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Prediction of Intrauterine Growth Restriction in High Pulsatility Index of Uterine Artery

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Authors' contributions

This work was carried out in collaboration between all authors. Author NS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SS, KJ and MS managed the analyses of the study. Authors KN and VR managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Intrauterine growth restriction is a significant cause of neonatal mortality. The uterine artery Doppler waveform becomes transformed into a high flow with low resistance at 22-24 weeks. The apt way to reduce intrauterine growth restriction is to identify the antenatal factors, which ascertain the uterine milieu and nutrient bioavailability. This study was conducted to outline the relation between abnormal uterine artery flow and resultant intrauterine growth restriction in a tertiary care center.
Aim and Objectives: To study the Maternal risk factors and uterine artery Doppler waveform in singleton mid trimester pregnancy and predict the occurrence of intrauterine growth restriction.

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Materials and Methods: This prospective study involved Doppler ultrasound examination of the uterine arteries at 20-23 weeks gestation in 697 women with singleton pregnancies attending a routine target scan. Intra Uterine Growth Restriction (IUGR) was recorded in 32 pregnancies.
Results: High Pulsatility Index (PI) (>95th percentile) as compared to low pulsatility Index confers a significant risk (31.58% v/s 2.19%) for Intrauterine Growth Restriction ($p<0.05$). Presence of high pulsatility is a significant risk factor for early onset IUGR as compared to late onset IUGR.
Conclusion: Abnormal Doppler waveforms within the uterine arteries are indicative of elevated resistance. The perfusion at the trophoblast-maternal interphase is high velocity, low volume and intermittent, resulting in intrauterine growth retardation. This subsequently leads to the damage of fetal tertiary stem villi floating in the intervillous space. The sensitivity is better for early onset IUGR. This study concludes that high pulsatility index in uterine arteries can lead to intrauterine growth restriction. The plausible explanation is reduced Vascular Endothelial Growth Factor (VEGF) from maternal decidual natural killer cells.

Keywords: Ultrasound; uterine artery; pregnancy; intrauterine growth restriction.

1. INTRODUCTION

Intrauterine growth restriction affects 3-7% of all pregnancies and is a leading cause of premature iatrogenic deliveries and perinatal morbidity [1].

Uterine Blood Flow and placental oxygen and nutrient transfer to the fetus may be compromised in a variety of maternal diseases like Anemia, pregnancy induced hypertension, gestational diabetes, renal disease, maternal infections and other connective tissue disorders. Fetal causes of IUGR are chromosomal and structural anomalies, multiple pregnancies and intrauterine infections. Placental bed causes include abnormal umbilical cord placental insertion and placental ischemia secondary to abnormal uteroplacental blood flow at the fetomaternal interface. Chronic hypertension and diabetes mellitus have also been implicated as maternal causes of intrauterine growth restriction.

The transfer of Oxygen across the maternal fetal interface is dictated by the Fick's Equation. The volume of oxygen transfer is calculated as cm^3/min/mmHg = (Villous surface area + capillary surface area) X K/2 X Mean Mth (the Harmonic mean thickness of the villous membrane which includes the trophoblast, the villous stroma and the endothelium of fetal capillaries) where K is the Krogh's diffusion coefficient [2]. The villous membrane thickness gradually decreases as gestation advances. In addition, the apical and basal membranes of syncytio trophoblast are richly endowed with amino acid and other Adenosine tri-phosphate (ATP) dependent transporters involved in active transport and maintenance of ionic homeostasis. The uterine artery blood flow rises exponentially from 50 ml/min in non pregnant state to 600 ml/min during pregnancy [3]. The uterine artery Doppler waveform becomes transformed into a high flow with low resistance at 22-24 weeks. The apt way to reduce intrauterine growth restriction is to identify the antenatal factors, which ascertain the uterine milieu and nutrient bioavailability Hence this study was conducted to outline the relation between abnormal uterine artery flow [4] and resultant intrauterine growth restriction in a tertiary care center.

