ORIGINAL ARTICLE

Comparison of Diagnostic Efficacy of Umbilical Artery and Middle Cerebral Artery Waveform with Color Doppler Study for Detection of Intrauterine Growth Restriction

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Abstract

Background and Objectives Intrauterine growth restriction is associated with increased perinatal mortality and morbidity, possibly extending also in adult life, as compared to fetuses and newborns presenting characteristics of normal growth. The present study had been planned to measure the pulsatility index (PI) and resistive index of the middle cerebral artery with pulsatility and resistive index of the umbilical artery in predicting fetal growth restriction.
Materials and Methods A total of 60 pregnant women with a clinical history and grayscale-screened patients were taken for Doppler analysis, and a final comparison of accuracy of Doppler indices was done with perinatal outcome.
Statistical Analysis The statistical analysis was done using the Statistical Package for Social Sciences version 15.0 statistical analysis software. The values were represented in number (%) and mean ± SD.
Observation and Results The umbilical artery PI had maximum sensitivity at the third visit (32–37 weeks) and maximum specificity also at the third visit (32–37 weeks). The umbilical artery resistive index had maximum sensitivity at the second visit (28–32 weeks) and maximum specificity at the third visit (32–37 weeks). The MCA PI had an overall diagnostic accuracy of 52.8 %.
Conclusion The PI of the umbilical artery was more sensitive than the PI of the middle cerebral artery. Umbilical artery PI has the maximum overall diagnostic accuracy of 75 %.

Keywords Pulsatility index · Resistive index · Sensitivity · Diagnostic accuracy · Obstetrical Doppler

Abbreviations
MCA   Middle cerebral artery
UA   Umblical artery
PI   Pulsatility index
RI   Resistive index
S/D   Systolic/diastolic
IUGR   Intrauterine growth retardation
PPV   Positive predictive value
NPV   Negative predictive value
Sens   Sensitivity
Spec   Specificity

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Introduction

Intrauterine growth restriction (IUGR) is associated with increased perinatal mortality and morbidity, possibly extending also in adult life, as compared to fetuses and newborns presenting characteristics of normal growth. It is

important to make a definite diagnosis based on the best criteria in order to decrease the perinatal mortality and morbidity associated with IUGR. Various studies all over the world have given different modalities to diagnose IUGR; the latest in the series to diagnosis IUGR antenatally is the analysis of Doppler blood flow velocity waveforms of fetal and maternal vessels. The clinical and ultrasound measurements diagnose IUGR at a very late stage when the fetus is already compromised, whereas Doppler waveform studies can detect IUGR at an early stage, so that the affected fetus can be delivered without significant compromise. The color Doppler ultrasound gives us information directly on vascular resistance and indirectly on blood flow. The present study had been planned to measure the pulsatility index (PI) and resistive index (RI) of the middle cerebral artery (MCA) and PI and RI of the umbilical artery (UA) in predicting fetal growth restriction.

Materials and Methods

A prospective, observational, non-interventional, and analytical study was conducted by the Department of Radiodiagnosis in association with the Department of Pediatrics and the Department of Obstetrics and Gynecology after getting approval from the Institutional Ethics Committee. The period of study was one and half years from December 2009 to June 2011, which was used for the development of study tools, collection of data, analysis, and presentation of findings. A total of 60 patients attending the antenatal clinic in the Department of Obstetrics and Gynecology, with the clinical criteria of IUGR, were recruited. The clinical examination result, obstetric color Doppler study, and perinatal outcome were recorded. The clinical criteria for suspected cases of IUGR from the Obstetrics & Gynecological Department were patients with history of PIH, renal disease, cardiac disease, stage three and four fetal chromosomal abnormalities in initial pregnancies. Torch infection, advanced IDDM and patients with history of smoking showing low longitudinal lie and symphysiofundalheight being less than the period of gestation by 4 weeks or more were considered as high risk for IUGR (Williams textbook of Obstetrics, 22nd Edition; Practical Guide of High Risk Pregnancy by Fernando Arias). These criteria were followed in every case before sending the patients for Doppler analysis. Gestational age determination was based on the best estimate from the last menstrual history and by USG or routine fetal biometry in the first trimester or early second trimester. All the patients were subjected to Doppler waveform analysis on a Color Doppler LOGIQ-5 PRO GE machine using 3.5 MHz probe by two radiologists unaware of grayscale findings. To use Doppler velocimetry, patients were first scanned in the routine fashion using B-mode. Then, the vessels of interest were confirmed by color Doppler. The Doppler signal was then obtained by placing the Doppler gate directly over the vessel of interest. The flow velocity waveforms were obtained in periods of fetal inactivity and apnea.

