Research Article

Doppler Index And Associated Artery Most Correlated To Intrauterine Growth Restriction Due To Maternal Preeclampsia At 28- 34 Weeks Gestational Age

Wisam Akram, [1] **Najlaa Hanoon,** *F.I.B.M.S., D.M.R.D,* [2] ***Sara Abid Abdalla,*** *M.B.Ch.B,* [3]

[1] Consultant Obstetrician And Gynecologist And Assistant Professor Of Gynecology And Obstrtics AL Mustansiriyiah Medical College

[2] Radiologist in Al-Yarmouk Teaching Hospital, Senior Lecture In Radiology, AL Mustansiriyiah Medical college

[3] Registrar In Gynecology And Obstetrics AL- Yarmook Teaching Hospital – 4th Year Arab Board Candidate

Date Submitted: 4/10/2016
Date Accepted:30/11/2016

Address for Correspondence:
Dr Wisam Akram Consultant Obstetrician And Gynecologist And Assistant Professor Of Gynecology And Obstrtics AL Mustansiriyiah Medical College

Abstract

Aim of the study: to find the artery and associated Doppler index most correlated to intrauterine growth restriction as a secondary complication to maternal preeclampsia

Type of the study: case control

Methods: over almost 3 years a total of 80 pregnant women with established IUGR were collected and their fetal weight and Doppler indices were taken for umbilical artery, middle cerebral artery and fetal renal artery and stored in excel sheets for further analysis. At the end of the study partial least square fit was used to find the Doppler index in any of the 3 mentioned arteries most correlated to fetal weight. All the data collected with regard to the umbilical artery and fetal weight was standardized so to overcome the natural changes in those variables which occur as pregnancy advances.

Results: the Doppler index and the artery with highest coefficient were the fetal renal artery and its resistance index. The coefficient for this Doppler index was 6.92. In other word the resistance index in fetal renal artery has the maximum predictive as well as diagnostic value for intrauterine growth retardation. Accordingly an equation was developed between resistance in the fetal renal artery as dependent index and gestational age as independent variable. From this equation an easy applicable table was constructed in clinical practice to evaluate the severity of the growth restriction from the calculated gestational age for the fetus with measured renal resistance Doppler index evaluated in the ultrasound department

Conclusion: this study has shown that resistance index in fetal renal artery is the Doppler index most correlated to fetal weight. And from the raw data an easy applicable table may be used as an auxiliary method in evaluation of fetuses with growth restriction. Under no circumstances this table should be used alone or as a 100% reliable table as useful in evaluation of fetuses with growth restriction until its clinical significance is evaluated by further searchers and clinical studies.

Key words: IUGR, Doppler, Renal artery, resistance index

INTRODUCTION

Intrauterine growth restriction or IUGR is one of the most widely complications which challenges the practicing obstetrician in charge all over the world. IUGR is said to be present when the fetal weight is less than the 10th centile of the corresponding gestational age. The most common causes are hypertension, multiple gestation, placenta previa, maternal renal disorders and placental shape abnormality.(1) The Doppler phenomena is the change in frequency or