2. MATERIALS AND METHODS

This prospective study involved Doppler ultrasound examination of the uterine arteries at 20-23 weeks gestation in women with singleton pregnancies attending a routine target scan. This study was approved by the ethical and research board. All women with no major fetal anomaly were offered the option of uterine artery Doppler evaluation. Written consent was obtained in all cases. A first trimester scan was done to measure Crown Rump Length to date the pregnancy in all cases.

Study was carried out on 697 pregnancies in the Department of Radiology and Department of Obstetrics and Gynecology at Saveetha Medical College and hospital, Chennai, India between 1 April 2015 and 31 December 2016. Multiple Pregnancies and pregnancies with congenital anomalies were excluded. Detailed maternal factors like age, gestational age, parity, pre pregnancy body mass index, previous low birth weight, hemoglobin levels, chronic hypertension, gestational diabetes and preeclampsia were recorded. Placental problems like infarcts, retro placental calcifications, small placenta, and premature separation were noted. The ultrasound machines used for the study were

PHILIPS HD11XE (Acuson, Mountain View, CA, USA); GE LOGICS7 Expert; Siemens Sonoline Acuson X150 (Siemens).

The uterine artery was identified in the longitudinal scan lateral to the uterus. Pulsed wave Doppler was used to obtain three similar consecutive waveforms. The same was repeated for the contra lateral uterine artery and the mean Pulsatility Index (Maximum-Minimum velocity/Mean velocity) of the two vessels was calculated. Presence or absence of an early diastolic notch was recorded. The curved transducer (3.5- or 5-MHz) had spatial peak temporal average intensities <100 m W/cm^2. Recordings for measurements were obtained in the absence of fetal breathing movements and fetal heart rate between 120-160 beats per minute. The angle between the ultrasound beam and the direction of blood flow was always less than 50°. Intrauterine Growth Restriction was diagnosed if the estimated fetal weight was below the 10th percentile for gestational age, together with a Doppler Pulsatility Index in the umbilical artery above the 95th percentile, or if the estimated fetal weight was below the 3rd percentile irrespective of the umbilical artery Doppler [5]. For the purpose of this study Intrauterine Growth Restriction was classified as early onset (<32 weeks) or late onset (>32 weeks).

Mean pulsatility index was not normally distributed and therefore expressed median ± interquartile range. Fischer exact test was used to analyze maternal history variables, and independent t-test –Mann Whitney U test was used for continuous variable analysis wherever possible. The sensitivity (S), specificity (E), positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio (LR) for a cut off mean PI of 1.55 (95th Percentile) were calculated and bilateral or unilateral notches in the prediction of IUGR were calculated. Differences were considered significant when p<0.05.Logistic regression was used to obtain the Odds ratio (OR) and 95% CI. Statistical analysis was done using SPSS 16.0 (SPSS, Chicago, III, USA).

3. RESULTS

Doppler examination was done in 750 pregnancies. Satisfactory wave forms were obtained in 743 pregnancies (99%). During the study period, a follow up was available for a total of 697 pregnancies. Uterine artery pulsatility index was not normally distributed but was found skewed to the right with the 95th percentile at 1.6 (Fig. 1). A total of 32 (4.59%) pregnancies resulted in intrauterine growth restriction neonates out of total 697 pregnancies. There were no intrauterine deaths.