Doppler velocimetry was performed on the umbilical and the MCA close to the transducer. Doppler velocimetry of the umbilical arteries was performed in a free-floating loop of the mid-portion of the umbilical cord away from the placental and fetal cord insertion. The umbilical cord was investigated by color flow Doppler, and flow velocity waveforms were obtained from each artery. The MCA was visualized in a plane immediately caudal to the trans-thalamic plane used to obtain the BPD and HC biometric data. Using color flow Doppler, the MCA was identified in the sylvian fissure arising from the circle of Willis. The Doppler sample was placed in the first third of the MCA and a flow velocity waveform was obtained. For the UA, Arudini and Rizzo took a cut-off level of 1.42 in prediction of perinatal outcome in fetuses suspected to have IUGR(1992) [1]. In this study, the reference value of the UA PI indices was taken from the study of Arudini and Rizzo. The value of UA PI >1.42 was taken as an indicator of IUGR and a value ≤1.42 was taken as normal. The cut-off value of the UA resistance index was taken as 0.72. This was according to the reference value of Kurmanavicius et al. [2]. The value of UA RI >0.72 was taken as an indicator of IUGR and a value ≤0.72 was taken as normal; for the MCA, the cut-off value of MCA PI was taken as 1.5. At this cut-off level, the MCA PI was considered abnormal when the MCA PI was <1.5, i.e., below the 5th percentile. The reference value of the MCA PI was taken from the study of Arduini and Rizzo [1]. MCA PI <1.5 was taken as an indicator of IUGR and a value ≥1.5 was considered to be normal in our study. The cut-off value of the MCA RI in our study was taken as 0.59. This reference value was taken from the study of Bahimaan et al. [3]. MCA RI <0.59 was taken as an indicator of IUGR and a value >0.59 was considered to be normal in our study. The Doppler signals were measured by measuring peak systolic and low diastolic velocities. Doppler indices like PI and RI of the UA and PI and RI of the MCA were noted. Standard treatment was given to all the patients of suspected IUGR.

After delivery, the birth weight (immediately within 6 h) was measured on an electronic weighing machine (machine's lower limit of measurement is less than 10 g). The Apgar's score after 5 min of birth and baby anthropometry, i.e., length, head circumference, abdominal circumference, upper segment and lower segment ratio, were measured. Ponderal index was calculated as birth weight (in gm) per length (in cm^3). Ponderal index of <10 indicates growth restriction (Clinical Methods of Pediatrics, Second

Edition, Meharban Singh). Adverse perinatal complications such as birth asphyxia, hypoglycemia, perinatal death, or admission to NICU were recorded. The statistical analysis was done using a Statistical Package for Social Sciences Version 15.0 statistical analysis software. The values were represented in number (%) and mean ± SD. The statistical formulas were sensitivity, specificity, positive predictive value, and negative predictive value.

Observations and Result

On the basis of Ponderal index at birth, out of a total of 60 patients followed up, 42 (70 %) were confirmed to be having IUGR, while 18 (30 %) did not turn out to be IUGR (Table 1). For further analysis, the patients were divided into two groups as follows: Group I had patients confirmed to have IUGR and Group II had patients not having IUGR. For the UA PI, the cut-off value was taken as >1.42. It was observed to be 61.9 % sensitive and 77.8 % specific at the first visit with a positive predictive and negative predictive value of 86.7 and 46.7 %, respectively. On the 2nd visit, the sensitivity increased to 73.8 %; however, there was a slight decline in specificity (66.7 %), while positive predictive and negative predictive values were 83.8 and 52.2 %, respectively. On the 3rd visit, the sensitivity was 85.7 %, while specificity was 88.9 %. The positive predictive and negative predictive values were 94.7 and 72.7 %, respectively. Overall, the sensitivity of the criteria was 73.8 %, specificity 75.9 %, PPV 87.7 %, and negative predictive value 55.4 %. The overall diagnostic accuracy of the test was 75.0 % (Table 2). For the UA RI, the cut-off value for IUGR detection was taken as >0.72. At the first visit, 24 out of 42

Table 1 Distribution of patients according to confirmed IUGR status

S. no.	Confirmed IUGR	No. of cases	Percentage
1.	No	18	30
2.	Yes	42	70

Table 2 Efficacy of pulsatility index of umbilical artery at different time intervals

