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Clinical profile of antenatal cases undergoing uterine artery Doppler

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Abstract
In human placenta, an organ without autonomic innervations, the control of vascular tone is dependent on local release of vasoconstrictors and vasodilators, released from endothelial cells in response to mechanical and chemical stimuli triggered by cardiac output and blood flow requirements. In placental and systemic circulation, the main stimulus regarding control of vascular resistance and blood flow, is related to increments of shear stress by high placental perfusion throughout pregnancy. In addition to the routine scan, bilateral uterine artery Doppler was done. Both uterine arteries were identified at their crossing with the external iliac artery. Pulsed wave Doppler imaging was used with the sampling gate set at 2 mm to cover the entire diameter of the uterine artery and 1 cm distal to the crossing site. The quality of the flow velocity waveform was maximized by using the smallest possible angle of insonation and care was taken to obtain a good waveform with a clear and sharp outline. Pulsatility index (PI) for each uterine artery was obtained by averaging the value of three clear consecutive measurements of waveforms. The incidence of normal outcome was four fold higher in low risk women with normal Doppler than those with abnormal Doppler. This indicates that most of the low risk women with normal PI will have normal pregnancy outcome.

Keywords: Uterine artery Doppler, clinical profile, pulsatile index

Introduction

Remodeling of the maternal uterine vasculature during pregnancy is a unique process resembling the cardiovascular process that occurs in the adult. This remodeling results in significant structural and functional changes in large and small arteries and veins, and in the formation of the placenta, a new fetomaternal vascular organ. This expansive, hypertrophic process results in an increase in both the circumference and the length of the lumen, and is affected through a combination of tissue and cellular hypertrophy, endothelial and vascular smooth muscle hyperplasia and matrix remodeling [1].

During the first few weeks of pregnancy, a number of changes take place in the maternal uterine vasculature resulting in increased blood flow to the intervillous space. Failure of the spiral arteries to remodel sufficiently is a common feature of various pathologies associated with placental insufficiency such as preeclampsia, intrauterine growth restriction, oligoamnios and preterm births [2, 3].

During pregnancy, the diameter of the main uterine artery approximately doubles in size. This enlargement in arterial caliber occurs most often with little or no thickening of the vascular wall. With or without wall thickening, the increase in lumen diameter nevertheless results in an increased cross-sectional area [4].

In human placenta, an organ without autonomic innervations, the control of vascular tone is dependent on local release of vasoconstrictors and vasodilators, released from endothelial cells in response to mechanical and chemical stimuli triggered by cardiac output and blood flow requirements. In placental and systemic circulation, the main stimulus regarding control of vascular resistance and blood flow, is related to increments of shear stress by high placental perfusion throughout pregnancy. The vascular response of placental circulation to shear stress depends of a variety of factors: local release of vasoactive molecules, endocrine signaling, and oxidative stress in vascular cells or vascular remodeling, among others. The maintenance of vascular tone and blood supply for placental circulation is a key factor for adequate placentation and fetal development [5].

The uteroplacental circulation develops in two stages. The first stage takes place between 8 and 10 weeks of gestation and begins with endovascular plugging of the spiral arteries by trophoblast cells. This is followed by trophoblastic invasion and destruction of the

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musculoelastic media of the intra-decidual segments of the spiral arteries. The second stage occurs between 14 and 16 weeks, and involves trophoblastic invasion of the spiral artery segments in the inner third of the myometrium [6].

Impaired trophoblast invasion into the spiral arteries has been related to abnormal uterine artery blood flow. A normal trophoblastic invasion results in a physiological decrease of resistance of the uterine artery. In the absence of trophoblast invasion the decrease of resistance does not occur. Hence, measurement of blood flow in the uterine artery is used in order to find pregnancies complicated by fetal growth restriction and preeclampsia [7].

An early preeclampsia could be predicted with the use of both Doppler measurements and a combination of several biomarkers. Apparently, screening of women with risk factors was actually less successful than screening of low-risk individuals [8].