wavelength of a wave for an observer standing to moving object producing sound wave like train serine. It was discovered by the Austrian physicist Christian Doppler, who presented it in 1842 in Prague scientific meeting. He noticed while waiting in the train station that serine sound pitch increase in frequency as the train become closer. While the serine pitch decrease as the train travel away.[2] He concluded the theory of frequency shift with regard to moving objects producing sound waves and formulated an equation to measure the speed of the moving object from this frequency shift. On the other hand the discovery of ultrasound waves is unknown exactly. First it was discovered in American submarines as radar to screen the Soviet submarines in the cold war in 1961. Ten years later it was implemented as medical devices which are used in every field of medicine without exception. The principle behind production of ultrasound wave is the unique behavior of piezoelectric crystals. Those crystals are deformed when they subject to electric current while they produce electric current when they are deformed even by sound waves above 20,000 Hertz which when directed to blood vessels the red blood cells reflects the wave with frequency shift enabling measurement of blood speed in the vessel.[3] The introduction of ultrasound waves into obstetrical applications in late seventies of the last century enables use of wide measurement of many fetal biometric parameters like bi parietal diameter and femoral length.[4] While Doppler studies of the umbilical vessels and other fetal arteries was introduced some 10 years later in last decade of the last century.[5] And from the Doppler of the umbilical arteries many standards and reference tables have been constructed with great success in evaluating fetuses with IUGR. Yet since new millennium many researches included many other arteries and even veins like the umbilical vein, uterine artery, middle cerebral artery, renal artery with even new reference tables. New indices have been included also like the early diastolic notch index. The evaluation of fetal well being has become more difficult with those new vessels. So the aim of this study is to extract among 9 Doppler indices for 3 arteries the index which most correlated with fetal weight among fetuses with IUGR. The indices are systolic/ diastolic, resistance index and pulsatility index with regard to the umbilical, fetal renal and fetal middle cerebral arteries. In other words finding which Doppler index and in which artery is the most correlated one to fetal weight with fetuses already have IUGR secondary to maternal preeclampsia.

PATIENTS AND METHODS

Settings

As it has been highlighted in the abstract the study has taken 3 years to be completed in AL- Yarmook teaching hospitals. Initially it was implemented that the patients consulting the antenatal clinic in the hospital as the source of patients. However because of some unexpected developments and adverse situations protocol was changed again. All the raw data we need in this study were collected from the ultra sonographer who include gestational age, Doppler indices as well a fetal weight and fetal weight centile. Since the study did not involve any invasive procedure rather giving the mother wealth of information about their fetuses' wellbeing all women involved accepted to participate in this study.

Protocol of data collection

All the pregnant women who have preeclampsia and primigravida as well as their fetuses have IUGR were collected from the Ultrasound department. Some 60 % of the patients were patients referred from the outside of the hospital as the cost of either ultrasound or associated Doppler is too expensive in the private clinics. In addition all the patients participated in this study were examined by the same physician specialist in ultrasonography in collaboration with us. The inclusion criteria included preeclampstic women whose pregnancy is further complicated by IUGR and gestational age between 28- 34 weekss. All other risk factors like placenta previa, multiple gestations were excluded from the study. IUGR is established by measuring the head circumference over the abdomen circumference which should be more than 1. In addition fetal weight centile is less than the 10^{th} for the corresponding gestational age. All measurements were done by the same ultrasonographer. Having the patient accepted the study Doppler indices were taken for the umbilical, middle cerebral and renal artery. Other patients with further high risk situation were excluded from the study.

Definitions

1- ***S/D index*** is defined as measurement of the systolic blood velocity divided by the diastolic or according to the formula equation

S/D= velocity of blood in systole / velocity of blood during diastole

2- ***Resistances index*** which is defined as index calculated subtraction of the diastolic blood velocity from systolic divided by systolic velocity or in formula format;

Resistance index= (S-D)/S

3- ***Pulsatility index*** which is defined as subtraction of the diastolic blood velocity from systolic blood velocity divided by the time averaged mean for both or in equation format

Pulsatility index=(S-D)/time averaged mean.

Measurement of fetal renal artery- Doppler indices

The technique for the fetal renal artery Doppler blood flow velocity waveform assessment was first obtained a frontal plane image of the fetal abdomen to allow identification of the abdominal aorta and its bifurcation at the level of the fetal kidneys. Using color flow Doppler a straight segment of the renal artery was identified as it approached the kidney parenchyma from the descending aorta. Subsequently, we optimized the sector angle and depth of the penetration. The scanning plane was adjusted to obtain an insinuation angle as closed to 0° as possible but always <30°. To preserve the end-diastolic component of the of the renal artery waveform we used appropriate low-filter (50-75Hz) settings. The Doppler gate (1.5 to 2.0 mm) was placed within the lumen of the renal artery away from the aorta and before any emergent branches. Renal artery pulsatility index (PI), resistance index (RI), systolic/diastolic (S/D) ratio, and presence or absence of end-diastolic blood flow were assessed. Three consecutive waveforms from each fetus were traced and the average values used for the final analysis. The device and probe model used for measurements are ***GE Volusion 6, Probe C4 convex 5 Hz.***

