.25±1.25	0.76±0.11	0.54±0.04	2.19±0.21
41	13	30.00±7.34	2.25±1.25	0.88±0.10	0.61±0.03	2.50±0.07

Where PSV=peak systolic velocity, PI=pulsatility index, RI=resistivity index, S/D ratio=systolic-diastolic ratio

Table 2: Shows the number of subjects according to gestational age in weeks, patients' characteristics; mean standard deviation (SD) for the MCA PSV, PI, PI, S/D ratio.

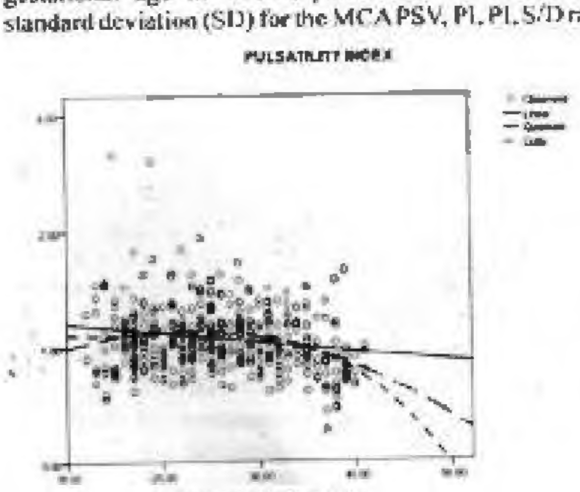

Figure 3: Regression curve of pulsatility index of the middle cerebral artery and gestational age.

The figure shows the regression curve of the middle cerebral artery pulsatility index with respect to fetal gestational age. The prediction model of normal middle cerebral artery pulsatility index (PI)= 1.290GA-0.009

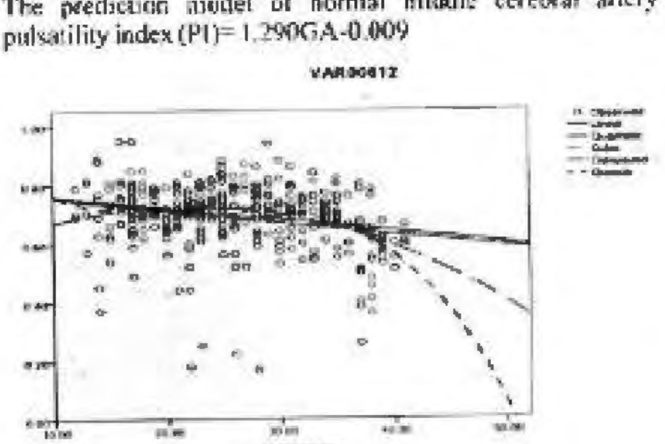

Figure 4: Regression curve of resistivity index and gestational age.

The figure shows the regression curve of the middle cerebral artery resistivity index with respect to gestational age. The prediction model of the normal resistivity index=0.860GA-0.004

Discussion

Application of Doppler in pediatrics is increasing day by day. Gray scale sonography is often 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 [17,18]. This is made possible 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 findings of this study showed that values of the middle cerebral artery pulsatility index rise gradually with gestation reaching a peak (1.22±0.22) at 24 weeks of gestation and then decrease towards the end of pregnancy thus, demonstrating parabolic pattern or an inverted U-shape. This finding is in agreement with reports of many investigators who showed age-related changes of pulsatility index with this parabolic fashion of values [19,20,21,22]; and Ebbing et al[23] however, demonstrated values of middle cerebral artery pulsatility index slightly higher than the results of this study especially in early second trimester and late trimester with their peak values between 28th and 30th weeks of gestation as against 24 weeks recorded by this study.