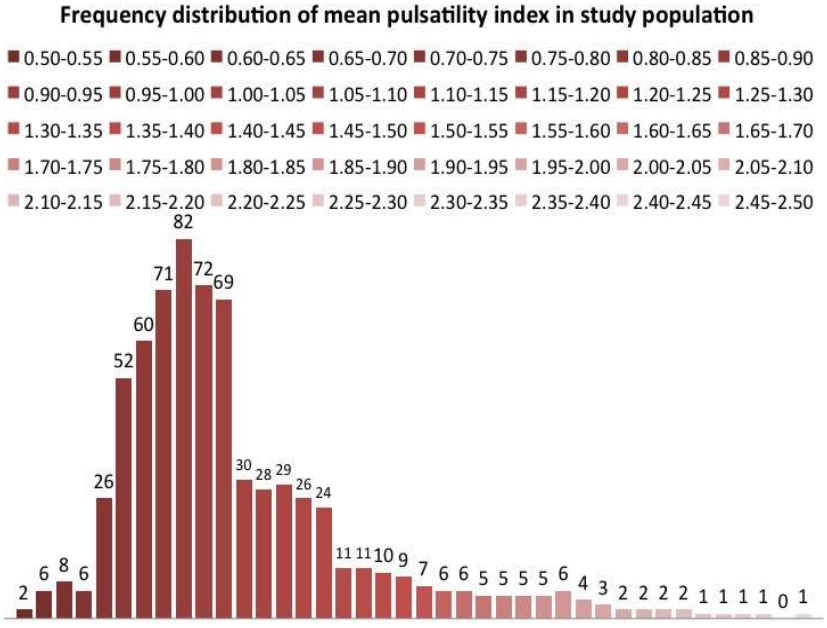

Fig. 1. Frequency distribution of mean pulsatility index in study population

There was a significant association off maternal age >34 with IUGR (Odds Ratio 241.5192, Confidence interval 72.0261 to 809.8671, Z statistic 8.889, p value <0.0001). Out of 32, 7 were early onset (<32 weeks) and 25 were late onset (>32 weeks). Thirteen cases of IUGR had pregnancy-induced hypertension. In twelve cases there was severe and very severe anemia. In 4 cases there was placenta praevia. There were 6 cases of grade 1 abruption. There were 2 cases of grade 3 abruption In two cases there was velamentous cord insertion. Out of 32 intrauterine growth restricted newborns, 31 survived beyond four weeks of life. Gestational age rather than weight was a predictor of neonatal mortality, as all IUGR babies beyond 34 weeks had no neonatal mortality. In 2 neonates (6.25%) no maternal cause of IUGR could be identified. Table 1 brings up the fact that presence of high pulsatility index as compared to low pulsatility confers a significant risk (31.58% v/s 2.19%) for Intrauterine growth retardation ($p<0.05$). Table 2 tells us that presence of high pulsatility is a significant risk factor for early onset IUGR as compared to late onset IUGR. Table 3 tells us the sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio positive and likelihood ratio negative of early and late onset IUGR when PI>1.55.

Table 1. Intrauterine growth restriction in high pulsatility and low pulsatility index

Uterine artery pulsatility index	IUGR	No IUGR	Total
PI>1.55	19	39	58
PI<1.55	13	626	639
Total	32	665	697

Table 2. Early and late onset intrauterine growth restriction in high and low pusatility index

Uterine artery	Early onset IUGR	Late onset IUGR	Total
PI>1.55	6	13	19
PI<1.55	1	12	13
Total	7	25	32

4. DISCUSSION

Internal iliac artery is the 3-4 cm division of common iliac artery and the main artery entering the pelvis, whose anterior division gives of the uterine artery (the end artery). While the uterine artery changes from a resistance vessel to a capacitance vessel (fall of Resistivity Index and Pulsatility Index) the Internal Iliac Artery increases its resistance (RI and PI remarkably increase). Interesting because Internal Iliac Artery is the direct precursor of uterine artery. This ensures that the low resistance uterine artery is rapidly filled by enhanced maternal cardiac output. This occurs due to release of VEGF (Vascular endothelial growth factor), PLGF (Placental growth factor) and angiopoietins released from natural killer cells present in uterine endometrium.