R. Napolitano *et al* were studied with the objective of first-trimester Doppler studies have reported that the lower uterine artery (UtA) resistance index (RI) is better for the prediction of pre-eclampsia (PE) than is either the mean or higher indices and to determine if this relationship is true in the second trimester. They concluded that performance of UtA-RI in predicting PE is no different for the lower, higher or mean RI of the two UtAs. The most likely explanation for the discrepancy with first-trimester studies is that the placental-side effect on Doppler indices may change with advancing gestational age and progressive trophoblast development and invasion.

Methodology

The study population consisted of pregnant women between 18 – 20 weeks of gestation with viable pregnancy. Using probability of Type 1 error (α) as 0.05(5%) and power of test (1-β) as 0.9 (90%), with an expected overall incidence of obstetric complications of 15 percent among those with abnormal Doppler i.e. with unilateral increase in PI value of >1.5 and the mean PI <1.5 and 5 percent in those with normal Doppler. To reject the null hypothesis that pregnancy outcome will be the same among women with normal and abnormal Doppler, minimum of 200 women need to be studied.

In addition to the routine scan, bilateral uterine artery Doppler was done. Both uterine arteries were identified at their crossing with the external iliac artery. Pulsed wave Doppler imaging was used with the sampling gate set at 2 mm to cover the entire diameter of the uterine artery and 1 cm distal to the crossing site. The quality of the flow velocity waveform was maximized by using the smallest possible angle of insonation and care was taken to obtain a good waveform with a clear and sharp outline. Pulsatility index (PI) for each uterine artery was obtained by averaging the value of three clear consecutive measurements of waveforms.

Based on the reference ranges for uterine artery pulsatility index (PI), proposed by Gomez O [6, 8] *et al* in 2008, in the present study cut off 1.5, upper limit of normal (above 95th percentile) had been taken into consideration as abnormal uterine artery Doppler.

The following uterine artery Doppler values were taken as abnormal

- If unilateral uterine artery pulsatility index was >1.5 but with Mean Pulsatility Index <1.5
- Women were subdivided based on placental location to central and lateral groups and the outcome among both groups were analysed.

- In cases with unilaterally abnormal uterine artery Doppler and lateral placenta whether it ipsilateral or contralateral was noted.
- The outcome was separately studied in ipsilateral and contralateral abnormal uterine Doppler and the results were analysed.
- All ultrasound information were documented and were not available to the Clinicians who managed the pregnancy.
- Pregnancy was managed as per the standard obstetric protocol. Patients in the study group were not managed separately from controls.
- The recruited patients were followed up till the end of pregnancy. Pregnancy outcomes were assessed withfetal and maternal outcomes.

Fetal/Neonatal Outcomes

- Second trimester Abortion – Spontaneous fetal loss before viability (28 weeks of gestation)
- Still births- Death of a fetus weighing 500g or more, or of 28 weeks gestation or more, if weight is unavailable
- Preterm Birth - Preterm birth was defined as delivery after 28weeks but before 37 completed weeks of gestation.
- Neonatal mortality– Death of neonate in first 1 month of life
- Intrauterine Growth Restriction (IUGR) - Birth weight below 10th percentile for the gestational age
- NICU admissions> 24 hours along with any of the following:
- Acidosis – Cord blood pH <7.2
- Respiratory Distress Syndrome (RDS)
- Assisted Respiratory support – requirement of CPAP (Continued Positive Airway Pressure) and ventilatory support
- Low APGAR at 5 mins <7