These parabolic pattern of values of cerebral vascular resistance is speculated to be due to the rapid increasing volume in the cerebral vascular bed in both early and late gestation week and the redistribution favouring blood supply to the brain influenced by physiological foetal oxygenation reduction near term [24] Some researchers suggest that the gradual fall in values of the pulsatility index with advancing foetal development especially in the last ten weeks of gestation after reaching peak values probably reflects a decrease in vascular resistance with advancing gestational age or an association with deoxyribonucleic acid production in fetal brain with consequent fall in vascular resistance [25]

A plausible reason for the differences observed in values of pulsatility index as reported in this study with others consulted could be due to the differences in study methodology adopted. For example while the present study was prospectively done with a sample size of 600 and covered between 12 to 41 weeks of gestation, the study by Mari et al [21] was retrospective and included only 135 participants at 15-20 gestational week and the end of pregnancy. Kachevar et al [22] in India used only 90 subjects for his study. This could lead to imprecise estimation of the regression model.This finding also goes to shows that perhaps genetic diversity and environmental geography could play vital role as part of population dynamics in determining Doppler parameters as suggested by Tarzamni et al [21] as these parameters are population-specific.

Studies have shown that foetuses that are intrauterine growth-restricted secondary to placental insufficiency redistribute their blood flow from the periphery to the brain in a phenomenon described as 'brain-sparing' and this forms the basis for clinical management of foetuses at risk of intrauterine growth restriction using pulsatility index . These Mari et al [26] and Vyas et al [11] demonstrated in their separate works that the MCA-PI is decreased in foetuse at risk of intrauterine growth restriction (IUGR) and suggested that it could be a good predictor of perinatal morbidity and mortality. The result of this study may be used to detect intrauterine restricted foetuses, foetal hypoxia and acidosis as this index change significantly in these conditions.

Pearson's correlation of MCA pulsatility index with fetal gestational age showed a negative relationship ($r = -0.276$ at 0.01 level 2-tailed).This relationship also yielded a regression curve equation and mathematically expressed as follows: pulsatility index=0.826 -0.009GA. This relationship was similar to reports of Tarzmani et al [18]. This mathematical model when used could be a good predictor of perinatal morbidity and mortality especially intrauterine restricted foetuses.

Result of this study showed that mean values of the foetal middle cerebral artery resistivity index increase gradually with increasing gestational age with a peak at 31 weeks of gestation. The pattern of result of this study as well as the attainment of peak valves were similar to those of Hecher et al [7], figures were similar to the work of Tarzamni et al [18] but consistently lower than those of Mari et al [20],and Ebbing et al [23]

Rujiwetpongstom's on the other hand, established his nomogram for MCA RI between 11-20 weeks of gestation demonstrated decreasing values of middle cerebral artery resistivity index without exhibiting parabolic pattern.

Again, the parabolic changes of cerebral vascular resistance has been attributed to the rapid increasing volume in the foetal cerebral vascular bed in early and late gestational week, and the redistribution favouring blood supply to the brain influenced by physiological foetal oxygenation reduction near term [16]

Pearson's correlation of resistivity index with gestational age shows a negative relationship($r=-0.407$; $p<0.05$).The regression curve of this relationship was characterized by a parabolic pattern and yield a regression curve equation: resistivity index=1.181-0.013GA. This result is comparable to the works of Arduiniet al [25] and Tarzamni et al [9].

This prediction model could be a useful aid in the early detection of abnormalities in the foetal cerebral flow especially in foetal anaemic, hypoxemic conditions and intrauterine growth restrictions as these processes are identified by low impedance in Doppler waveform of the MCA(Vyas et al [11] Mari et al [20]

Conclusion.

The study has established mean values of Doppler resistance indices of the foetal middle cerebral artery for different gestation and these were shown to exhibit inverted U or parabolic pattern of values. The relationships established were negative with varying degrees of statistical significance. This prediction models established by this study could be useful aids in the early detection of abnormalities in the foetal cerebral flow especially in foetal anaemic, hypoxemic conditions and intrauterine growth restrictions as these processes are identified by low impedance in Doppler waveform of the middle cerebral artery.

CONFLICT OF INTEREST

I declare that I have no financial or personal relationship which may have inappropriately influenced me in writing this paper.

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