Statistical analysis

Initially all the data except the maternal age and gestational age which was calculated by the ultrasonographer where standardized by the widely distributed function available in all modern statistical software. That was the most important challenge which we have to overcome. All biochemical, hormonal and biophysical parameters related to pregnancy undergoes progressive change as pregnancy advance due to the effect of hemo dilution. In order to overcome this all parameters used in this study including gestational age for the purpose of constructing 3D surface plot, fetal weight, S/D, Pulstaility and resistance index Doppler were arranged for the corresponding gestation age and standardized with this function converting them either from 0 to 1 or from 1 to 100 depending on the application or graph to be constructed. And in this way we overcome the variation in pregnancy for all parameters. Next we used the standardized fetal weight as dependent variable and all 9 Doppler indices as independent variables in the statistical procedures known as partial least square fit. This multivariate equation fit has nothing to do with the data type of distribution. And any data with normal or non normal distribution may be analyzed with it. Rather it is highly sensitive to the concept of Variance which is the standard deviation divided by the square root of the sample size. And through this unique application the Doppler index which has the maximum correlation to fetal weight can be elicited by showing the Doppler index which scores the highest coefficient. Those are presented in the results. And from this Doppler index an equation has been developed in which gestational age is used as independent variable while this Doppler index as dependent variable has been constructed in the form of second degree polynomial equation due to the extreme non linear style of those indices changes with pregnancy. From the equation an easy reference table has been constructed which make the doctor carry this table as a pocket object to verify whether it is truly correlate with fetal condition and to ease any further researches which may be done on similar subject.

RESULTS

As it has been mention in the section of method very few demographic criteria has been taken in the study. In table 1 the mean, standard deviation, 10^{th} and 90^{th} centiles were given for the 80 patients participated in this study.

Table 1: The mean birth weight and the 10^{th} and 90^{th} are shown

Gestational age	Sample size	Fetal weight (gram)	10^{th} centile	90^{th} centile
28	6	766±12.10	750	782
29	6	810±23.19	784	833
30	13	870±20.62	848	898
31	10	922.2±7.53	914	933
32	14	975.14±28.42	937	1006
33	13	1041.23±14.57	1021	1057
34	18	1096.11±19.17	1070	1119

It goes without saying that from the 10th and 90th centiles of all fetuses are so far from the 10th centiles of normal fetuses without IUGR. Table 2 shows the overall results of analysis of all Doppler indices among the 3 arteries involved in this study. Obviously the coefficient which has the highest value than others for the same artery and for the index is the renal artery resistance index which is = 6.92. In general partial least square fit which shows negative coefficients or less that less than 1 has no significant correlation if any to the fetal weight. It should be stressed that all the Doppler indices as well as fetal weight were standardized before being analyzed by this statistical procedure.

Table 2: Coefficients for each Doppler index used in the study in partial least square fit

Coefficients in equations	Renal artery	Umbilical artery	MCA artery
PI Renal	**0.97**		
RI Renal	**6.92**		
S/D Renal	**-0.24**		
PI umbilical		**-6.79**	
RI Umbilical		**5.76**	
S/D Umbilical		**6.64**	
PI Middle cerebral			**5.73**
RI middle Cerebral			**-1.52**
S/D Middle Cerebral			**2.39**

In order to show visually the above findings as figures for the sake of better clarity, 3 dimensional sketch of the mesh style has been constructed to show how resistance index changes with advancement of gestational age from 28 to 34 weeks of gestation and given in figure 1,A, B, and C