Maternal Outcomes

- Gestational Hypertension- Defined as blood pressure >140/90 mm of Hg after 20 weeks period of gestation with no proteinuria, blood pressure returns to normal in less than 12 weeks postpartum. (NHBEP: working group report on high blood pressure)
- Preeclampsia- Defined as pregnancy specific syndrome characterized by blood pressure >140/90 mm of Hg after 20 weeks period of gestation with proteinuria > 300mg/24 hrs or 1+ on a random urine analysis by dipstick. (NHBEP: working group report on high blood pressure)
- Early onset preeclampsia- Onset of preeclampsia before 34 weeks of gestation.
- Late onset preeclampsia- Onset of preeclampsia after34 weeks of gestation.
- Superimposed Preeclampsia On Chronic Hypertension:
- New-onset proteinuria 300 mg/24 hours in hypertensive women but no proteinuria before 20 weeks' gestation
- A sudden increase in proteinuria or blood pressure or platelet count < 100,000 in women with hypertension and proteinuria before 20 weeks' gestation (NHBEP: working group report on high blood pressure)

Results

Table 1: Demographic Characteristics

Characteristics	Mean±SD	Range
	(n=343)	
Maternal age(in years)	28.63±3.704	20-41
Gestational age at Doppler sampling	18.48±0.666	18-20
(in weeks)		
Primigravida	197(57.43%)	
Multigravida	146(42.56%)	

The study population involved relatively more number of primigravida. In this study, primigravida were 57% and multigravidae were 43%. Multigravidae included in the study were up to 4th gravida with previous history of abortions or intrauterine death or neonatal death or good outcome, were studied.

The mean age of the study population was 28.63±3.704years and women with age ranging from 20- 41 years were included in the study. Mean gestational age at the time of uterine artery Doppler sampling was found to be 18.48±0.668 weeks.

Table 2: Correlation of cases with parity status

Parity n (%) 343(100%)	Uterine A. Doppler Abnormal (PI >1.5) n (%)	Uterine A. Doppler Normal (PI <1.5) n (%)
	122 (35.56)	221 (64.43)
Primigravida 197(57.43)	63(51.63%)	134(60.63%)
Multigravida 146(42.56)	59(48.36%)	87(39.36%)

Presences of other risk factors have been evaluated and enumerated. Autoimmune pathology for recurrent pregnancy loss like Antiphospholipid syndrome was ruled out. Both the groups (Primigravida and multigravida) showed almost equal number of abnormal Doppler studies.

Table 3: Risk profile of the cases

1. Risk factors in **previous** pregnancy	n = 60
Previous abortions/IUD/NND	26
Previous history of IUGR	11
Hypertensive disorders	23
2. Risk factors in present pregnancy	n =13
Gestational Diabetes on medication	10
Overt Diabetes on treatment	2
Dermatomyositis	1

Rest of the 270 cases (78.71%) was at low risk for developing the adverse pregnancy outcome.

Bilateral uterine artery Doppler was done between 18 – 20 weeks of gestation and Pulsatility index (PI) of individual uterine arteries and the mean PI were noted. At the same time, placental location was also noted.

Table 4: Correlation of risk status with uterine artery Doppler

Uterine artery Doppler Pulsatility index (Uterine A. PI) n (%)	Risk status, n (%), 343 (100)	
	High risk Pregnancy n (%) 73(21.28)	Low risk Pregnancy n (%) 270(78.71)
Uterine A. Doppler Abnormal (PI >1.5) 122(35.56)	51 (69.86)	71 (26.29)
Uterine A. Doppler Normal PI < 1.5 221 (64.43)	22 (30.1)	199 (73.70)

Expecting the higher incidence of obstetric complications in the high risk pregnancy, the efficacy of unilaterally increased pulsatility index in the second trimester as a screening tool was evaluated and the results were compared to those of low risk pregnancy.

In the study population, the percentage of unilaterally increased pulsatility index with high risk pregnancy was 2.6 fold higher than those of women with unilaterally increased pulsatility index and with low risk pregnancy.