	IUGR (n = 42)		No IUGR (n = 18)		Sens	Spec	PPV	NPV
	>1.42	<1.42	>1.42	<1.42				
1st visit	26	16	4	14	61.9	77.8	86.7	46.7
2nd visit	31	11	6	12	73.8	66.7	83.8	52.2
3rd visit	36	6	2	16	85.7	88.9	94.7	72.7
Total	93	33	12	42	73.8	75.9	87.7	55.4
Overall diagnostic accuracy = 75.0 %								

Table 3 Efficacy of resistive index of umbilical artery at different time intervals

	IUGR (n = 42)		No IUGR (n = 18)		Sens	Spec	PPV	NPV
	>0.72	<0.72	>0.72	<0.72				
1st visit	24	18	2	16	57.1	88.9	92.3	47.1
2nd visit	27	15	1	17	64.3	94.4	96.4	53.1
3rd visit	26	16	0	18	61.9	100.0	100.0	52.9
Total	77	49	3	51	61.1	94.4	96.3	51.0
Overall diagnostic accuracy = 71.1 %								

(57.1 %) subjects in Group I were found to be having RI >0.72; at the second and third visits, this number increased to 27 (64.3 %) and 26 (61.9 %), respectively. In Group II, only 2 (11.1 %) of 18 subjects had RI >1.41 at the first visit; however, by the 3rd visit, this number declined to 0 (0 %). The sensitivity and negative predictive value of the criteria were the maximum at the 2nd visit (64.3 and 53.1 % respectively), while specificity and positive predictive value were the maximum at the third visit (100 %). Overall, the test's sensitivity, specificity, positive predictive value, and negative predictive value were 61.1, 94.4, 96.3, and 51 %, respectively. Overall, the diagnostic accuracy of the test was 71.1 % (Table 3).

For the MCA PI, the cut-off value was taken as 1.5. At the first visit, the criteria was observed to be 38.1 % sensitive and 88.9 % specific with a positive predictive value of 88.9 % and a negative predictive value of 38.1 %. At the 2nd visit, there was a slight fall in sensitivity (33.3 %), while specificity, positive predictive value, and negative predictive value increased slightly (94.4, 93.3, and 37.8 %, respectively). At the third visit, the sensitivity was 35.7 %, whereas specificity (94.4 %), positive predictive value (93.8 %), and negative predictive value (38.6 %) were the maximum. Overall, the criteria had a sensitivity of 35.7 %, specificity of 92.6 %, positive predictive value of 91.8 %, and negative predictive value of 38.2 %. Overall, diagnostic accuracy of the criteria was 52.8 (Table 4). For the MCA RI, the cut-off value for IUGR was taken as >0.59. At all the visits, its sensitivity was very low. At the first visit, the sensitivity of the criteria was 26.2 %, with a specificity and positive predictive value of 88.9 and 84.6 %, respectively, and a negative predictive value of 34 %. At the 2nd visit, the sensitivity improved slightly (31 %), while specificity and positive predictive values were 88.9 and 86.7 %. The negative predictive value during these visits was 35.6 %. At the third visit, the sensitivity was 21.4 % only, while specificity and PPV were 100 %. The NPV at the third visit was 35.3 %. Overall, the test was 26.2 % sensitive, had a specificity and positive predictive value of 92.6 and 89.2 %, respectively, and a

Table 4 Efficacy of pulsatility index of MCA at different time intervals

	IUGR (n = 42)		No IUGR (n = 18)		Sens	Spec	PPV	NPV
	>1.5	<1.5	>1.5	<1.5				
1st visit	16	26	2	16	38.1	88.9	88.9	38.1
2nd visit	14	28	1	17	33.3	94.4	93.3	37.8
3rd visit	15	27	1	17	35.7	94.4	93.8	38.6
Overall	45	81	4	50	35.7	92.6 </p		

Table 5 Efficacy of resistive index of MCA at different time intervals

	IUGR (n = 42)		No IUGR (n = 18)		Sens	Spec	PPV	NPV
	<0.59	>0.59	<0.59	>0.59				
1st visit	11	31	2	16	26.2	88.9	84.6	34.0
2nd visit	13	29	2	16	31.0	88.9	86.7	35.6
3rd visit	9	33	0	18	21.4	100.0	100.0	35.3
Overall	33	93	4	50	26.2	92.6	89.2	35.0
Overall diagnostic accuracy: 46.1 %								

negative predictive value of 35 %. The overall diagnostic accuracy was 46.1 % (Table 5).