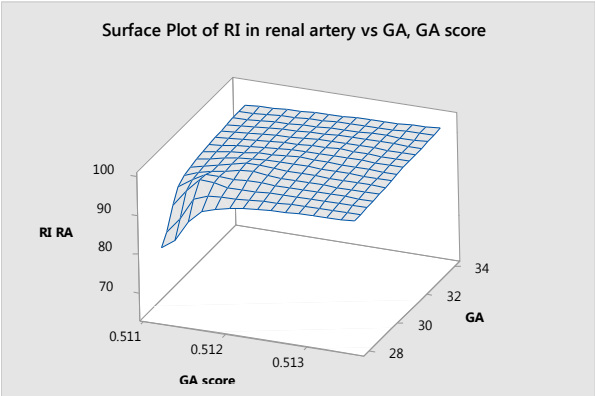

Figure 1A: RI renal artery versus gestational age

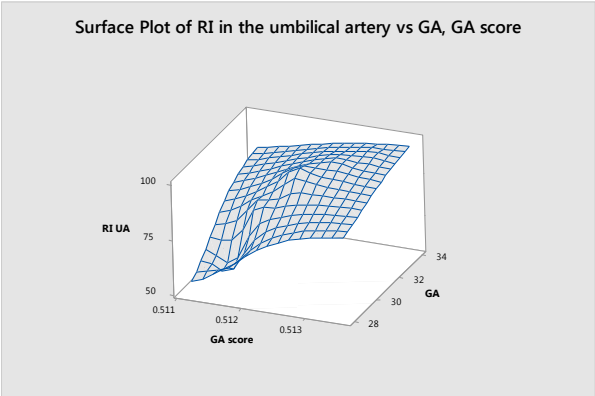

Figure 1B: Umbilical artery RI versus GA

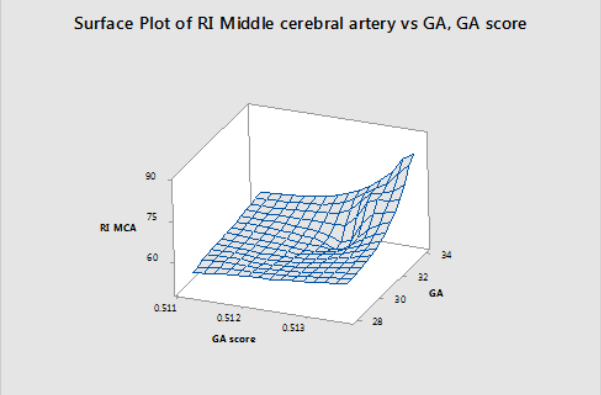

Figure 1C: Middle cerebral artery RI versus gestational age

Figure 1, A, B and C; The change of resistance index with gestational age in weeks and standardized gestational age shows who RI in the fetal renal, umbilical and middle cerebral artery occur

In figure 1A the resistance index in the renal artery versus gestational age is shown. Obviously starts since the very beginning of the 28 weeks while that of the umbilical artery start to increase some 1-2 weeks later at 30 weeks. This suggests physiological changes to hypoxia from placental insufficiency affect the fetal circulation earlier than the umbilical artery. In figure

1C the resistance index of the middle cerebral artery is shown and clearly it goes in a different manner than the above two arteries. While initially it remains the same some reduction occur at 30 weeks to divert as much as blood to the fetal brain, yet it doesn't start to show increase until 33- 34 weeks of gestation when every defensive mechanism fail and this will be discussed in the section of discussion in detail. Finally in order to make the results obtained in this study as simple and easily applicable as possible an equation has been formed through which Resistance index in the renal artery can be calculated directly from the gestational age. In figure 2 the changes of resistance index through the advancement of gestational age is shown with various 10^{th} to the 90^{th} centile. In fact in normal pregnancy the renal resistance index should show progressive decline with gestational age progress. Yet in this figure shows progressive increase up 32-33 weeks of gestation and slight decline there after due to the fact that all fetuses in this study have been taken from mother with preeclampsia and complicated with IUGR.