Table 5: Distribution of cases among High Risk pregnancy

High Risk pregnancy n (%) 73(21.28)			
Pregnancy outcome n (%)	Uterine A. Doppler Abnormal (PI >1.5) n (%) 51 (69.86)	Uterine A. Doppler Normal (PI <1.5) n (%) 22 (30.13)	P value
Adverse pregnancy outcome 44(60.27)	40(78.43)	4(18.18)	
Normal pregnancy outcome 29(39.72)	11(21.56)	18(81.81)	0.000

*Chi Square test (Significant p value < 0.05)

High risk women with unilateral increased pulsatility index had 3.6 fold higher incidence of adverse pregnancy outcome than those with normal pulsatility index. Eleven women had normal pregnancy outcome with unilateral PI >1.5. Four of them had overt diabetes. Eleven women had normal pregnancy outcome with unilateral PI >1.5. This perhaps may be explained by the presence of diabetes which could have masked the occurrence of IUGR.

Eighteen women of high risk pregnancy were started on aspirin prophylaxis around 6 to 8 weeks of gestation. Four of them still had abnormal Doppler but with normal outcome. Remaining ten women who were on aspirin had normal Doppler and had normal pregnancy outcome.

Four women developed Gestational hypertension at 37 weeks inspite of having normal PI on Doppler. This could be due to the failure of placental function at term due to atherosclerosis of the placental vasculature.

High risk women with normal pulsatility index in second

trimester Doppler had four fold less incidence of adverse pregnancy outcome than those with unilaterally increased pulsatility index. Most of the women with normal PI had normal pregnancy outcome.

The above results from table 7, were suggestive of statistically significant association of unilaterally increased uterine artery Pulsatility index of second trimester in the prediction of adverse pregnancy outcome in high risk women ($p<0.001$).

They also indicate the higher sensitivity (90.91%) with 95% confidence interval (CI) of 78.33% to 97.47%] of abnormal Doppler in screening high risk pregnancies for adverse outcome. This suggests that abnormal Doppler in high risk pregnancy has high adverse pregnancy outcome.

Table 6: Distribution of cases among low risk pregnancy

Low Risk pregnancy, n (%) 270(78.71)			
Pregnancy outcome	Uterine A. Doppler Abnormal (PI >1.5)	Uterine A. Doppler Normal (PI < 1.5)	P value
n (%)	n (%)	n (%)	
	71 (26.29)	199 (73.70)	
Adverse pregnancy outcome 94(34.81)	57(80.28)	37(18.59)	0.000
Normal pregnancy outcome 176(65.18)	14(19.71)	162(81.40)	

*Chi Square test (Significant p value < 0.05)

Low risk women with unilateral increased pulsatility index had four fold higher incidence of adverse pregnancy outcome than those with normal pulsatility index.

Twenty three patients developed gestational hypertension 36 weeks and one had preeclampsia at 36+weeks. This might be the result of the atherosclerotic changes in the placental vasculature leading to its failure of utero-placental function at term. This indicates that most of the low risk women with normal PI will have normal pregnancy outcome. As the unilateral increase in PI is only a screening test, but not diagnostic test. It will have its own limitations per se.

The incidence of normal outcome was four fold higher in low risk women with normal Doppler than those with abnormal Doppler. This indicates that most of the low risk women with normal PI will have normal pregnancy outcome.

These results were suggestive of statistically significant association of unilaterally increased uterine artery Pulsatility index of second trimester in the prediction of adverse pregnancy outcome in low risk women.

Above data suggestive of higher specificity (92.05%) with 95% confidence interval (CI) of 87.01% to 95.58%] of unilateral increased pulsatility index among low risk pregnancies and also the strong association of unilateral increased pulsatility index with adverse pregnancy outcome that was statistically significant ($p< 0.001$).

Discussion

Trophoblastic invasion plays a significant role in the development of the feto-placental unit. Normal and progressive development of placental circulation is associated with normal pregnancy outcome. Inadequate trophoblastic invasion leads to increased impedance in spiral artery that lead to uteroplacental insufficiency and placental ischaemia. This can be demonstrated through adverse pregnancy outcome in the form of maternal,

fetal or neonatal outcome.

Obstetric disorders that can result from utero-placental insufficiency are gestational hypertension, preeclampsia, abruption, eclampsia, intrauterine growth restriction, preterm deliveries or still birth.