Discussion

As the pathogenesis of intrauterine growth retardation is strictly connected with the poor supply of the feto-maternal unit with well-oxygenated blood rich in all nutritional substances, color Doppler flowmetry is a utility through which we can monitor the blood supply from the mother to the fetus. The introduction of color Doppler technology has provided the first opportunity for repetitive non-invasive hemodynamic monitoring in pregnancy. The assumption is that a poor supply of the blood to the fetus might affect its growth. There is ample evidence that Doppler indices from the fetal circulation can reliably predict adverse perinatal outcome in an IUGR pregnancy. Compared to other methods of fetal monitoring, Doppler has proved to be more sensitive in detecting fetal compromise early and aids in the guiding and making of decisions regarding the appropriate timing of delivery.

The present study was conducted to establish the accuracy of the ratio of PI and RI of the MCA with PI and RI of the UA in predicting IUGR. In the present study, we carried out flowmetry evaluations at two locations: (a) UA—the UA is the signature vessel in the Doppler study of the fetus as it is a direct reflection of the flow within the
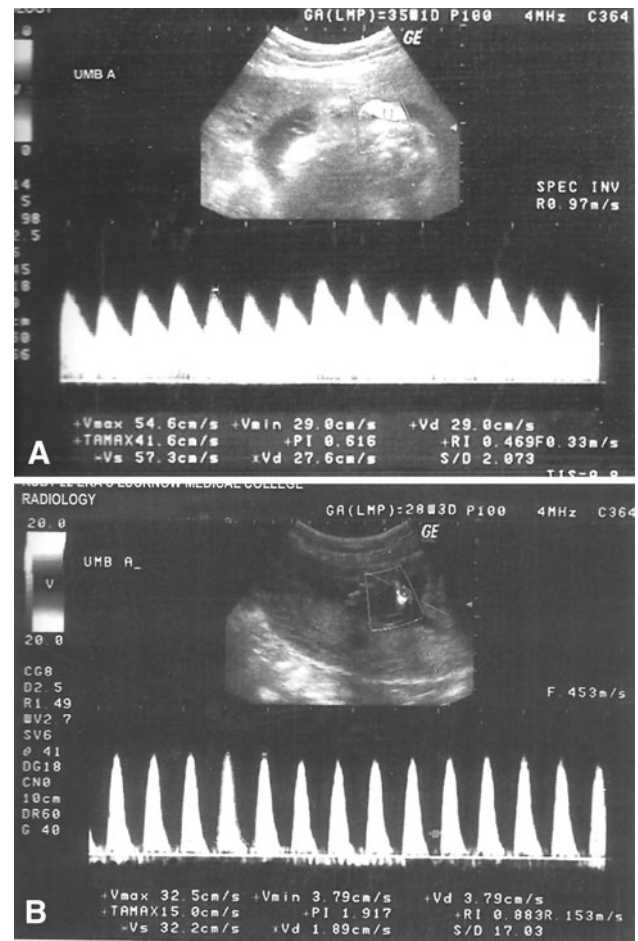

Fig. 1 a Normal umbilical artery waveform with high diastolic flow. **b** Abnormal umbilical artery waveform with reversal of diastolic flow

placenta (Fig. 1a, b). It is usually the first vessel to be studied when suspecting an IUGR fetus. (b) Fetal MCA—the MCA is the vessel of choice to assess the fetal cerebral circulation because it is easy to identify and has a high reproducibility (Fig. 2). In a normal pregnancy, the three indices, S/D, PI, and RI, decrease with advancing gestation. But, in IUGR, at first there is decreased diastolic flow in the UA due to increase in the resistance that occurs in small arteries and arterioles of the tertiary villi [4]. This raises the S/D ratio, PI, and RI of the UA. In the present study, we have observed that the UA PI had a sensitivity and specificity of 61.9 and 77.8 % (first visit), 73.8 and 66.7 % (second visit), and 85.7 and 88.9 % (third visit), respectively. Overall, the sensitivity of the criteria was 73.8 %, specificity was 75.9 %, PPV was 87.7 %, and negative predictive value was 55.4 %. The overall diagnostic accuracy of the test was 75.0 %.