$$RI_{renal} = -22.9274 + 1.1584\ Age - 0.0003654\ Age^3$$

Analysis of Variance; F-ratio= 14.3492, Significance level= P<0.0001

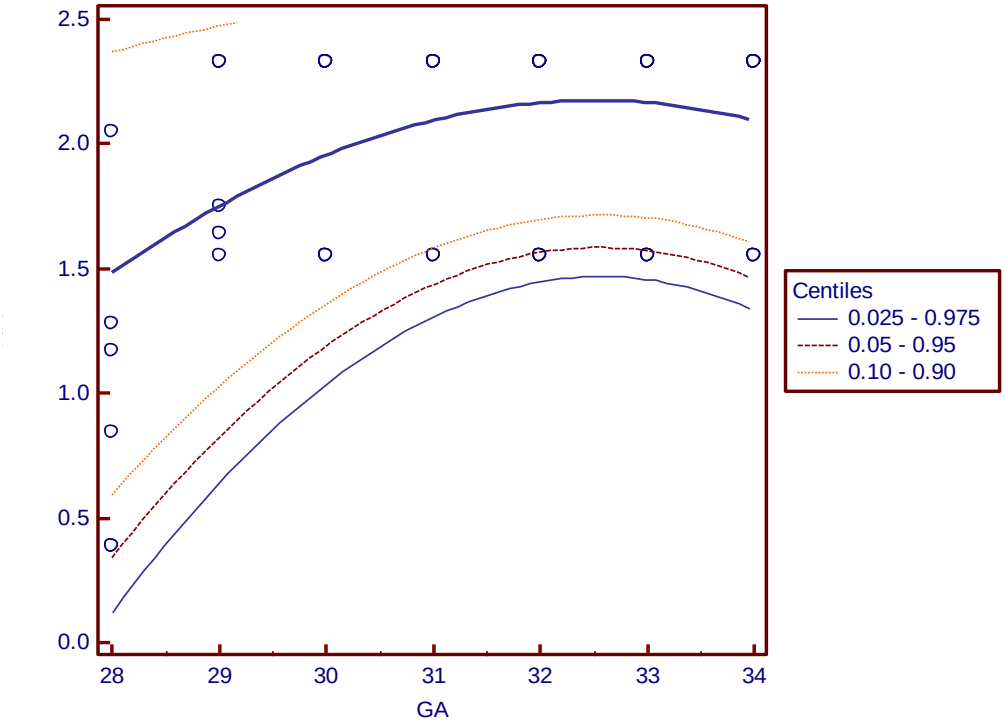

Figure 2: Changes of resistance index through the advancement of gestational age is shown with various 10^{th} to the 90^{th} centile.

At last in order to make the equation as much as applicable in assessment of fetal well being table 3 has been constructed. It should be stressed that this table originally taken from raw data for women with preeclampsia and complicated with IUGR. Accordingly and logically it should be used only for women with same criteria to assess how much their fetuses are affected by the hypoxia effect associated with placental insufficiency. Bellow the table some virtual examples which explains how this table is used.

Table 3 showing the 10th and 90th centiles of resistance index as sampled from patients in this study and derived from the equation

Age variable	Age variable					
GA	**0.025**	**0.05**	**0.10**	**0.90**	**0.95**	**0.975**
28	**0.1295**	**0.3474**	**0.5985**	**2.3705**	**2.6217**	**2.8396**
29	**0.6487**	**0.8261**	**1.0307**	**2.4740**	**2.6786**	**2.8560**
30	**1.0433**	**1.1902**	**1.3594**	**2.5537**	**2.7229**	**2.8698**
31	**1.3114**	**1.4374**	**1.5826**	**2.6074**	**2.7526**	**2.8786**
32	**1.4506**	**1.5655**	**1.6980**	**2.6329**	**2.7654**	**2.8803**
33	**1.4587**	**1.5724**	**1.7035**	**2.6281**	**2.7591**	**2.8728**
34	**1.3336**	**1.4558**	**1.5967**	**2.5907**	**2.7316**	**2.8538**