The impairment of this physiological process is associated with increased vascular resistance and increased impedance to blood flow and ultimately affects blood flow to the placenta. These sequences of events precede the onset of complications. This process commences in the first trimester and ends in second trimester.

Because of the heterogeneity of the etiology of complications like pre-eclampsia, fetal growth restriction, preterm labour and stillbirth, due to impaired implantation of placenta, there is no uniformity in favour of using uterine artery Doppler. Uterine artery Doppler is a useful modality toevaluate uteroplacental resistance in the second trimester. Accurate prediction of pregnancy outcome is possible at this stage by measuring the increased impedance flow in uteroplacental circulation.

Over the past few years, various studies done by Bower *et al* [9], Papageorghiou AT [10], Groom KM [11], Yu CK *et al* [12] focused on uterine vasculature and its relation to placental insufficiency. Second trimester uterine artery Doppler had been used as a screening tool and has revolutionized the screening tests in prediction of pregnancy outcome.

They used various uterine artery Doppler impedance indices such as resistance index, S/D ratio or Pulsatility index. Very few studies were done using Pulsatility index exclusively as a tool for prediction of pregnancy outcome and there were contradictory results in relation to the same.

In the past, many studies were done to establish correlation between placental pathology and uterine artery Doppler. Murat Akbas *et al* [13] also studied 510 pregnant women between 11-14 weeks and 20-24 weeks and noted strong association between uterine artery Doppler indices and preeclampsia and intrauterine Growth restriction. They correlated Doppler with placental bed biopsies taken at the time of delivery with the criteria that biopsy contains trophoblasts, spiral artery and myometrial component and concluded that there was significant relationship between uterine artery Doppler and placental insufficiency involving defective trophoblastic invasion, atherosis/ thrombosis and luminal obliteration of spiral arteries.

Most of those studies mainly analyzed the indices as a mean of the right and left side values, without taking into account the discordancy of the blood flow between the two sides.

Bellamy *et al*, [14] and Mc Donald SD *et al*, [15] stated that a screening test that could identify women, early in pregnancy who would develop preeclampsia in the latter half of pregnancy, would allow increased surveillance of those at risk and reduce surveillance for those unlikely to develop the syndrome.

We selected women between 18- 20 weeks for uterine artery Pulsatility index evaluation taking all the above facts into consideration and to evaluate exclusively the early stages of secondary trophoblastic invasion because, as gestational age advances, the uterine artery may adopt to the underlying pathology and also the decrease in impedance to flow may result in normal Doppler values in spite of having the underlying pathology of placental insufficiency.

Among women with lateral placenta, there is observation of increased utero-placental resistance on the side, opposite to that of the placenta, i.e. contralateral side. If the placenta is on the right side, then the resistance in the left uterine artery will be on the higher side. It can be explained by decreased trophoblastic invasion into the vascular bed which is away from the placental

location and the ipsilateral artery developing the physiologic changes before the contralateral artery. This discordancy in the flow may result in abnormally high resistance in one vessel resulting in adverse outcomes in the pregnancy.

Sergio L *et al* [16] conducted a study in 318 viable pregnancies between 6 and 12 weeks of gestation. Out of 318 pregnancies, 24(8%) resulted in spontaneous abortion before 20 weeks of gestation. They found that a significant number of early viable pregnancies that would end in a miscarriage, have an abnormal hemodynamic pattern characterized by discordant uterine artery blood flow velocity waveforms related to an abnormally high PI value in one uterine artery. It was concluded that in patients with discordant uterine artery velocity waveforms, invasion capabilities of cytotrophoblastic cells are impaired, resulting in defective placentation, and hence, spontaneous miscarriages.

Conclusion
Second trimester uterine artery Doppler done between 18-20 weeks was feasible and appealing as it can be done along with the target scan, there by screening the disorders resulting from uteroplacental insufficiency and placental ischemia

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