In a similar design, Dhand et al. [5] observed a sensitivity and specificity of 44 and 61.5 %, respectively, in prediction of the IUGR outcome. The positive and negative predictive
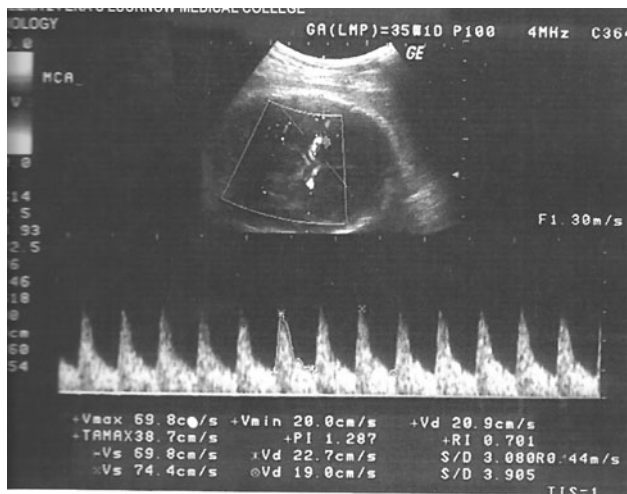
Fig. 2 Abnormal middle cerebral artery waveform with increased diastolic flow

values in their study were in 83 and 20 %, respectively. In the present study too, we encountered high specificity and high positive predictive value with a low negative predictive value. The reason for the low negative predictive value could be the inclusion of grayscale-proven IUGR cases, thus contributing to a higher prevalence. In a higher prevalence scenario, the negative predictive value is bound to fall [6]. However, as compared to the findings of Narula et al. [7] who reported a sensitivity of 94 % for combined indices of the UA, the findings in the present study show a significantly lower sensitivity. However, Narula et al. did not specify the criteria of combined indices of the UA.

The findings in the present study are in consonance with the findings of Mulders et al. [8] who found a sensitivity of 53.3 % and a specificity of 87.9 % for the UA PI at around 32–34 weeks of pregnancy. In the present study, the findings at the first visit (23–27 weeks) resemble the findings of Mulders et al. Except for Narula et al. [7] who had indicated no specific criteria, all the studies show that the UA PI is relatively a more specific criteria than a sensitive criteria. In the present study, though the shift in sensitivity was from 61.9 % at the first visit to 85.7 % at the third visit, the shift in specificity was from 77.8 to 88.9 %. In fact, by the 3rd visit, diagnostic efficacy in general increased for all the components viz. sensitivity, specificity, PPV, and NPV. In the literature, it has been reported that PI decreases initially and then increases; thus, by the third visit (late third trimester), the PI is at its peak and hence the criteria becomes more sensitive. In cases with placental insufficiency, the diastolic flow decreases and thus results in a higher PI value [4]; that is why the specificity also increases with the advancing pregnancy. In the present study, we observed the overall diagnostic accuracy of the UA PI to be 75 %. The higher accuracy of the test

might be attributed to the selection criteria of the subjects, wherein clinically suspect and grayscale-proven cases were included. In a similar study, Lakhkar et al. [9] reported a sensitivity of 44.4 %, specificity of 81.8 %, PPV of 80 %, and NPV of 47.3 % for predicting any major adverse outcome including neonatal IUGR among pregnancies beyond 30 weeks of gestation complicated by severe pre-eclampsia and IUGR or both.

In the present study, the UA RI was found to have a relatively lower efficacy as compared to the UA PI efficacy at all the visits as well as for the overall evaluation. It had a sensitivity and specificity of 57.1 and 88.9 %, 64.3 and 94.4 %, and 61.9 and 100 % at the first, second and third visits, respectively. Overall, the sensitivity was 61.1 % and specificity was 94.4 %. Lakhkar et al. [9] reported that the UA RI had a sensitivity of 58 %, specificity of 71.7 %, positive predictive value of 35 %, and NPV of 86.8 %, thereby showing a diagnostic accuracy of 56.8 % for a major adverse outcome in clinically suspect IUGR cases and a sensitivity, specificity, PPV, and NPV of 44.4, 81.8, 80, and 47.3 %, respectively, for minor adverse outcomes. Aali et al. [10] evaluated the efficacy of the UA RI for evaluation of pregnancy complications such as pre-eclampsia and found that at a cut-off value of 0.64, it was 100 % sensitive, but only 44 % specific; however, at a higher cut-off of 0.81, it was only 28 % sensitive and 100 % specific. In the present study, owing to clinically suspect and grayscale-confirmed IUGR cases, both sensitivity and specificity were fair. However, the lower negative predictive value could be explained easily on the basis of a higher prevalence of IUGR in the present study.