Finally as an example how to use this table if an infant with calculated gestation age for the LMP shows 32 weeks and then sent for RI of the renal artery came back with value less than 1.43 or the 10th centile for 31 week yet this lie in the green zone; results may be good as far as hypoxia severity. On the other hand if the result of the same fetus came back with reading of 2.67- 2.85 those results corresponding to gestational age reading of 29 weeks and lie in the red zone. Such fetus may have only hours of life if delivery is not achieved soon. Severe hypoxia in such cases is assumed. Accordingly the rule the more back fetal reading than his true gestational age and the higher within the week the reading is showing; the more hypoxia the fetus is threatened.

.

DISCUSSION

As it has been concluded in the result section of this study the renal artery of the fetus is the first artery which starts to increase relative to both umbilical and middle cerebral artery. In fact the first hint which came across our mind stimulating us to make this complicated protocol and study was the frequent and recurrent papers issued over last 20 years which stress that Doppler indices of the renal artery among women with post term complicated pregnancy is much more accurate and surpass the umbilical artery in predicting fetuses at high risk of hypoxia. Selam B et al,[6] in the beginning of new millennium have shown that resistance index in the renal artery is more sensitive and more useful in clinical practice in predicting

fetuses at risk of hypoxia in post term complicated pregnancy. While Bar et al,[7] have suggested that oligohydramnios seen among women with post term pregnancy is associated with redistribution of blood so brain have extra perfusion which is diverted from normal perfusion to other organs like kidney On the other hand papers which refer to low Doppler indices in the middle cerebral artery in IUGR were also quite diverse in the medical literature. Severi et al,[8] has stressed on the fact that infants with IUGR irrespective of the cause have low middle cerebral artery Doppler indices while elevated umbilical artery indices. Simanaviciute et al,[9] have shown the ratio of (middle cerebral artery PI/ uterine artery PI) ratio bellow 5th centile is associated with adverse pregnancy outcome like preeclampsia and IUGR suggesting middle cerebral artery has low resistance throughout normal pregnancy. As a matter of fact and to clarify this vague situation the solution comes from basic facts of medicine. Kelestimur H et al,[10] has shown that increase in hypothalamic vasopressin and oxytocin production in induced hypoxia among rat models. Both oxytocin and vasopressin are well known to increase the uptake of water from the renal collecting duct while thy increase resistance of kidneys to blood flows. While Raff H et al,[11] has shown that hypoxia

associated with carbon dioxide accumulation has strong stimulant effect on aldosterone secretion from adrenal cortex. This hormone is well known to increase the uptake of sodium and decrease blood flow to kidneys. The release of aldosterone is done through rennin dependent mechanism. Both pathways adrenal and hypothalamic aiming to increase the renal resistance as well as to maximize the re absorption of water in collecting ducts to keep the blood volume constant at all cost so the massive activation of the autonomic nervous system can divert the maximum poorly oxygenated blood to the brain. Assuming fetuses after 14 weeks of gestation normal fetus reacts to hypoxia associated with IUGR as adults with greater tolerance to hypoxia the same hormonal profile occur in adults occurs also among fetuses. Massive release of oxytocin, vasopressin is released from the fetal posterior pituitary gland. And in the same context aldosterne is secreted from the adrenal cortex. Both are aiming to divert the highest possible amount of poorly oxygenated blood to the brain as shown in figures A1 and A3. In figure A1 the resistance index in the renal artery is elevated from the very beginning at 28 weeks of gestation and last to 34 weeks. While low resistance index in the middle cerebral artery from the very beginning at 28 weeks of gestation which undergoes further reduction as mediated by the autonomic nervous system at 32 weeks of gestation. During this RI in the umbilical artery remain normal until 30 weeks possibly mediated by fetal autonomic nervous system to start increase after 30 weeks as it is also controlled by maternal and placental factors. At the level of placenta failure to achieve secondary wave of trophoblastic invasion in early second trimester renders the spiral arterioles responsive to vasoconstrictors released in the maternal circulation. While the placenta of women with preeclampsia release large amount of placental rennin and prostaglandin $F_{2\alpha}$ which is strong vasoconstrictors directly affects all placental vessels and strong platelets aggregator ultimately ending with low grade DIC. Placental rennin elevates maternal blood pressure. The mechanism is still by angiotensin I and II. The most recent breakthrough in preeclampsia as being discovered to be on form of insulin resistance disorders.[12] At this point all findings in this study were simply explained by logics and basic knowledge of physiology.