At the fetomaternal interphase, the first stage of remodeling of spiral arterioles, as early as 9 weeks, is associated with vacuolations in the tunica media and intima of spiral arterioles under the influence of VEGF, PLGF and angiopoietins secreted from the maternal decidual natural killer cells. The second stage of remodeling is proliferation of endovascular and interstitial trophoblast. In the second stage the endovascular trophoblast actually blocks the lumen of spiral arteriole. This is important because a low oxygen tension is required at the fetomaternal interphase, especially because the blood brain barrier in fetus is not developed [6,7,8]. The third stage of remodeling is associated with loss of smooth muscle cells and elastic tissue from the vessel walls, resulting in expansion of the mouth of the artery as it opens into the Intervillous space within the placenta. The remodeled arteries are incapable of constriction, protecting the blood supply to the placenta. In addition, the velocity and pressure of the inflowing blood are significantly reduced, minimizing hemodynamic damage to the delicate fetal tertiary stem villi. At this point the blood brain barrier is complete. In the fourth stage there is re-endothelialization of spiral arterioles.

Table 3. Screening characteristics of protodiastolic notch and high pusatility index for early and late onset intrauterine growth restriction

Outcome	Sensitivity (%)	Specificity (%)	PPV%	NPV%	LR+	LR-
IUGR	59.38	94.14	32.76	97.97	10.12	0.43
IUGR<32 WEEKS	87.71	92.46	10.34	99.84	11.37	0.15
IUGR>32 WEEKS	52.00	93.30	22.41	98.12	7.77	0.51

Impaired secretion of VEGF, PLGF and angiopoietins from maternal decidua natural killer cells can lead to persistent protodiastolic notch and high resistance, high velocity diastolic flow [9]. Impaired blocking of spiral arterioles by endovascular trophoblast can lead to high oxygen tension at fetomaternal interphase. Furthermore, impaired phagocytosis by trophoblasts leads to retention of varying amounts of smooth muscle in the vessel walls and causes the mouths of the spiral arteries to be narrower. Consequently, blood enters the intervillous space at a higher velocity in jet-like spurts, and perfusion may also be intermittent due to constriction of the vessel walls. Impaired remodeling is usually associated with abnormal Doppler waveforms within the uterine arteries, indicative of elevated resistance. However, the hemodynamic basis for the relationship between VEGF secretion and uterine artery low impedance flow is still uncertain. Fetal growth restriction may occur in women with impaired secretion of VEGF from maternal decidua (maternal cause) or impaired trophoblastic proliferation (fetoplacental cause) and inadequate sealing of spiral arterioles leading to high oxygen tension at the fetomaternal interphase. Impaired secretion of VEGF, PLGF and angiopoietins and other mediators of vasodilatation lead to high resistance, low volume and high velocity diastolic flow in uterine arteries.

Screening characteristics of pulsatility Index are better for early onset as compared to late onset intrauterine growth restriction [10,11]. Abnormal Uterine artery Doppler has also been associated with fetal Brain hemodynamic deterioration [12]. Sonographic fetal abdominal circumference in combination with uterine artery Doppler has been used to differentiate preeclampsia associated with IUGR from the preeclampsia without IUGR [13]. Association of high uterine pulsatility index and IUGR is supported by various other studies [14,15,16].

5. CONCLUSION

This study concludes that high pulsatility index in uterine arteries is associated with intrauterine growth restriction. The plausible explanation is reduced VEGF from maternal decidua resulting in high velocity, low volume diastolic flow in the uterine artery supplying the spiral arterioles, that subsequently leads to the damage of fetal tertiary stem villi floating in the intervillous space. As resistance increases in uterine arteries, the velocity of blood flowing also increases from 10 cm/sec to 1-2 m/s. The uterine artery supplies both the trophoblast maternal interphase and the uterine arterial venous circulation. Most blood increases uterine arterial venous circulation and helps in the development of uterine musculature and local milieu of gestation and protects against post partum hemorrhage. Only a partial amount of blood flowing through uterine arteries is pumped into the dilated spiral arteries and sprinkled (cf shot) over tertiary fetal stem villi in the intervillous space. The damage to placental bed may be ischemic, hemodynamic, oxidative or immunological. The high velocity, low volume, intermittent perfusion by the uterine artery supplying the intervillous space at the trophoblast-maternal interphase can cause hemodynamic and oxidative damage resulting in intrauterine growth retardation. The sensitivity and negative predictive value are better for early onset IUGR.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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