In the present study, the MCA PI was found to have a very low sensitivity and negative predictive value at all the gestational ages. In the present study, the sensitivity of the MCA PI ranged from 33.3 to 39.1 %, while specificity and positive predictive values ranged from 88.9 to 94.4 % and 88.9 and 93.8 %, respectively. The negative predictive value of the criteria ranged from 37.8 to 38.1 %. Overall, the sensitivity, specificity, PPV, and NPV of the criteria were 35.7, 92.6, 91.8, and 38.2 %, respectively, with a diagnostic accuracy of 36.1 %. Thus, the criteria were found to be more specific and having a higher positive predictive value than being sensitive and having a higher negative predictive value. These findings are in consonance with the findings of Bano et al. [11] who observed the sensitivity, specificity, PPV, and NPV of the MCA PI to be 8.9, 100, 100, and 52.3 %, respectively, with a diagnostic accuracy of 54.4 %. The common criteria in both the studies were the PI cut-off of >1.5 adapted from Gramellini et al. [12]. However, in another study, Fong et al. [13] reported the sensitivity, specificity, PPV, and NPV of the MCA PI to be 72.4, 58.1, 37.7, and 85.7 %, respectively, for predicting any adverse perinatal outcome, whereas for

prediction of major adverse outcomes the sensitivity, specificity, PPV, and NPV of the MCA PI were 91.7, 53.9, 15.1, and 98.6 %, respectively. The findings in the present study lie in between these two extremes. However, the difference was in the selection of cut-off value for the MCA PI. Fong et al. had chosen the cut-off value from the nomograms obtained from one of the largest published cross-sectional studies involving 1,556 fetuses [1]. These findings suggest that with selection of a better cut-off, the predictive value of PI of the MCA could be increased substantially.

Just like the MCA PI, the MCA RI also did not show a fair sensitivity and negative predictive value. The sensitivity at its best was only 31 % for the second visit, while negative predictive value was only 35.6 % at the second visit. However, at the third visit, the specificity and positive predictive values were a perfect 100 %. Overall, the efficacy of the criteria in terms of sensitivity, specificity, PPV, NPV, and diagnostic accuracy was, respectively, 26.2, 92.6, 89.2, 35.0, and 46.1 % only.

The trend observed was that with increasing gestational age, the overall efficacy was improving. Kurmanavicius et al. [2] in their study had mentioned a dynamic behavior of the MCA RI. They observed a parabolic pattern of change in the MCA RI with increasing age; this implies that a single cut-off value should not be employed for prediction of IUGR. In fact, in their article, they had given a regression equation dependent on gestational age to calculate the appropriate cut-off for different gestational ages. In the present study, we have used single cut-off criteria and found the results that did not have much predictive value. In a study by Narula et al. [7], the RI showed a dynamic change with increasing gestational age. The mean-1SD value at different gestational ages ranged from 0.80 to 0.68 which is much larger than the cut-off value taken in the present study. The utility of a population-specific cut-off value cannot be denied for such considerations. However, the pool of nomograms on the Indian population is still lacking. One such study comes from Iran [14], which showed that the cut-off values suggested by Kurmanavicius were much lower than the values observed by them for prediction of IUGR. In the present study too, we find that a higher cut-off value for the MCA RI could yield better results.

Conclusion

The following conclusions were drawn from the present study. The incidence of clinically confirmed IUGR in clinically suspect and grayscale-confirmed pregnant women was 70 %. The UA PI had maximum sensitivity (85.7 %) at the third visit (32–37 weeks) and maximum specificity (88.9 %) also at the third visit (32–37 weeks). Its overall diagnostic sensitivity, specificity, NPV, PPV, and diagnostic accuracy were 73.8, 75.9, 87.7, 55.4, and 75 %, respectively. The UA RI had maximum sensitivity (64.3 %) at the second visit (28–32 weeks) and maximum specificity (100 %) at the third visit (32–37 weeks). Its overall diagnostic sensitivity, specificity, NPV, PPV, and diagnostic accuracy were 61.1, 94.4, 96.3, 51, and 71.1 %, respectively. The MCA PI had an overall diagnostic sensitivity, specificity, PPV, NPV, and diagnostic accuracy of 35.7, 92.6, 91.8, 38.2, and 52.8 %, respectively. There was a low negative predictive value for all the parameters owing to a high incidence of IUGR (70 %). The high variability in diagnostic efficacy of different markers at different visits indicated that a single cut-off value is not suitable for prediction of IUGR.

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