In fact many articles published I the literature supports the findings of this study. Manal et al,[13] has found that pulsatility indx in the renal artery among IUGR infants is inversely correlated to the amniotic fluid index. Pulsatility idex is a measure of acceleration rather than resistance. Precisely it measures how fast flood increase to peak during systole and how fast it declines to lowest speed during diastole. Though acceleration depends directly on resistance yet it depends also on other factors like heart beat force and elasticity of the arteries. While Haugen et al,[14] has shown that reading of Doppler indices were no different at proximal, middle and distal position of the renal artery. In other word reading taken near the aorta, renal end or in between them are not statistically different. At last Azpurua et al,[15] have used the fetal renal artery Doppler in preterm labor and premature rupture of membrane or PROM and found that Doppler indices were not changed by those conditions. Neither preterm labor nor non complicated PROM is associated with fetal hypoxia and acidosis, which may explain the negative role of renal Doppler indices in diagnosing those conditions

The last issue is the table constructed from the formula. The rationale behind building this table is very easy; every case of fetal hypoxia which is not treated by prompt delivery ultimately ends with intrauterine death from severe ketoacidosis.[16] Ketoacidosis per se is associated with massive shift of potassium from the intracellular compartment freely into the fetal circulation which ends with progressive bradycardia and cardiac standstill or simply fetal death. So all efforts should be done to predict correctly the prompt time of delivery for infants complicated with IUGR as fetal hypoxia is essential pathophysiology icon in IUGR.[17, 18] Accordingly this table has been constructed which may be part of physician pocket contents. Since all patients in this study were 28- 34 weeks of gestation and complicated with IUGR it is strongly recommended that its use should be to patients with same criteria also. Under no circumstances it should be used for other causes of IUGR or those bellow 28 weeks or above 34 weeks as extrapolated from the equation. Its use should never be the primary method of evaluation rather to follow the standard procedure like NST, biophysical profile with the table as auxiliary method only to match its finding with well documented antenatal and intra partum fetal test like CTG. In addition to that since 2011 preeclampsia was found to be on form of insulin resistant disorders and many trials with insulin sensitizing drugs have been published.[12] Monitoring of such drugs can be done with reliable table as the table constructed in this study. At least 3 further trials are needed to confirm the results obtained in this study and not until then extreme caution should be exercised in its use.

REFERENCES

1. Pinheiro TV, Brunetto S, Ramos JG, Bernardi JR, Goldani MZ. Hypertensive disorders during pregnancy and health outcomes in the offspring: a systematic review. J Dev Orig Health Dis. 2016 Aug;7(4):391-407
2. Evans, D. H.; McDicken, W. N. Doppler Ultrasound (2nd ed.). New York: John Wiley and Sons. ISBN (2000) 0-471-97001-8
3. Sheiner E, Hackmon R, Shoham-Vardi I, et al. "A comparison between acoustic output indices in 2D and 3D/4D ultrasound in obstetrics". Ultrasound Obstet Gynecol 2007. 29 (3): 326–8.
4. Manbachi, A. & Cobbold, R.S.C. "Development and Application of Piezoelectric Materials for Ultrasound Generation and Detection". Ultrasound.(2011) 19 (4): 187–196
5. Hsieh, FJ; Kuo, PL; Ko, TM; Chang, FM; Chen, HY "Doppler velocimetry of intraplacental fetal arteries". Obstetrics and gynecology. 199; 77 (3): 478–82
6. Selam B, Koksal R, Ozcan T Fetal arterial and venous Doppler parameters in the interpretation of oligohydramnios in postterm pregnancies. Ultrasound Obstet Gynecol. 2000 May; 15(5):403-6.
7. Bar-Hava I, Divon MY, Sardo M, Barnhard Y Is oligohydramnios in postterm pregnancy associated with redistribution of fetal blood flow? Am J Obstet Gynecol. 1995 Aug;173(2):519-22.
8. Severi FM, Bocchi C, Visentin A, Falco P, Cobellis L, Florio P, Zagonari S, Pilu G. Uterine and fetal cerebral Doppler predict the outcome of third-trimester small-for-gestational age fetuses with normal umbilical artery Doppler. Ultrasound Obstet Gynecol. 2002 Mar; 19(3):225-8.
9. Simanaviciute D, Gudmundsson S. Fetal middle cerebral to uterine artery pulsatility index ratios in normal and pre-eclamptic pregnancies. Ultrasound Obstet Gynecol. 2006 Nov;28(6):794-801.
10. Kelestimur H, Leach RM, Ward JP, Forsling ML Vasopressin and oxytocin release during prolonged environmental hypoxia in the rat. Thorax. 1997 Jan; 52(1):84-8.
11. Raff H, Jankowski B Effect of CO2/pH on the aldosterone response to hypoxia in bovine adrenal cells in vitro. Am J Physiol. 1993 Oct;265(4 Pt 2):R820-5
12. Hauth JC, Clifton RG, Roberts JM, Myatt L, Spong CY, Leveno KJ, Varner MW, Wapner RJ, Thorp JM Jr, Mercer BM, Peaceman AM, Ramin SM, Carpenter MW, Samuels P, Sciscione A, Tolosa JE, Saade G, Sorokin Y, Anderson GD; Eunice Kennedy Shriver National Maternal insulin resistance and preeclampsia. Am J Obstet Gynecol. 2011 Apr;204(4):327.e1-6
13. Manal Mohamed El Behery*, Moustafa A Ibrahiem, Soha Siam and Mohmoud A Seksaka Fetal Renal Volume and Fetal Doppler in Normal and Growth Restricted Fetuses: Is there a Correlation? Gynecol Obstet 2012, 2:2:pp 1-5
14. Haugen G, Godfrey K, Crozier S, Hanson M. Doppler blood flow velocity waveforms i n t he fetal renal arteries: variability at proximal and distal sites in the right and left arteries Ultrasound Obstet Gynecol 2004; 23: 590–593
15. Azpurua H, Dulay AT, Buhimschi IA, Bahtiyar MO, Funai E, Abdel-Razeq SS, Luo G, Bhandari V, Copel JA, Buhimschi CS. Fetal renal artery impedance as assessed by Doppler ultrasound in pregnancies complicated by intraamniotic inflammation and preterm birth. Am J Obstet Gynecol. 2009 Feb; 200(2):203.e1-11.
16. Bekmukhambetov Y, Mamyrbayev A, Dzharkenov T, Kravtsova N, Utesheva Z, Tusupkaliev A, Ryzhkova S, Darzhanova K, Bekzhanova M. Metabolic and immunologic aspects of fetoplacental insufficiency. Am J Reprod Immunol. 2016 Oct;76(4):299-306
17. Mureșan D, Rotar IC, Stamatian F. The usefulness of fetal Doppler evaluation in early versus late onset intrauterine growth restriction. Review of the literature. Med Ultrason. 2016 Mar;18(1):103-9
18. Keenaghan M, Sun L, Wang A, Hyodo E, Homma S, Ten VS. Intrauterine growth restriction impairs right ventricular response to hypoxia in adult male rats. Pediatr Res. 2016 Oct;80(4):547-53